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To:	medboardconsultation
Cc:	[redacted]
Subject:	Feedback - AHPRA Good Medical Practice - Revised Edition 2018
Date:	Monday, 2 July 2018 2:59:24 PM
Attachments:	2018 FPM CNCP Cannabinoids Statement.pdf 2018 Pain Cannabinoids CNCP In Press.pdf NASEM 2017 CB Report.pdf Whiting et al 2015 Cannabinoid Sys Review and Meta Analysis JAMA.pdf

Dear AHPRA,

Thank you for the invitation to comment on the revision of Good Medical Practice.

Comment re Issues of Concern Relating to the Code of Conduct:

I believe the proposed, revised Good Medical Practice has several serious deficiencies.

These deficiencies are specifically in relation to the promotion and use of medical therapies with very limited evidence and significant risk of harm.

Such therapies might best be deemed as therapies with potential but significant uncertainty of outcome, and or, best described as experimental / research therapies.

Either way, the information given, patient communication and informed consent should meet the higher standards expected of therapies which are essentially in need of further research to define their use and benefit.

These therapies also invoke serious concerns regarding risk versus benefit which is mentioned at 3.2.4, 4.3.4 and 4.5.

These concerns also relate to concepts of safe and effective therapy which in contrast has minimal mention eg 3.2.4.

I believe these aspects of evidence informed risk, benefit, safety and efficacy in relation to patient centred care, patient communication and informed patient consent, need significant strengthening in a changing environment.

Example to Illustrate the Issues of Concern:

An example is the use of unregistered products containing cannabinoids which have bypassed the usual TGA registration safety and efficacy requirements and as a consequence do not have the common and clearly required, TGA approved elements, such as dosing regimes.

The most recent and reputable statements in respect of this matter come from:

1. The Faculty of Pain Medicine ANZCA (June 2018) (see attached);
2. The research team from NDARC who reported to the TGA in Dec 2017 on the use of products containing cannabinoids in Australia, who now have the most up to date journal article about to be published in the most widely read Pain Medicine journal PAIN (see attached).

From the latter, for information, 24 persons need to be treated for 1 person to get 30 % pain relief or benefit (NNTB = 24). Pooled change in pain intensity was 3 mm on a 100 mm Pain Visual Analogue Scale. In comparison 6 persons need to be treated for 1 person to suffer harm (NNTH = 6).

This is in contrast to previous research related to this subject:

For example, an often quoted US National Academies of Science, Medicine and Engineering (NASEM) 2017 Report into the health effects of cannabinoids (see attached) stated:

a. Conclusion 4.1: *'There is **substantial evidence** that cannabis is an effective treatment for chronic pain in adults'* (page 90).
b. Of 5 reviews considered by the NASEM, Whiting et al 2015 *'was the most comprehensive'* and *'the primary source of information for the effect on cannabinoids on chronic pain' (2015)'* (page 88).

c. Harms cited by NASEM included a 2015 US cannabis use disorder prevalence of 4.2 million persons in 22.2 million users (19 %) (page 333).

Whiting et al (2015) (see attached):

a. *'There was **moderate quality evidence** to support the use of cannabinoids for the treatment of chronic pain'.*
b. Other findings may be summarised as: the majority of the 28 primary studies (65% or greater) had a high risk of bias versus 7% at low risk of bias; most studies did not show statistical significance for pain relief; there was significant study heterogeneity in drug, dose regime, route of administration and condition;

Problem:

In my opinion, a serious problem has arisen as a consequence of the unrestricted drug environment.

I believe AHPRA needs to specifically consider whether or not:

a. AHPRA registered health care practitioners,
b. are utilising or not utilising the available evidence
c. to make public or patient care statements
d. in manner that is inaccurate and or inadequate and or inappropriately selective and or
e. without proper balance and or
f. without appropriate reference to contemporary, evidence informed, safety and efficacy, risk and benefit data,
g. to the detriment of patients and the public.

Conclusions:

The medical practice and pharmacological agent environment is changing and thus the medical practitioner behaviours that Good Medical Practice seeks to manage are also changing.

In order to preserve the integrity of good medical practice as being truly patient centred, I thank you for giving consideration to this feedback and I request AHPRA give consideration to:

a. the inclusion of additional requirements into the Good Medical Practice Code of Conduct related to the safety, efficacy, risk and benefit of limited evidence and or TGA unregistered therapies, and, the standards and requirements related to patient care, communication and informed consent that should be associated with the use of such therapies;
b. Establishing whether or not AHPRA registered medical practitioners making public or patient care statements about therapies with very limited evidence of efficacy - especially those associated with significant harms – are making such statements or withholding information in a manner that represents professional misconduct.

Thank you,

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Statement on "Medicinal Cannabis" with particular reference to its use in the management of patients with chronic non-cancer pain

1. The Faculty of Pain Medicine (FPM) acknowledges the changed regulatory environment for the use of medicinal cannabis in Australia and New Zealand. In Australia this includes the rescheduling of tetrahydrocannabinol (THC) from S9 (Prohibited substances) to S8 (Controlled drugs) and the granting of licences for the cultivation of Cannabis sativa and the manufacture and production of medicinal cannabinoids. In New Zealand this includes proposed changes to the Misuse of Drugs Act 1975 to allow terminally ill people to possess and use illicit cannabis, to enable regulations to be made setting quality standards for products, and to deschedule cannabidiol (CBD) as a controlled drug. THC would remain a class B controlled drug, except when contained in a class C controlled drug, and except when contained in a CBD product.
2. FPM recognises both the political imperatives underpinning these changes and the community demands that have generated them.
3. FPM adheres to the principle that substances intended for therapeutic purposes be fully characterised chemically, pharmacologically and toxicologically, to the extent that they would be eligible for registration by regulatory authorities (Therapeutic Goods Administration in Australia; Medsafe in New Zealand).
4. The sociopsychobiomedical framework that informs the assessment and management of people with chronic non-cancer pain requires active engagement of patients in a multimodal management program, and recognises the adverse effects that may be associated with polypharmacy in general and with cannabinoids in particular.
5. FPM is very concerned about the adverse event profile in cannabis users, especially in young people, including impaired respiratory function, psychotic symptoms and disorders and cognitive impairment.
6. At the present time, the scientific evidence for the efficacy of cannabinoids in the management of people with chronic non-cancer pain is insufficient to justify endorsement of their clinical use.
7. FPM recognises the difficulties inherent in performing trials of any medications in patients with chronic non-cancer pain. Nonetheless FPM believes that if pragmatic trials of cannabinoids are considered to be necessary they should be conducted on a coordinated national basis.

BACKGROUND NOTES

THE LANDSCAPE

- Worldwide, cannabis is the third most commonly used substance after alcohol and tobacco.
- Unauthorised use of cannabis as a medicine in Australia is widespread (Swift et al, 2005).
- 92% of respondents to the 2012 Illicit Drug Reporting System survey in Australia reported that hydroponic cannabis was "easy" or "very easy" to obtain (Stafford & Burns, 2012)
- In the general population, 4.7% of those aged over 40 years had used cannabis in the past year (Australian Institute of Health and Welfare, 2011)

In populations of pain patients:

- Prevalence of use in chronic pain clinics: 12-15% (Ware et al, 2002, 2003)[1]
- Chronic pain is the most common "reason" for patients to report "medical" use of cannabis in the United States (USA) (Dyer 2013) (inverted commas added).

Complexity of chronic pain phenotype

Baseline data from the POINT study[2] being conducted by the National Drug and Alcohol Research Centre at UNSW Sydney have illustrated in more detail the complexity of the phenotype of chronic non-cancer pain (Campbell et al, 2015; Degenhardt et al, 2015).

Findings include:

- Complex clinical profiles were more prevalent among the younger age-groups ('working' and 'nearing retirement' age groups). These groups reported more mental health problems, more experience of childhood abuse/neglect and lifetime suicidality, and more substance use than the retirement age-group.
- These two groups were also prescribed higher doses of opioids, were more likely to be prescribed codeine as well, and were likely to be taking concurrently prescribed benzodiazepines, antidepressants and antipsychotics.
- Just under half met criteria for current moderate/severe depression, with a substantial minority meeting criteria for
  - current moderate/severe anxiety or agoraphobia
  - lifetime suicidal ideation
  - lifetime alcohol use disorder
- Almost half (43±2% 95% CI) of the sample had used cannabis for recreational purposes at some time.
- One in eight (12±2%) of the entire cohort met ICD-10 criteria for lifetime cannabis use disorder
- One in six of the cohort (15±2%) had used cannabis for pain relief.
- A quarter (24±2%) reported that they would use cannabis for pain relief if they had access to it.

THE SUBSTANCES[3]

Cannabis (from Latin, meaning hemp)

- Various preparations derived from the plant Cannabis sativa
- Synonyms: marijuana (USA), dope, draw, ganja, grass, pot, puff, smoke, toke, weed. Street names for varieties of cultivated cannabis are: Northern Lights, Haze, Purple Haze, White Widow, Skunk#1, Sensie Star, Orange Bud, Bubblegum, Hindu Kush, Chronic, and Jack Herer.
- Herbal cannabis: leaves and compressed female flower heads of Cannabis sativa; also known as weed, grass, ganja, herb, green, thai stick, and bud or bush.
- Resin: compressed tetrahydrocannabinol (THC)-rich bracts from Cannabis plants; also known as hashish, hash, black, blonde polm, rocky, dark rocky, slate, and soapy or soap bar.
- Concentrations of chemical constituents can vary by plant strain and by conditions of growing, storage, harvest and preparation.
- Pharmacological effects may be enhanced by synergies between constituents of cannabis not present in isolated or synthetic cannabinoid pharmaceuticals.\
- Standardisation of any plant material, extract or blend for medicinal use is essential, and the chemovar (or chemotype) is the most reliable predictor of medicinal value.

[1] Note: USA data; some from more than a decade ago

[2] A prospective study in Australia of 1500 patients who have been prescribed opioids for CNCP.

[3] From Mather 2005, Mather et al 2013, RCP 2005, APM4e

Cannabinoids

- Substances (regardless of chemical structure or whether they are natural or synthetic) that bind to biological receptors and produce the classical spectrum of pharmacological effects demonstrated by extracts of C. sativa.
- Principal botanical cannabinoids are
  - delta9-tetrahydrocannabinol (THC)
  - cannabidiol (CBD)
  - cannabinol[4] (CBN)

Preparations currently available

A. Medical extracts from *Cannabis* sativata:

- nabiximols (Sativex®)
  - oromucosal spray
  - 2.7mg THC and 2.5mg CBD per 100µl
  - max 16 sprays per day
  - indications:
    - adjunctive treatment for the symptomatic relief of neuropathic pain in patients with multiple sclerosis (Canada)
    - adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain (Canada)
    - spasticity in multiple sclerosis (Australia, UK, EU)
- whole plant extract (Cannador)
  - THC 2.5g and CBD 1.2mg
  - Oral capsule
- standardised plant matter in granular form (produced by Bedrocan BV for the Netherlands Ministry of Health, Welfare and Sport; pharmacy-supplied for vaporisation or tea preparation)
  - THC:CBD 19:1 (Bedrocan),
  - 12:<1 (Bedrobinol),
  - 6:75 (Bediol),
  - 14:< 1 (Bedica)

B. Synthetic cannabinoids:

- dronabinol (Marinol®)
  - synthetic THC
  - oral capsule, 2.5mg, 5mg, 10mg
  - max dose 20mg per day
  - Indications:
    - stimulation of appetite in AIDS-related anorexia and weight loss
    - severe nausea and vomiting associated with cancer chemotherapy
- nabilone (Cesamet®)
  - synthetic THC analogue
  - oral capsule, 0.25mg. 0.5mg, 1mg
  - max dose 6mg per day
  - indications:
    - severe nausea and vomiting associated with cancer chemotherapy

[4] CBD and CBN have not been adequately evaluated in treatment of pain

Pharmacology

Some pharmacokinetic considerations:

Transpulmonary (inhaled)

- rapid absorption
- rapid onset of effect
- bioavailability ~18%
- inaccurate dosing
- levels fall within 2h

Oral (and transmucosal)

- poor absorption
- low bioavailability (<10%)
- difficult to titrate

Mather 2005: "Any successful future clinical development of cannabinoid pharmacotherapy depends upon a dosage form that is reliable, rapidly titratable to effect, non-smoked, non-injected, and preferably parenteral to avoid hepatic first pass metabolism."

TGA GUIDANCE

In December 2017 the Therapeutics Goods Administration (TGA) of the Australian Government Department of Health published **"Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia"**. https://www.tga.gov.au/node/732373

This authoritative document arose out of a systematic review, commissioned by the Department of Health, by a team from the University of New South Wales, University of Sydney and University of Queensland under the coordination of the National Drug and Alcohol Centre (NDARC), which was tasked to assess the available evidence for the use of medicinal cannabis in chronic non-cancer pain (Stockings et al, 2018) and four other settings (palliative care, epilepsy, chemotherapy-induced nausea and vomiting, and multiple sclerosis.

The Recommendations in the TGA guidance document are as follows:

- A comprehensive sociopsychobiomedical assessment of the patient with CNCP is appropriate.
- The use of medications, including medicinal cannabis, is not the core component of therapy for CNCP;
- Patient education is a critical component of therapy for CNCP, particularly with respect to expectations of drug therapy.
- There is a need for larger trials of sufficient quality, size and duration to examine the safety and efficacy of medicinal cannabis use in CNCP. (p. 3)
- In the absence of strong evidence for dosing and specific preparations of cannabis or cannabinoids in the treatment of CNCP, it is recommended that any treating physician who elects to initiate cannabinoid therapy should assess response to treatment, effectiveness and adverse effects after 1 month. This is best achieved as part of a research project or clinical audit. (p.14)

FPM endorses these recommendations.

THE EVIDENCE

1. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, Murnion B, Farrell M, Weier M, Degenhardt L. Cannabis and cannabinoids for the treatment of people with chronic non- cancer pain conditions: A systematic review and meta-analysis of controlled and observational studies. Pain 2018, in press.

This rigorous, comprehensive review identified 104 studies (n = 9958 participants), comprising 47 randomised controlled trials (24 parallel, 23 cross-over) and 57 observational studies. Diagnostic groups included "neuropathic[5] pain" (48 studies), "fibromyalgia" (7), MS[6]-related pain (13), and "mixed or undefined CNCP" (29).

The most commonly studied outcomes were pain intensity (100 studies), adverse events (81) and withdrawals (71). Fewer studies reported on physical functioning (52), emotional functioning (43), and patient's global impression of change (24). Only two studies in which pain was the primary indication reported on all six outcomes.

Pain was the primary indication in 76 studies and a secondary indication in 28 studies. Of the 104 included studies, four (n = 47 participants) examined cannabinoids as a first-line therapy, and 87 examined cannabinoids as a second-line therapy in addition to existing medication regimens. In nearly all RCT studies, patients were required to be on a stable dose of current medication before commencement of the trial. The most commonly studied cannabinoid was nabiximols, followed by *Cannabis sativa*.

The main findings regarding pain included:

- Across all CNCP conditions, cannabinoids were more likely than placebo to produce a 30% reduction in pain (OR 1.46, 95%CI 1.16-1.84) . The NNTB[7] was 24 (95% CI 15 to 61).
- There was no significant evidence that cannabinoids reduced pain by 50% compared to placebo (OR 1.43, 95% CI 0.97-2.11)
- Cannabinoids overall were associated with a larger reduction in pain intensity than placebo (SMD -0.14, 95%CI -0.20 to -0.08). This was calculated to be a reduction of about 3mm (95%CI -5 to -1) on a 0-100mm VAS.

CNCP patients who received a cannabinoid had twice the odds of withdrawing from a trial for any reason than patients who received placebo, and 3.5 times the odds of withdrawing because of adverse events. Similarly CNCP patients who received a cannabinoid had 2.3 times the odds of experiencing an adverse event compared to placebo. The NNTH[8] for any adverse event was 6 (95%CI 5 to 8).

There were no significant impacts upon physical or emotional functioning, and low-quality evidence of improved sleep and patient global impression of change.

The authors concluded: "It appears unlikely that cannabinoids are highly effective medicines for CNCP."

Preceding literature

In the literature that preceded the publication of the TGA Guidance document, there are several reviews on which opinion and advocacy have been based. These are summarised here for completeness.

2017

2. National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press.

This document concluded, "There is substantial evidence that cannabis is an effective treatment for chronic pain in adults." [CONCLUSION 4-1 (page 4-2)] This was based largely on Whiting et al (2015), as the authors commented:

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[5] No distinction made between the pre- and post-2011 definitions of "neuropathic pain"

[6] MS: multiple sclerosis

[7] NNTB: number needed to treat to benefit

[8] NNTH: number needed to treat to harm

> "The rigorous screening approach used by Whiting et al. (2015) led to the identification of 28 randomized trials in patients with chronic pain (2,454 participants). Twenty-two of these trials evaluated plant-derived cannabinoids (nabiximols, 13 trials; plant flower that was smoked or vaporized, 5 trials; THC oramucosal spray, 3 trials; and oral THC, 1 trial) while five trials evaluated synthetic THC (i.e., nabilone). All but one of the selected primary trials used a placebo control, while the remaining trial used an active comparator (amitriptyline). The medical condition underlying the chronic pain was most often related to a neuropathy (17 trials); other conditions included cancer pain, multiple sclerosis, rheumatoid arthritis, musculoskeletal issues, and chemotherapy-induced pain. Analyses across seven trials that evaluated nabiximols and one that evaluated the effects of inhaled cannabis suggested that plant-derived cannabinoids increase the odds for improvement of pain by approximately 40 percent versus the control condition (odds ratio [OR] 1.41, 95% confidence interval [CI] = 0.99–2.00; 8 trials). The effects did not differ significantly across pain conditions, although it was not clear that there was adequate statistical power to test for such differences." (P. 4-3)

3. **Nugent SM, Morasco BJ, O'Neil ME, Michele Freeman, M, Low, A, Kondo K, Elven C, Zakher B, Motu'apuaka M, Paynter R, Kansagara D. The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. Ann Intern Med 2017;10.7326/M17-0155.**

This review identified 30 RCTs and 3 cohort studies. Of the 13 trials on"neuropathicpain", only 4 post-dated the 2011 change in definition, of which 3 used vaporised or smoked THC. In these 4 trials, NNTBs varied from 8.7 (for nabiximols in peripheral neuropathy) to 2.3 (for 6.7%THC in spinal cord injury). Ten trials were only or predominantly in patients with MS: there was "insufficient evidence to characterize the effects of cannabis on pain in patients with MS because of the small number of methodologically rigorous studies, inconsistent findings across studies, lack of long-term outcomes, and small number of patients included in the trials".

The authors concluded: "Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain. Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects".

2016

4. **Barnes MP, Barnes JC. Cannabis: The Evidence for Medical Use. Northumberland, Tyne & Wear NHS Foundation Trust, May 2016**

This is a non-critical narrative review of the literature, grouped by agent: nabilone, dronabinol, nabiximols and smoked cannabis. The authors "...amalgamated the studies of chronic pain and neuropathic pain as there appears to be no difference in efficacy between these two modalities" (p. 22).

The authors concluded (p. 33):

> "This is a difficult literature to summarise as a number of different formulations have been used and a number of different types of pain have been studied. The authors are also aware of the considerable literature in terms of anecdotal reports, case studies, questionnaires and uncontrolled trials that have also showed efficacy in various types of pain with various formulations.
>
> However, nabilone, dronabinol, nabiximols and smoked marijuana have all been shown to be efficacious to varying extents in a variety of pain settings in good quality studies. We conclude that there is **good** evidence for efficacy of cannabis for pain relief in various formulations and in a number of settings." (Emphasis in original)

2015

5. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use A Systematic Review and Meta-analysis. JAMA 2015; 313:2456-2473.

Until recently this review was the main source of reference. The authors identified 28 studies in chronic pain, involving 2,454 patients in heterogenous groups, ranging from "neuropathic" pain[9] (12 studies), cancer pain (3 studies), diabetic peripheral neuropathy (3 studies), fibromyalgia (2 studies) and HIV-associated peripheral neuropathy (2 studies). Seventeen studies were considered to be a high risk of bias; 2 were at low risk and 9 were of uncertain risk. Thirteen studies were of nabiximols, 4 studies were of smoked THC, 3 for THC oromucosal spray, 5 of nabilone, 2 of dronabinol; all but one were placebo-controlled.

Overall, "The average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials". In 6 trials of nabiximols, the weighted mean difference in pain on a 0-10 NRS was −0.46 [95% CI, −0.80 to −0.11] (in favour of the cannabinoid).

The authors concluded: "There was moderate quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity... Cannabinoids were associated with an increased risk of short-term AEs".[10]

6. Boychuk DG, Goddard G, Mauro G, et al. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J Oral Facial Pain Headache. 2015; 29:7-14.

This review identified 24 studies of "chronic neuropathic pain" but 11 were excluded for various quality reasons. Five of the 13 included studies (published between 2003 and 2013) were of nabiximols, 5 of smoked or vaporised cannabis, 1 of dronabinol, 1 of nabilone, with a total of 771 subjects.

The authors found:

> "The quasi-totality of the high-quality studies included in the present systematic review suggests that cannabinoids provide significant pain reduction in both the short term and longer term, without significant side effects..." and noted that "Nine out of 13 studies clearly stated a NNT ranging from 2 to 4, with no differences among type of cannabinoids". Furthermore, "... the present systematic review found very few risks related to the use of cannabinoid compounds in the treatment of chronic neuropathic pain. The vast majority of adverse events listed were considered minor in nature".

7. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. Can Fam Physician 2015; 61:e372-81.

This review examined 6 RCTs (n=226 patients) of nonsynthetic smoked or vaporised cannabinoids, mainly in "neuropathic" pain, as adjuncts to other drugs including opioids and anticonvulsants. All studies were of short duration (<5 days) and were limited by problems with masking, variability in dosing and strength of THC and lack of functional outcomes. Only 3 of the 6 studies reported a "clinically meaningful pain reduction", defined as a decrease of 2 points on a 0-to10 numerical pain rating or a 30% improvement in pain intensity. Neurocognitive adverse effects were common but "well tolerated".

The authors concluded: "Generalizing the use of medical marijuana to all CNCP conditions does not appear to be supported by existing evidence".

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[9] See footnote 5

[10] From this study, Stockings et al (2018) calculated NNTB for 30% pain reduction of 22 and for 50% pain reduction 26. These indices do not support the conclusion of Whiting and colleagues.

Prior to 2015

8. a) Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol 2011; 72:735-44.

This paper reviewed 18 trials published between 2003 and 2010, involving 766 patients. Of these trails, 4 were of smoked cannabis in "neuropathic" pain[11], 7 of oromucosal preparations in mixed pain populations, 4 of nabilone in mixed pain populations, and 2 of dronabinol in mixed pain populations, all placebo-controlled. In 15 trials, a "significant analgesic effect" of the cannabinoid was noted.

8. b) Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials.

J Neuroimmune Pharmacol 2015DOI 10.1007/s11481-015-9600-6.

These same authors identified another 11 trials published between 2010 and 2014, with 1185 patients. Two trials were of smoked cannabis in "neuropathic" pain, 4 of nabiximols in "neuropathic" pain and 4 of nabilone in mixed pain populations; control groups were variable. In 7 trials there were " significant analgesic effects" of cannabinoids.

The authors concluded overall (7a and 7b): "...there are a total of 22 of 29 RCTs demonstrating that cannabinoids demonstrate a modest analgesic effect and are safe in the management of chronic pain."

9. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JLR. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med 2009; 8:1353-68.

This review identified 18 double-blind randomised controlled trials of sufficient quality that compared any cannabis preparation to placebo among subjects with chronic pain. There was marked variability in study design, methodology and analysis, the last especially with respect to reporting of outcomes. The efficacy analysis (VAS) found a standardised mean difference of -0.61 [95%CI: -0.84 to -0.37] (in favour of cannabinoid). A high risk of harms was found: for alteration of perception OR was 4.5 [95%CI: 3.0 to 6.7] and NNH 7 [6-9]; for altered cognitive function, OR was 4.5 [95%CI: 2.4 to 8.4] and NNH 8 [6-12].

[11] Pre-2011 definition

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Cannabis and Cannabinoids for the Treatment of People with Chronic Non-Cancer Pain Conditions: A Systematic Review and Meta-Analysis of Controlled and Observational Studies

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Abstract

This review examines evidence cannabinoids in chronic non-cancer pain (CNCP), and addresses gaps in the literature by: considering differences in outcomes based on cannabinoid type and specific CNCP condition; including all study designs; and following IMMPACT guidelines. MEDLINE, Embase, PsycINFO, CENTRAL and clinicaltrials.gov were searched in July 2017. Analyses were conducted using Revman 5.3 and Stata 15.0. A total of 91 publications containing 104 studies were eligible (n = 9958 participants), including 47 RCTs and 57 observational studies. Forty-eight studies examined neuropathic pain, seven studies examined fibromyalgia, one rheumatoid arthritis, and 48 other CNCP (13 MS-related pain, 6 visceral pain, and 29 samples with mixed or undefined CNCP). Across RCTs, PERs for 30% reduction in pain were 29.0% (cannabinoids) vs 25.9% (placebo), significant effect for cannabinoids, number needed to treat to benefit (NNTB): 24 (95%CI 15-61); for 50% reduction in pain, PERs were 18.2% vs. 14.4%; no significant difference. Pooled change in pain intensity (standardised mean difference: -0.14, 95%CI -0.20, -0.08) was equivalent to 3mm on a 100mm visual analogue scale greater than placebo. In RCTs, PERs for all-cause AEs were 81.2% vs. 66.2%; number needed to treat to harm (NNTH): 6 (95%CI 5-8). There were no significant impacts upon physical or emotional functioning, and low-quality evidence of improved sleep and patient global impression of change. Evidence for effectiveness of cannabinoids in CNCP is limited. Effects suggest NNTB are high, and NNTH low, with limited impact on other domains. It appears unlikely that cannabinoids are highly effective medicines for CNCP.

Keywords: Cannabis, chronic non-cancer pain, neuropathy, systematic review, meta-analysis, number needed to treat

Introduction

There has been increasing attention to the use of cannabis and cannabinoids in the treatment of chronic non-cancer pain (CNCP). Changes in legislation and use globally mean that it is likely that there will be an increase in the coming years in availability and use of cannabis and cannabinoid products for CNCP. In the United States, these products are most commonly cited for use in CNCP [29]. CNCP conditions are prevalent, and rank among the most significant causes of disability globally [14].

Recent reviews of cannabis and cannabinoids for medicinal purposes have increased our knowledge in the understanding of their effectiveness on pain [30; 50; 51], though they are limited in the case of CNCP management and conclusions have been conflicting, with some reviews reporting moderate to large effects [29; 51], while others have reported minimal [35] or no benefit [3]. Existing reviews have been limited in their searching for CNCP studies (e.g. with a focus on specific types of cannabinoids [2], or study designs [35]) and no single review has considered: all types of evidence; different CNCP conditions individually; potential differential effects of different cannabinoids; and the safety of cannabis for CNCP patients. Each of these limitations reduces our understanding of the evidence for the use of cannabinoids for CNCP.

CNCP conditions are varied, and many people with CNCP live with complex physical and mental health comorbidities [4; 40]. Pain is considered by leading clinicians and researchers to be only one of a range of core outcomes that must be considered evaluating interventions for CNCP [48]. The current review addresses the limitations of previous reviews and is the first to examine the evidence for the effectiveness of cannabinoids for CNCP for all study designs, all CNCP types, all types of cannabis and cannabinoids, and using the outcomes specified in the Initiative on Methods, Measurement, and Pain Assessment in

Clinical Trials (IMMPACT) [48].

Methods

Search strategy and study eligibility

To ensure full coverage of the literature, we conducted a multi-phase search, comprising an initial review of reviews for cannabis and cannabinoids to treat CNCP, followed by four condition-specific systematic reviews.

A systematic review of reviews in October 2016 in the electronic databases MEDLINE, Embase, PsycINFO and the Cochrane Database of Systematic Reviews to identify all reviews (and empirical studies contained within) that evaluated the evidence base for the administration of cannabis and cannabinoids to treat CNCP (PROSPERO registration CRD42016049475).

This search was supplemented by four systematic searches of empirical studies in July 2017 in the electronic databases MEDLINE, Embase, PsycINFO, the Cochrane Database of Systematic Reviews and clinicaltrials.gov to identify any trial that evaluated cannabis or cannabinoids in treating the specific pain conditions: neuropathic pain (PROSPERO registration: CRD42017065248), fibromyalgia (PROSPERO registration: CRD42017067057), arthritis (PROSPERO registration: CRD42017067059) and other or mixed groups of CNCP (Supplementary Material, page 6). Date of publication was restricted to between 1980 and July 2017. No restrictions were placed on language or publication type. Medline search strategies are shown in **Appendix A** of the supplementary appendix (available online at http://links.lww.com/PAIN/A592). Corresponding subject headings were used in each database where specialised thesauri existed.

Individual studies that were identified (N= 107) in the systematic review of reviews of cannabinoids for the treatment of pain were screened for eligibility in full by two independent reviewers. For reviews of empirical studies for neuropathic pain, fibromyalgia, arthritis, and CNCP, two reviewers independently examined titles and abstracts using the web-based systematic review program Covidence [49]. All articles identified as potentially relevant (including review articles) were obtained in full and screened by two independent reviewers. Study screening was conducted in duplicate by two independent reviewers (any of GC, ES, MW, DZ, SN and RR). Inter-rater disagreement was resolved via consultation with an independent third reviewer (any of LD, GC, ES, MW, DZ and RR).

Types of pain conditions

We included studies that examined impacts of cannabis and cannabinoids on any CNCP condition. We followed Cochrane protocols determining studies for inclusion and extracting data; at least 80% of the patient population was required to be experiencing one of the included pain conditions (neuropathic pain, CNCP, arthritis or fibromyalgia). If less than 80% of the sample had one of the target pain conditions but results were presented separately for the sub-sample experiencing one of these pain conditions, we included the study and extracted data for the target subgroup. Studies were required to examine cannabis and cannabinoids as a primary or secondary indication for pain, and to measure at least one of our three primary pain outcomes: pain intensity, 30% or 50% reduction in pain.

Types of interventions

We considered studies examining: tetrahydrocannabinol; cannabidiol; combination tetrahydrocannabinol + cannabidiol; plant-based cannabis (e.g. cannabis sativa); and other cannabinoids e.g. tetrahydrocannabinolic acid (thca), cannabidiolic acid, cannabidivarin, and the synthetic delta-9-tetrahydrocannabinol formulations nabilone and dronabinol.

Types of studies

We included randomised controlled trials (RCTs), non-randomised controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies, analytical cross-sectional studies, observational studies, self-report, and N-of-1 studies. For studies with a comparison group, we considered any type of comparator, including placebo, waitlist controls and other interventions.

Outcomes

Guided by the IMMPACT core outcome domains for clinical trials in CNCP [48], we grouped the outcomes of interest into six categories: pain intensity, physical functioning, emotional functioning, global impression of change, adverse events and withdrawals. We assessed the clinical significance of the changes by extracting data for a 30% reduction in pain (a 'moderate' effect) and a 50% reduction in pain (a 'substantial' effect) [11].

Assessment of risk of study bias

We used the Cochrane Collaboration risk of bias tool for RCTs [19]. RCTs were judged to have an overall 'low risk' of bias if they had 6-8 risk domains rated as having a low risk of bias, 'unclear risk' if 4 or more domains were judged as being unclear, and 'high risk' if 3 or more domains were judged as being high risk. We additionally examined risk of bias due to sample size, where studies comprising at least 100 participants per treatment arm were classified as 'low risk', studies comprising 30-100 per arm were classified as 'unclear risk' and studies comprising <30 participants per arm were classified as 'high risk'. Observational studies or case study reports were evaluated using an adapted version of the Cochrane Collaboration risk of bias in non-randomised studies of interventions (ROBINS-I) assessment tool [44]. Overall risk of bias was determined by the most serious risk of bias allocated to that study across the tool.

Grading of evidence

As the review included RCTs and observational trials we used an adapted version of the standard Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool to grade the overall study methodology [36]. RCTs began with a high rating that was downgraded if important limitations were identified in the study methodology. Observational trials began with a low rating and were upgraded if important strengths were identified. We additionally conducted a GRADE assessment using GRADEPro (https://gradepro.org/) for each reported pooled estimate that evaluated the risk of bias, inconsistency, indirectness, imprecision and publication bias (via visual inspection of funnel plots).

Data extraction

We extracted details on the participants, interventions, comparisons, outcomes and study design (PICOS) of each study, including: sample N, age, gender, medical and pain condition/s, length and type of treatment (including route of administration, place in therapeutic hierarchy, dose, and co-interventions), comparator type, study country, year and design. Outcomes were extracted following IMMPACT recommendations. When data were not reported in full, we contacted authors for additional information. When studies reported multiple measures of a single domain (e.g. pain intensity), we applied a hierarchy of evidence. Where authors reported multiple analyses (e.g. intention to treat [ITT], available case or per protocol), we extracted the more conservative with a preference for ITT analyses. We reported adverse events according to high-level Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/) categories and report the 18 most common single adverse events.

Data extraction, risk of bias, and GRADE assessments were conducted in duplicate by two independent reviewers (any of GC, ES, MW, DZ, SN and RR). Inter-rater disagreement was resolved via consultation with an independent third reviewer (any of LD, GC, ES, MW, DZ and RR).

Data analysis

We extracted data from all reported time points in each trial. Our primary analysis included data from the primary endpoint (or longest follow-up) in each trial. If multiple assessments were made on participants on the same day, we analysed the data taken from the longest follow-up.

Data were analysed separately for RCTs and observational study designs. All analyses were conducted using Review Manager (RevMan) version 5.3 [46] and Stata 15.0 [43]. Continuous outcomes were pooled using fixed-effects generic inverse variance meta-analysis and expressed as standardised mean differences (SMDs) with 95% confidence intervals (CIs). To aid clinical interpretation of the continuous outcome of change in pain intensity, we additionally re-expressed the SMD for overall change in pain intensity as a mean difference on a 100mm visual analogue scale (VAS) by multiplying the pooled SMD by a typical baseline among-person standard deviation on a 100mm VAS, obtained from the included studies [19; 21]. Dichotomous outcomes were summarised as odds ratios (ORs) using the Mantel-Haenszel fixed effect model [9]. For observational studies, we pooled event rates using the Stata **metaprop** command [32]. Heterogeneity was assessed using the I^2 statistic, and described as low (≤25%), moderate (>25% and ≤50%) or high (≥75%) [18]. Where data permitted, we assessed publication bias in the pooled estimates using the Stata15.0 **metabias** command to detect small study effects [16]. If the test of small study effects was significant, we used the Stata15.0 metatrim command to conduct Duval and Tweedie's non-

parametric trim and fill procedure and provide an adjusted treatment effect [10]. We conducted sensitivity analyses using the inverse variance random effects model where I^2 values exceeded 50%. For the primary pain intensity outcomes (30% reduction in pain, 50% reduction in pain and change in pain intensity) we conducted subgroup analyses to assess for differences in RCT pooled estimates based on overall study risk of bias (low, unclear or high), study risk of bias due to sample size (low [100+ participants per treatment arm], unclear [30-100 per arm], high [<30 per arm]), intervention length (one-day studies, very short term [<4 weeks], short term [4-12 weeks], intermediate term [13-26 weeks] or long term [>26 weeks]), and imputation method (none/ITT, completer-only, or last observation carried forward [LOCF]). We followed Cochrane Collaboration methods to overcome unit-of-analysis errors for multi-arm studies [18]. Where raw data were not reported, we used the Generic Inverse Variance fixed effect model to pool effect estimates and their standard errors [18].

For dichotomous outcomes with at least a moderate GRADE rating, we calculated numbers needed to treat to benefit (NNTB) and numbers needed to treat to harm (NNTH) and their 95% CIs. We used pooled estimates of relative effect measures (ORs) to take into account the event rate in control groups [6]. NNTB was calculated for the outcomes 30% reduction in pain, 50% reduction in pain, and change in patient global impression of change. NNTH was calculated for all-cause adverse events and study withdrawals due to adverse events. **Panel G1 in Appendix G** summarises the core statistics and metrics used in this paper (available online at http://links.lww.com/PAIN/A592).

Results

The combined searches resulted in 2525 results. In total, 91 publications were eligible and included in the review, which reported on 104 distinct studies (**Figure 1, Figure B1 Appendix B**). **Tables 1** (RCTs) and **B1** in **Appendix B** (observational studies) contain the list of included studies. The search additionally identified 17 ongoing studies for which results are yet to be reported (Appendix **Table B2**). Excluded studies are listed in Appendix **Table B3** (appendices available online at http://links.lww.com/PAIN/A592).

Figure 1 about here

Study characteristics

Characteristics of included studies, including sample characteristics, pain classification, cannabinoid classification, treatment length, dose, study outcomes, risk of bias rating and imputation method are provided in **Table 1** (RCTs) and Appendix **Table B1** (observational studies, available online at http://links.lww.com/PAIN/A592). The 104 studies comprised 47 RCTs (24 parallel RCTs, 23 cross-over RCTs), and 57 observational studies, comprising a total of 9958 participants (n= 4271 RCTs; 5687 observational studies). We contacted nine authors for additional information; six responded and two provided data which were used in analyses. Most studies were conducted in Western Europe (n=47) or the United States (n=34, see **Table 2**).

Where possible, we have examined CNCP categories separately. Overall, we found 48 studies of neuropathic pain (of which 16 were MS-related and 32 were non-MS-related), seven studies for fibromyalgia, one for arthritis (specifically rheumatoid arthritis), and 48 studies for other = CNCP (of which 13 were MS-related pain, 6 were visceral pain, and 29 were studies of samples with mixed or undefined non-MS-related CNCP, and, **Table 3**).

Characteristics of participants

Detailed characteristics of participants in the studies are provided in **Table 1** (RCTs) and Appendix **Table B1** (observational studies). Details of ongoing studies with no data available at time of current review are detailed in Appendix **Table B2**. Details of studies excluded at the full text review stage are presented in Appendix **Table B3** (available online at http://links.lww.com/PAIN/A592). The number of participants ranged from 1 to 649, with a median of 42 (mean 136.8). All studies were conducted in adult samples, except for two case series of two adolescents (aged 14 and 15) [38] and an open label trial in young girls with adverse drug effects following vaccination [34]. Where reported, mean age of adult participants ranged from 28 [25] to 67 [5] years (median 49.2, mean 50.5), and percentage of males ranged from 0-100% (median 46.7%; mean 45.1%). Mean baseline pain intensity scores were 59.6 (SD = 14.6; range: 30.1 to 87.5) on a 100mm VAS, suggesting patients had moderate to severe pain intensity at study intake [17].

Pain was the primary indication in 76 studies and a secondary indication in 28 studies. Of the 104 included studies, four [7; 37; 39; 45] (n = 47 participants) examined cannabinoids as a first-line therapy, and 87 examined cannabinoids as a second-line therapy in addition to existing medication regimens. In 13 studies, the place of cannabinoids in the therapeutic hierarchy was not reported or unclear. The most common other adjunct medications were opioids, NSAIDS and anti-spasticity medications. In nearly all RCT studies, patients were required to be on a stable dose of current medication before commencement of the trial.

The most commonly studied cannabinoid was nabiximols, followed by cannabis sativa. See **Table B4** for more information on the cannabinoids used in the included trials, including route of administration, duration and dose.

Risk of bias ratings

Most parallel and cross-over RCTs were rated as unclear risk of bias across all domains because information was not fully reported or could not be obtained from the authors (see **Appendix C** for ratings of risk of bias, available online at http://links.lww.com/PAIN/A592). Several were rated as at high risk of bias because of selective reporting or other biases, such as omission of data and confidence intervals, changes in selection of the primary endpoint or a failure to take account of within-subjects effects in cross-over studies (see **Appendix C Figures C1, C2**, available online at http://links.lww.com/PAIN/A592). Observational studies were judged to be at serious or critical risk of bias for key domains because of confounding, intervention measurement, high dropout, and selection of the reported result (see **Figure C3**).

Outcomes

Tables D1 and **D2** in **Appendix D** (available online at http://links.lww.com/PAIN/A592) describe IMMPACT outcomes collected in RCTs and observational studies respectively. The most commonly studied outcomes were pain intensity (n=100), adverse events (n=81) and withdrawals (n=71). Fewer studies reported on physical functioning (n=52), emotional functioning (n = 43), and patient's global impression of change (n = 24). Only two studies in which pain was the primary indication reported on all six outcomes [23; 47].

Pain

30% reduction in pain

RCT evidence

Of the 47 included RCTs, 13 assessed 30% reduction in pain (See **Table D1** in Appendix D; available online at http://links.lww.com/PAIN/A592), of which 8 RCTs (based on 9 data points) reported sufficient data and were used in the meta-analysis. Across all cannabinoids

and CNCP conditions, cannabinoids were more likely than placebo to produce a 30% reduction in pain ([1; 20; 22; 23; 31; 41; 42; 52], n = 1734, OR 1.46, 95%CI 1.16-1.84, see **Table 4** and **Table E1** and **Figure E1** in **Appendix E**; available online at http://links.lww.com/PAIN/A592). A summary of key outcomes, including NNTB is shown in Table 6. No evidence of small study effects was detected (p = 0.08). We found significant effects for plant-based cannabis, THC:CBD extract and ajulemic acid but these were each based on a single study and our GRADE ratings for these estimates was moderate to very low. Among the specific pain conditions, we found effects for neuropathic pain, and MS-related CNCP (see **Table 4 and Figure E1**). Of the remaining 5 studies that assessed 30% reduction in pain but for which data were not reported or obtained from study authors, three reported a significant positive effect and two reported no benefit. When examined by overall study risk of bias rating and risk of bias due to sample size, the effect estimate remained significant for studies classified as having low risk and for studies with more than 100 participants per treatment arm, but was not significant for studies at unclear risk of bias, or for studies with less than 100 participants per arm, with notably larger but non-significant effects for the smallest studies (<30 participants per arm; see Figures E1.1 and E1.1a),. No significant differences in effect sizes were identified between studies with interventions of very short term (<4 weeks), short-term (4-12 weeks) and intermediate term (13-26 weeks, see Figure E1.2). All studies assessed outcomes using ITT analyses without imputation.

Observational evidence

In observational studies with a comparison group, one small open-label study with a randomised-withdrawal phase (n = 26[47])and found that nabilone was significantly more likely to produce a 30% reduction in pain relative to placebo (See **Table 4**). In observational

studies with no comparison group, the pooled prevalence of receiving cannabinoids reported achieving a 30% reduction in pain was 72% (95%CI 66-78%) (see **Figure E5 and Appendix F** available online at http://links.lww.com/PAIN/A592)**.**

50% reduction in pain

RCT evidence

Five of the 47 included RCTs assessed 50% reduction in pain, all of which provided sufficient data for meta-analysis. We found no significant evidence that cannabinoids reduced pain by 50% compared to placebo (OR 1.43, 95% CI 0.97-2.11, see **Table 4** and **Table E1** and **Figure E2** in **Appendix E** available online at http://links.lww.com/PAIN/A592). We found no effect for any of the specific cannabinoids, however among pain conditions, a significant effect was found for non-MS-related neuropathic pain (see **Table 4**). No evidence of small study effects was detected (p = 0.12). No subgroup analysis was able to be conducted for overall study risk of bias as all studies were classified as low risk. When examined by risk of bias due to sample size, effects were larger and had substantial uncertainty for studies of <100 participants per treatment arm compared to studies with 100+ participants, but all estimates fell within overlapping bounds of uncertainty and were non-significant (see **Figure E2.1.a**). No differences were detected between studies with interventions of very short term (<4 weeks), short-term (4-12 weeks) and intermediate term (13-26 weeks, see Figures E2.1 and E2.2). All studies assessed outcomes using ITT analyses without imputation.

Observational evidence

Two observational studies with a comparison group found evidence of a significant effect for 50% reduction in pain, however the GRADE rating for this outcome was very low(see **Table 4** and **Table E1** in **Appendix E** available online at http://links.lww.com/PAIN/A592).

Outcomes for observational studies with no comparison group were equivocal and are summarised narratively in **Appendix F.**

Change in pain intensity

RCT evidence

Of the 47 RCTs included in the review, 45 reported data on pain intensity of which 30 (comprising 34 data points) reported sufficient data and were used in the meta-analysis for change in pain intensity. We found that cannabinoids overall produced a larger reduction in pain intensity than placebo (SMD -0.14, 95%CI -0.20 to -0.08, see **Table 4** and **Table E1** and **Figure E3** in **Appendix E** available online at http://links.lww.com/PAIN/A592). We calculated this to be roughly equivalent to a reduction of 2.9mm on a 100mm VAS (95%CI: -4.61 to -1.46) greater than placebo groups. Among the cannabinoids, there were significant effects for nabiximols and THC extract, both with a moderate GRADE rating (Table E1). We found an effect for neuropathic pain (MS and non-MS-related), and rheumatoid arthritis, but the latter was based on one small study and had a very low grade rating (see **Table 4**). No evidence of small study effects was detected (p = 0.49). Of the remaining 15 studies that assessed pain intensity but for which data were not reported or obtained from study authors, 12 reported a significant positive effect and three reported no benefit. When examined by overall risk of bias rating, the effect estimate remained significant for studies classified as low risk but was not significant for studies at unclear or high risk of bias (**Figure E3.1**), and effect sizes were larger for studies with smaller sample sizes (Figure E3.1a) . When examined by study intervention length effects appeared to dissipate with increasing study length: one-day and very short term (< 4 weeks) studies remained significant, however studies conducted in the short (4-12 weeks), intermediate (13-26 weeks) or long-term (>26 weeks) did not, with decreasing effect sizes as study length increased (see **Figure**

E3.2). The effect remained significant for studies using ITT analyses, however was smaller and not significant for studies using LOCF imputation methods, or where the handling of missing data was not reported (**Figure E3.3**).

Observational evidence

In the observational studies with a comparison group, we found no significant evidence of effect for cannabinoids in reducing pain intensity (see Table 4). A significant reduction in pain intensity was identified in within-person pre-post assessments of pain in observational studies with no comparison group (see **Appendix F** available online at http://links.lww.com/PAIN/A592)**.** Five RCTs examined reductions in analgesic use. People taking nabiximols had a greater reduction in the frequency and quantity of use of rescue analgesics compared to placebo (SMD -0.13, 95% CI -0.26 to -0.01, I^2 =48%); this had a moderate GRADE rating.

Physical functioning

No significant effect of cannabinoids on overall physical functioning in 18 RCTs, see **Table E2** and **Figure E6**) or quality of life (n=11 RCTs) compared with placebo (see **Table E2** and **Figure E8)**. There was a significant effect of cannabinoids in reducing sleep problems when compared to placebo (SMD -0.29, 95%CI -0.40 to -0.19), but the GRADE assessment for this was low (see **Table E2** and **Figure E7**). We found a reduction in sleep problems when compared to placebo for nabiximols with a moderate GRADE rating (SMD -0.32, 95%CI -0.44 to -0.20, see **Table E3** in Appendix E available online at http://links.lww.com/PAIN/A592). No small study effects were detected for any of these outcomes (p's range from 0.14 to 0.84).

Emotional functioning

Patients receiving any cannabinoids did not report any difference compared to comparator groups in overall emotional functioning, or in depressive or anxiety symptoms specifically (see **Table E2** and **Figures E9-E11**). No evidence of small study effects was identified for overall emotional functioning (p = 0.10_ or anxiety symptoms (p = 0.06), however a significant effect was detected for depression (p = 0.01). The trim and fill procedure to account for small study effects revealed that the adjusted estimate did not differ significantly from the original estimate (SMD 0.04, 95%CI -0.14 to 0.22, see **Table E2**). A significant improvement in emotional functioning was identified for dronabinol compared to placebo based on a single study; we had low confidence in this effect (see **Table E3** in Appendix E available online at http://links.lww.com/PAIN/A592).

Patient global impression of change

In the four RCTs which reported patient global impression of change as a continuous outcome on the seven-item PGIC scale, there were significant increases among patients receiving any cannabinoid compared to placebo (see **Table E2** and **Figure E12**), with no evidence of small study effects (p = 0.28). Nine RCTs reported PGIC scores as a dichotomous outcome (much or very much improved vs slightly improved, no change or worse), with significant improvement among patients receiving any cannabinoid compared to placebo (see Table 4 and Figure E13), and no evidence of small study effects (p = 0.3). Confidence in these outcomes was low to very low. Most of the evidence was for nabiximols, with some evidence for nabilone, cannabis sativa and THC extract.

Study withdrawals

CNCP patients who received a cannabinoid had two times the odds of withdrawing from a trial for any reason than patients who received placebo (see **Table E4** in Appendix E available online at http://links.lww.com/PAIN/A592). They had 3.47 times the odds of withdrawing because of adverse events (see **Table 5**), no evidence of small study effects (p = 0.44). CNCP patients who received placebo were slightly more likely to withdraw from trials because of a lack of efficacy than those receiving cannabinoids. There was some variation between cannabinoids in reasons for withdrawal (see **Table E4** in **Appendix E** available online at http://links.lww.com/PAIN/A592).

Adverse events

CNCP patients receiving cannabinoids had 2.33 times the odds of experiencing an adverse event compared to placebo. (see **Table 5 and Table E4 in Appendix E** available online at http://links.lww.com/PAIN/A592). Significant evidence of small study effects was detected (p = 0.01), however the adjusted estimate did not differ significantly from the original (OR = 2.22, 95%CI 1.60 to 3.01). Serious adverse events were reported in a smaller number of studies (see **Table 5**), and patients receiving cannabinoids had higher rates of serious adverse events, but this did not reach statistical significance. No small study effects were detected (p = 0.52). Compared with placebo, patients receiving cannabinoids were more likely to report individual adverse events such as: dizziness (OR 5.52, 95%CI 4.47 to 6.83), cognitive attention or disturbance (OR 5.67, 95%CI 2.72 to 11.79) and confusion and disorientation (OR 5.35, 95%CI 2.31 to 12.39, **Table 5**).

Summary statistics

Table 6 summarises the pooled ORs, pooled event rates for cannabinoids vs. placebo groups, and NNTB or NNTH for dichotomous outcomes with a moderate or higher GRADE rating in RCTs. Note since we only had continuous measures of sleep outcomes, cannabinoids' impacts on improving sleep cannot be included in these summary statistics.

For cannabinoids' impact on pain outcomes, pooled event rates for 30% reduction in pain intensity were 29.0% vs 25.9%, respectively. The NNTB was 24 (95%CI 15 to 61, see **Table 6**). For a 50% reduction in pain, the pooled event rate for cannabinoids was 18.2%, compared with 14.4% for placebo (see **Table 6**).The NNTB for 50% reduction in pain was unable to be calculated as the estimate crossed the line of no effect.

For studies where outcomes were presented dichotomously, participants receiving cannabinoids had slightly increased odds of reporting global improvements (PGIC) than patients who received placebo (see **Table 6**). In participants receiving cannabinoids, the pooled percentage reporting "much" or "very much" global improvement was 18.9% compared to 11.8%; the NNT was 38 (95%CI 27 to 62).

Pooled statistics for AEs and study withdrawals are also presented in **Table 6**. The estimated pooled rate of all-cause AEs was 81.2% among people receiving cannabinoids, compared with 66.2% of those receiving placebo; the NNTH was 6 (95%CI 5 to 8). The pooled event rate for study withdrawals due to AEs was 15.8% in those receiving cannabinoids compared to 4.6% of those receiving placebo, and the NNTH was 40 (35 to 49).

Discussion

To our knowledge, this is the first systematic review of the evidence for the effectiveness and safety of cannabinoids for CNCP that included all cannabinoids, all study designs, and considered all outcomes recommended by the IMMPACT group. We also assessed the clinical relevance of these findings using event rates, NNTB and NNTH.

We found moderate evidence for a reduction in pain for cannabinoids when compared to placebo. Pooled analyses suggested that 30% reduction in pain was reported by 29.0% in cannabinoids, compared with 25.9% in placebo groups. A 50% reduction in pain was reported by 18.2% in cannabinoid groups and 14.4% in placebo groups, however this did not reach statistical significance. The NNTB to achieve a 30% reduction in pain for one person using cannabis or cannabinoids (compared to placebo) was estimated at 24 (95% CI 15 to 61), and the NNTH for one person to experience any adverse event was 6 (95% CI 5 to 8). Although caution needs to be used in comparing NNTs across studies involving different groups and timeframes [26], these NNTB are much higher than those for other analgesics: previous studies in neuropathic pain suggested NNTs for strong opioids of 4.3 (95%CI 3.4–5.8), pregabalin (7.7, 95%CI 6.5–9.4) and tricyclic antidepressants (3.6, 95% 3.0–4.4) [13]. The NNTH in our review was similar to that for opioids for CNCP, with a recent Cochrane review indicating that the NNTH for one person using opioids to experience any adverse event (compared to placebo) was 5 (95% CI 4 to 9) [12]. When re-expressed as a mean change on the commonly used 100mm VAS, the pooled SMD for the continuous outcome of change in pain intensity was equivalent to a 3mm greater reduction on this scale compared to placebo, which is well below the 30mm reduction regarded to represent a clinically important difference in pain intensity [24; 33]. In contrast to more optimistic conclusions from earlier reviews (e.g. [2; 29]), our findings are largely consistent with a recent Cochrane

review examining cannabinoids for neuropathic pain, indicating that these medicines are unlikely to be effective in the treatment of pain [28]. In their review, Mücke and colleagues [28] report an NNTB of 20 for 50% or greater reduction in pain, and NNTHs of 3 and 6 for adverse events relating to nervous system and psychiatric disorders respectively, suggesting a similar efficacy and safety profile of cannabinoids for pain as reported in our review.

The evidence on the effectiveness of cannabinoids for CNCP is limited for several reasons. First, sample size is an issue, with only 21 of the 104 included studies having at least 100 participants per treatment arm. While we made multiple attempts to minimise risk of bias in the effect estimates due to small sample sizes, this risk cannot be fully mitigated. For some estimates, effect sizes were notably larger in studies with <30 participants per treatment arm compared to studies of 100+ per arm, however these estimates fell within overlapping bounds of uncertainty. There is a growing body of evidence indicating that effect estimates tend to be larger in studies with small sample sizes [8], and as such, caution should be taken when interpreting outcomes based on studies with small sample sizes in this review. Well conducted, large RCTs comprising at least 100 participants per treatment arm should be considered a priority in this spaceSecond, most studies were of limited duration (median of eight weeks): given that CNCP is a chronic condition, this sheds little light on the appropriateness of long-term use of cannabinoids in CNCP, in terms of both treatment efficacy and safety. Of the little evidence available, we found that reductions in pain intensity were largest for one- day studies, and smaller and non-significant in studies of 13 weeks duration or longer, providing some initial suggestion that the effectiveness of cannabinoids for CNCP may diminish over time. Third, the issues of cannabinoid tolerance, risks of iatrogenic dependence, and of withdrawal symptoms if long-term cannabinoids are ceased, remain poorly understood. Short term clinical trials such as those included in this

review are often of insufficient power and duration to detect potential harms and adverse events associated with long-term cannabis use, such as elevated risk of psychosis and substance dependence [15; 27]. It is crucial that these long-term outcomes identified in the epidemiological literature are considered alongside evidence of efficacy from clinical trials when determining overall suitability of cannabinoids as medicines for CNCP. Fourth, cannabinoid dose was often poorly recorded. Often only a maximum recommended dose was reported and data on participants' actual cannabinoid consumption were seldom recorded, so it is difficult to make strong recommendations on doses that are maximally effective and safe. Fourth, by far the greatest amount of high quality evidence was for nabiximols, resulting in small numbers of studies (and in some cases, single studies) in some analyses for other types and formulations of cannabinoids (e.g. ajulemic acid), meaning we are be less confident about their efficacy. Fifth, although almost all studies reported data on change in pain intensity, very few reported outcomes for 30% and 50% reduction in pain. Given that pain was a secondary outcome in many studies, it is possible that authors did not report these outcomes as they are drawn from the pain-specific IMMPACT guidelines, however, there is also the possibility that study authors chose not to report outcomes for 30% and 50% reduction in pain when the continuous pain intensity outcome indicated no benefit. While we have made multiple attempts to account for publication bias throughout this review, there remains the possibility that the studies for which 30% and 50% reduction in pain were not reported did not find evidence of effect. If this is the case, NNTBs for these outcomes may be higher than reported here, however our overall conclusion that cannabinoids are unlikely to be effective medicines for CNCP will remain unchanged. Finally, to ensure all the available evidence of cannabinoids as a treatment for CNCP was considered in this review, we included evidence from RCTs and less rigorous observational study

designs. This approach allows researchers, clinicians and policy makers to map current research activity and to identify knowledge gaps. While observational studies provide some insight into the efficacy of cannabinoids for CNCP, ultimately only data from high quality RCTs will be used to inform national treatment guidelines. We noted that most of the higher quality, RCT evidence was for neuropathic pain and MS-related pain. There is scant, low quality evidence on cannabinoids used for fibromyalgia or visceral pain, and very few studies of cannabinoids' use in the most common and burdensome CNCP conditions, namely back/neck problems, migraines and arthritides. Thus, the conclusions of this review primarily relate to neuropathic or MS-related pain. Several ongoing studies targeting these more common CNCP conditions were identified and will be analysed when results become available.

Most studies used a placebo comparator and added cannabinoids to stable doses of analgesics, NSAIDS and anti-spasticity drugs, so the evidence for cannabinoid use in CNCP is largely around cannabinoids as adjuvant medicines. Often multiple analgesics were used, which varied between groups, and the ways they were used was not consistently reported. Most studies held doses of other analgesic medications constant, though some studies documented changes in breakthrough medication or adjunctive analgesia.

Limitations of this review

The findings of this review need to be considered in light of several potential limitations. Some of these limitations have already been noted and include the high risk of bias in many studies because of small N, and missing information on study design and rigour of controls; most studies also evaluated cannabinoids as adjunct to other analgesic medications. We attempted to assertively minimise these limitations. Many documents were reviewed by a

small research team, which might have led to errors in assessing eligible studies. However, internal checks were conducted by members within this team and a process of double and triple checking existed; we also checked all identified reviews to ensure that no studies had been missed that had been reported in any other reviews of evidence. Third, errors may have been made in data interpretation. To reduce such errors, all sources and data extracted were double-checked by at least two reviewers and conflicts were resolved by third reviewer when necessary.

Conclusions

It appears unlikely that cannabinoids are highly effective medicines for CNCP. There is moderate to high grade evidence supporting use of nabiximols to achieve modest reductions in pain as adjunctive therapy in MS-related pain. However, NNTB were high and NNTH low, with high rates of dropout for adverse events, and long-term efficacy and safety is unknown. We also found minimal evidence that cannabinoids are effective in improving other important domains in people with CNCP such as emotional and physical functioning. Cannabinoids are unlikely to be a monotherapy for CNCP. People living with CNCP often have complex comorbidities [4; 40], and multidisciplinary treatment that includes physical and psychological therapy rather than reliance on medicines alone is likely to be most effective.

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Non-author contributions

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Author contributions

LD and MF conceived the Review. ES, GC, SN, DZ, RR, and MW did the systematic search, selected papers, and extracted data. ES conducted statistical analyses. GC, LD and WH drafted the manuscript with critical revisions from all authors. BM provided clinical important intellectual content. All authors reviewed the paper before submission.

Conflicts of interest

GC, SN, MF and LD have all been investigators on untied investigator-driven educational grants funded by Reckitt Benckiser. MF and LD have received an untied educational grant from Mundipharma for post-marketing surveillance studies of a potentially tamper-resistant formulation of controlled-released oxycodone. SN, MF and LD have been investigators on untied investigator-driven educational grants funded by Indivior. MF and LD have been investigators on an untied investigator-driven educational grant funded by Seqirus.

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Supplemental video content

Video content associated with this article can be found at http://links.lww.com/PAIN/A593.

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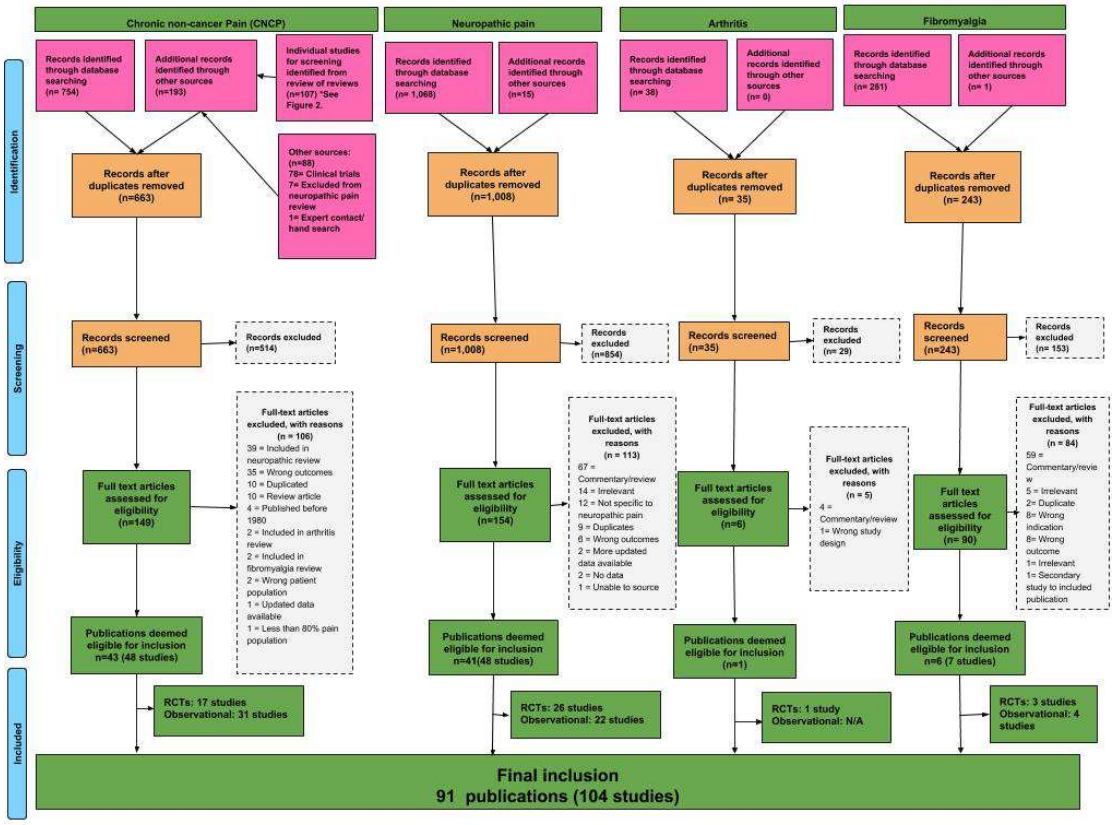
Figure legends

Figure 1. PRISMA flowchart showing the process of selection of studies into the review. See Figure B1 in Supplementary Appendix B for the PRISMA flowchart of the systematic review of reviews.



Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

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IMPORTANCE Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

OBJECTIVE To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

DATA SOURCES Twenty-eight databases from inception to April 2015.

STUDY SELECTION Randomized clinical trials of cannabinoids for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome.

DATA EXTRACTION AND SYNTHESIS Study quality was assessed using the Cochrane risk of bias tool. All review stages were conducted independently by 2 reviewers. Where possible, data were pooled using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Patient-relevant/disease-specific outcomes, activities of daily living, quality of life, global impression of change, and AEs.

RESULTS A total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0 99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10-point scale; weighted mean difference [WMD], −0.46 [95% CI, −0.80 to −0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, −0.12 [95% CI, −0.24 to 0.01]; 5 trials). There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

CONCLUSIONS AND RELEVANCE There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

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Last corrected on April 12, 2016.

Cannabis is a generic term used for drugs produced from plants belonging to the genus *Cannabis*.[1] It is one of the most popular recreational drugs; worldwide, an estimated 178 million people aged 15 to 64 years used cannabis at least once in 2012.[2] Cannabis was included as a controlled drug in the United Nations' Single Convention on Narcotic Drugs, held in 1961,[3] and its use is illegal in most countries.

Medical cannabis refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms. Cannabinoids can be administered orally, sublingually,or topically; they can be smoked, inhaled, mixed with food, or made into tea. They can be taken in herbal form, extracted naturally from the plant, gained by isomerisation of cannabidiol, or manufactured synthetically.[4] Prescribed cannabinoids include dronabinol capsules, nabilone capsules, and the oromucosal spray nabiximols.[4] Some countries have legalized medicinal-grade cannabis for chronically ill patients. Canada and the Netherlands have government-run programs in which specialized companies supply quality-controlled herbal cannabis.[5] In the United States, 23 states and Washington, DC (May 2015), have introduced laws to permit the medical use of cannabis[6]; other countries have similar laws. The aim of this systematic review was to evaluate the evidence for the benefits and adverse events (AEs) of medical cannabinoids across a broad range of indications.

Methods

This review followed guidance published by the Centre for Reviews and Dissemination and the Cochrane Collaboration.[7,8] We established a protocol for the review (eAppendix 1 in Supplement 1).

Study Eligibility Criteria

Randomized clinical trials (RCTs) that compared cannabinoids with usual care, placebo, or no treatment in the following indications were eligible: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis (MS) or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, intraocular pressure in glaucoma, or Tourette syndrome. These indications were prespecified by the project funders, the Swiss Federal Office of Public Health. If no RCTs were available for a particular indication or outcome (eg, long-term AEs such as cancer, psychosis, depression, or suicide), nonrandomized studies including uncontrolled studies (such as case series) with at least 25 patients were eligible.

Identification and Selection of Studies

Twenty-eight databases and gray literature sources were searched from inception to April 2015 without language restriction (Embase search strategy and details of databases searched available in eAppendix 2 in Supplement 2). The search strategy was peer reviewed[9] by a second information specialist. Reference lists of included studies were screened. Search results and full-text articles were independently assessed by 2 reviewers; disagreements were resolved through consensus or referral to a third reviewer.

Data Collection and Study Appraisal

We extracted data about baseline characteristics and outcomes (patient-relevant and disease-specific outcomes, activities of daily living, quality of life, global impression of change, and specified AEs). For dichotomous data such as number of patients with at least 30% improvement in pain, we calculated the odds ratio (OR) and 95% CI. For categorical data, we extracted details about each category assessed and the numbers of patients with an outcome in each category. Continuous data such as the Ashworth spasticity score[10] were extracted as means and SDs at baseline, follow-up, and the change from baseline and used to calculate mean differences with 95% CIs. Results (mean difference, 95% CIs, and *P* values) from the between-group statistical analyses reported by the study were also extracted. All relevant sources were used for data extraction including full-text journal articles, abstracts, and clinical trial registry entries. Where available, the journal article was used as the primary publication because it had been peer reviewed.

RCTs were assessed for methodological quality using the Cochrane Risk of Bias tool.[11] If at least one of the domains was rated as high, the trial was considered at high risk of bias. If all domains were judged as low, the trial was considered at low risk of bias. Otherwise, the trial was considered as having unclear risk of bias. Data extraction and risk-of-bias assessment were performed independently by 2 reviewers; disagreements were resolved by a third reviewer.

Synthesis

Clinical heterogeneity was assessed by grouping studies by indication, cannabinoid, and outcome. If there were 2 or more trials within a single grouping, data were pooled using random-effects meta-analysis.[12] For continuous outcomes, we analyzed the mean difference in change from baseline; if this was not reported and could not be calculated from other data, we used the mean difference at follow-up.[13] For dichotomous data, we used the OR. In order to avoid double counting, we selected a single data set from each study to contribute to the analysis. For studies evaluating multiple interventions, we selected the intervention or dose that was most similar to the other interventions being evaluated in the same analysis. Heterogeneity was investigated using forest plots and the I^2 statistic. Where data were considered too heterogeneous to pool or not reported in a format suitable for pooling (eg, data reported as medians), we used a narrative synthesis.

Sensitivity analyses were used to assess the statistical effect of trial design. The primary analysis included only parallel-group trials, results from crossover trials were included in an additional analysis. For the analysis of AEs, data for all conditions were combined. We conducted stratified analyses and meta-regression to investigate whether associations varied according to type of cannabinoid, study design (parallel group vs crossover trial), indication (each of the indication categories included in this report), compara-

tor (active vs placebo), and duration of follow-up (<24 hours, 24 hours-1 week, >1 week-4 weeks, >4 weeks) for the outcome of any AE. Statistical analyses were performed using Stata statistical software (version 10).

GRADE (Grading of Recommendations Assessment, Development and Evaluation) was used to rate the overall quality of the evidence for risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect. The GRADE ratings of very low-, low-, moderate-, or high-quality evidence reflect the extent to which we are confident that the effect estimates are correct.[14]

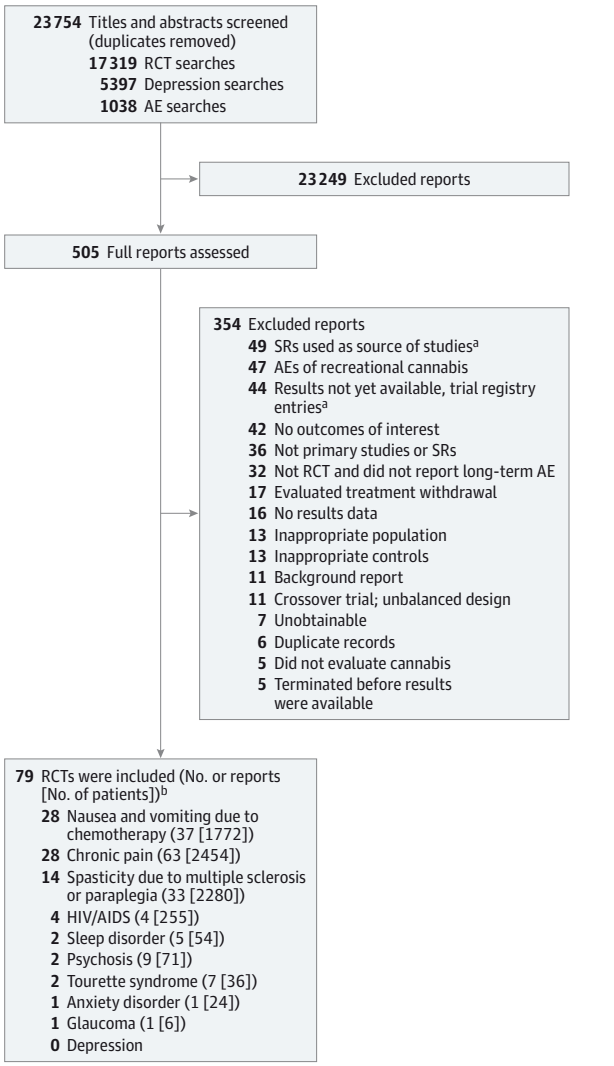
Results

The searches identified 23 754 hits (records) of which 505 were considered potentially relevant, based on title and abstract screening, and obtained as full-text studies. A total of 79 studies (6462 participants), available as 151 reports, were included; 3 studies (6 reports) were included in multiple indication categories (**Figure 1**). Thirty-four studies were parallel-group trials (4436 participants), and 45 were crossover trials (2026 participants). Four studies were available only as an abstract,[15-18] a further 3 were available only as abstracts[19-21] but with additional details available on trial registries including full results in one,[19] and details of 2 trials (including full trial results) were available only as trial registry entries[22,23]; all other trials were reported in full-length journal articles. Where reported, the proportion of participants who were men ranged from 0% to 100% (median, 50% [57 studies]), and the proportion of white participants ranged from 50% to 99% (median, 78% [18 studies]). Publication dates ranged from 1975 to 2015 (median, 2004 [with one-third of trials published before 1990]). Studies were conducted in a wide range of countries. A variety of cannabinoids were evaluated and compared with various different active comparators or placebos; most active comparators were included in the nausea and vomiting indication (**Table 1**). eAppendices 3 to 12 in Supplement 1 provide an overview of the included studies and their findings.

Four (5%) trials were judged at low risk of bias, 55 (70%) were judged at high risk of bias, and 20 (25%) at unclear risk of bias (eAppendix 13 in Supplement 2). The major potential source of bias in the trials was incomplete outcome data. More than 50% of trials reported substantial withdrawals and did not adequately account for this in the analysis. Selective outcome reporting was a potential risk of bias in 16% of trials. These studies did not report data for all outcomes specified in the trial register, protocol, or methods section or changed the primary outcome from that which was prespecified. Most studies reported being double-blinded but only 57% reported that appropriate methods had been used for participant blinding and only 24% reported that outcome assessors had been appropriately blinded.

Full results from included studies are presented in eAppendices 3-12 in Supplement 2; pooled results and GRADE ratings are presented in **Table 2**.

Figure 1. Flow of Studies Through the Review Process



AE indicates adverse event; RCT, randomized controlled trial; and SR, systematic review.

[a] These excluded reports were screened as full-text articles/reports.

[b] The number of included RCTS does not sum because some were included in more than 1 indication category.

Nausea and Vomiting Due to Chemotherapy

Nausea and vomiting due to chemotherapy was assessed in 28 studies (37 reports; 1772 participants).[15,16,24-58] Fourteen studies assessed nabilone and there were 3 for dronabinol, 1 for nabiximols, 4 for levonantradol, and 6 for THC. Two studies also included a combination therapy group of dronabinol with ondansetron or prochlorperazine. Eight studies included a placebo control, 3 of these also included an active comparator, and 20 studies included only an active comparator. The most common active comparators were prochlorperazine (15 studies), chlorpromazine (2 studies) and domperidone (2 studies). Other comparators (alizapride, hydroxyzine, metoclopramide and ondansetron) were evaluated in single studies (Table 1). Of all 28 studies,

Table 1. Evaluation of Interventions by Included Studies

Intervention	US Legal Status and Approved Use	Cannabis-Related Properties	Administration Method	Dose Evaluated	Comparator	No. of Studies[a]	Indication
Ajulemic acid (JBT-101, CT3)	Not currently in clinical use	Synthetic nonpsychoactive cannabinoid Derivate of the THC metabolite 11-nor-9-carboxy-THC	Capsules (oral)	Maximum 40 mg 2 ×/d	Placebo	1	Pain
CBD	Use does not appear to be explicitly restricted	Active cannabinoid part of cannabis	Capsules (oral)	200-800mg/d	Placebo	2	Psychosis, anxiety
					Amisulpride	1	Psychosis
			Oromuscosal spray	20 mg 1 ×/d or 40 mg 1 ×/d (2 doses evaluated)	Placebo	1	Glaucoma
Cannabis (marijuana)	Regulated under Schedule I of the Controlled Substances Act 1970 Legal for medical use in 23 states	Numerous active cannabinoids that will vaporize at different temperatures	Vaporized	Two concentrations: 1.29% and 3.53% 4 puffs after 1 h then 4-8 puffs after 3 h	Placebo	1	Pain
			Smoked	Maximum 3 cigarettes/d	Placebo	1	HIV
Dronabinol	Licensed for treatment of anorexia associated with weight loss in patients with AIDS Also for nausea and vomiting associated with cancer chemotherapy (United States and Germany)	Synthetic THC	Capsules (oral)	Maximum 5-30 mg/d 1-4 doses/d (most common, 2 doses)	Placebo	10	Nausea and vomiting, pain, spasticity, HIV, sleep
					Megestrol acetate	1	HIV
					Dronabinol + prochlorperazine or prochlorperazine	1	Nausea and vomiting
					Dronabinol + ondansetron, ondansetron, or placebo	1	
Levonantradol	Not currently in clinical use	Synthetic analogue of dronabinol	Capsules (oral)	Maximum 5 mg/d 1 mg 2 hours before chemotherapy then 1 mg every 4 hours	Prochlorperazine	1	Nausea and vomiting
			Intramuscular	Maximum 1.5 mg -4 mg 0.5 mg-1 mg, 1-2 h before chemotherapy then every 4 h	Prochlorperazine	1	
					Chlorpromazine	1	
					Metoclopramide	1	
Nabilone	Approved by the US FDA in 1985 for treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemtics Also marketed in the United Kingdom, Mexico, and Austria	Synthetic cannabinoid derivate mimicking THC	Capsules (oral)	Maximum 0.5 mg-8 mg Most common dose 2 mg 2 ×/d	Placebo	7[b]	Spasticity, pain, sleep, nausea and vomiting
					Dihydrocodeine	1	Pain
					Amitriptyline	1	Pain, sleep
					Chlorpromazine	1	Nausea and vomiting
					Alizapride	1	
					Domperidone	2	
					Prochlorperazine	7	
Nabiximols	Licensed for use in the United Kingdom, Spain, Czech Republic, Germany, Demark, Sweden, Italy, Austria, Canada, Poland, France (for spasticity due to multiple sclerosis) Not currently licensed in the United States Initial target indication for US FDA approval is cancer pain	Each mL contains 27 mg THC and 25 mg CBD	Oromuscosal spray	Titrated to a maximum of 4-48 sprays/24 h Most common maximum was 8 sprays/3 h or 48 sprays/24 h	Placebo	19	Spasticity, pain, nausea and vomiting
ECP002A	No current marketing authorization	Pure (≥98%) Natural Δ^9-THC	Oral tablet	Individualized dose	Placebo	1	Spasticity

(continued)

risk of bias was high for 23 or unclear for 5. All studies suggested a greater benefit of cannabinoids compared with both active comparators and placebo, but these did not reach statistical significance in all studies. The average number of patients showing a complete nausea and vomiting response was greater with cannabinoids (dronabinol or nabiximols) than placebo (OR, 3.82 [95% CI, 1.55-9.42]; 3 trials). There was no evidence of heterogeneity for this

Table 1. Evaluation of Interventions by Included Studies (continued)

Intervention	US Legal Status and Approved Use	Cannabis-Related Properties	Administration Method	Dose Evaluated	Comparator	No. of Studies[a]	Indication
THC	Same as cannabis	Active cannabinoid part of cannabis	Capsules (oral)	Maximum 5 mg-60 mg/d, given 1 ×/d or every 4-6 h in chemotherapy patients	Placebo	3	Pain, Tourette syndrome
					Placebo and codeine	1	Pain
					Placebo and prochloreperazine	2	Nausea and vomiting
					Prochlorperazine	3	
					Hydroxizine	1	
			Smoked	1-5 cigarettes/d Potency, where reported, ranged from 2.5%-9.4%	Placebo	5	Spasticity, pain
			Oromuscosal spray	Single daily dose to a maximum of 8 actuations/24 h Concentration 1%-7%	Placebo	4	Pain, glaucoma
THC/CBD	See individual components	Combination of CBD and THC	Capsules (oral)	Maximum 10 mg-60 mg/d, given as 2 doses	Placebo	4	Spasticity

Abbreviations: CBD, cannabidiol; US FDA, US Food and Drug Administration; THC, tetrahydrocannabinol.

[a] The number of studies does not sum to 79 because some reported more than 2 treatment groups and were accounted more than once.

[b] One trial evaluated nabilone as an adjunctive to gabapentin.

analysis (I^2 = 0%) and results were similar for both dronabinol and nabiximols.

Appetite Stimulation in HIV/AIDS Infection

Appetite stimulation in HIV/AIDS was assessed in 4 studies (4 reports; 255 participants).[59-62] All studies assessed dronabinol, 3 compared with placebo (1 of which also assessed marijuana), and 1 compared with megastrol acetate. All studies were at high risk of bias. There was some evidence that dronabinol is associated with an increase in weight when compared with placebo. More limited evidence suggested that it may also be associated with increased appetite, greater percentage of body fat, reduced nausea, and improved functional status. However, these outcomes were mostly assessed in single studies and associations failed to reach statistical significance. The trial that evaluated marijuana and dronabinol found significantly greater weight gain with both forms of cannabinoid when compared with placebo.[59] The active comparison trial found that megastrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megastrol acetate did not lead to additional weight gain.[60]

Chronic Pain

Chronic pain was assessed in 28 studies (63 reports; 2454 participants).[19,20,22,23,63-120] Thirteen studies evaluated nabiximols, 4 were for smoked THC, 5 for nabilone, 3 for THC oromucosal spray, 2 dronabinol, 1 vaporized cannabis (included 2 doses), 1 for ajuvenic acid capsules, and 1 for oral THC. One trial compared nabilone with amitriptyline[64]; all other studies were placebo controlled. One of these studies evaluated nabilone as an adjunctive treatment to gabapentin.[121] The conditions causing the chronic pain varied between studies and included neuropathic pain (central, peripheral, or not specified; 12 studies), 3 for cancer pain, 3 for diabetic peripheral neuropathy, 2 for fibromyalgia, 2 for HIV-associated sensory neuropathy, and 1 study for each of the following indications: refractory pain due to MS or other neurological conditions, for rheumatoid arthritis, for noncancer pain (nociceptive and neuropathic), central pain (not specified further), musculoskeletal problems, and chemotherapy-induced pain.

Two studies were at low risk of bias, 9 at unclear risk, and 17 at high risk of bias. Studies generally suggested improvements in pain measures associated with cannabinoids but these did not reach statistical significance in most individual studies.

The average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo (OR, 1.41 [95% CI, 0.99-2.00]; 8 trials; **Figure 2**). One trial assessed smoked THC[77] and reported the greatest beneficial effect (OR, 3.43 [95% CI, 1.03-11.48]), and 7 trials assessed nabiximols (Figure 2). Pain conditions evaluated in these trials were neuropathic pain (OR, 1.38 [95% CI, 0.93-2.03]; 6 trials) and cancer pain (OR, 1.41 [95% CI, 0.99-2.00]; 2 trials), with no clear differences between pain conditions. Nabiximols was also associated with a greater average reduction in the Numerical Rating Scale (NRS; 0-10 scale) assessment of pain (weighted mean difference [WMD], −0.46 [95% CI, −0.80 to −0.11]; 6 trials), brief pain inventory-short form, severity composite index (WMD, −0.17 [95% CI, −0.50 to 0.16]; 3 trials), neuropathic pain scale (WMD, −3.89 [95% CI, −7.32 to −0.47]; 5 trials), and the proportion of patients reporting improvement on a global impression of change score (OR, 2.08 [95% CI, 1.21 to 3.59]; 6 trials) compared with placebo. There was some evidence to support this based on continuous data but this was not consistent across trials. There was no difference in average quality-of-life scores as measured by the EQ-5D health status index (WMD, −0.01 [95% CI, −0.05 to 0.02]; 3 trials) between nabiximols and placebo. Two of the studies included in the meta-analysis for the NRS (0-10 scale)

Table 2. Summary Estimates From Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes With Associated GRADE Ratings

Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[b]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
Nausea and vomiting due to chemotherapy	3 (102)	Dronabinol (2), Nabiximols (1)	Placebo	Nausea and vomiting Complete response	OR (95% CI), 3.82 (1.55 to 9.42)	CBM	0	Low
HIV/AIDS	1 (88)	Dronabinol	Placebo	Weight gain No. of patients who gained ≥2 kg within 6 weeks	OR (95% CI), 2.2 (0.68 to 7.27)	CBM	NA	Low
Chronic pain (neuropathic and cancer pain)	8 (1370)	Smoked THC (1), Nabiximols (7)	Placebo	Pain reduction ≥30% NRS or VAS scores Follow-up 2-15 weeks	OR (95% CI), 1.41 (0.99 to 2.00)	CBM	48	Moderate
	6 (948)	Nabiximols (6)	Placebo	Pain NRS scores (0-10) Follow-up 2-14 weeks	WMD (95% CI), −0.46 (−0.80 to −0.11)	CBM	59	Moderate
	3 (613)	Nabiximols (3)	Placebo	Pain Brief Pain Inventory-Short Form scale (0 to 10) Follow-up 3-15 weeks	WMD (95% CI), −0.17 (−0.50 to 0.16)	CBM	0	Moderate
	6 (267)	Nabiximols (5), Nabilone (1)	Placebo	Patient global impression of change Follow-up 3-14 weeks	OR (95% CI), 2.08 (1.21 to 3.59)	CBM	68	Low
	5 (764)	Nabiximols (5)	Placebo	Neuropathic pain Neuropathic Pain Scale (0-100) Follow-up 5-15 weeks	WMD (95% CI), −3.89(−7.32 to −0.47)	CBM	41	Moderate
	3 (573)	Nabiximols (3)	Placebo	Quality of life EQ-5D scale (0 to 100) Follow-up 12-15 weeks	WMD (95% CI), −0.01 (−0.05 to 0.02)	Placebo	0	Moderate
Spasticity due to multiple sclerosis or paraplegia	2 (519)	Nabiximols (2)	Placebo	50% Reduction in spasticity symptoms NRS (0-10) Follow-up 6-14 weeks	OR (95% CI), 1.40 (0.81 to 2.41)	CBM	0	Low
	2 (519)	Nabiximols (2)	Placebo	30% Reduction in spasticity symptoms NRS Follow-up 6-14 weeks	OR (95% CI), 1.64 (0.95 to 2.83)	CBM	44	Low
	5 (1244)	Nabiximols (4), THC/CBD (1), Dronabinol (1)	Placebo	Spasticity Ashworth Spasticity Scale Follow-up 3-15 weeks	WMD (95% CI), −0.11 (−0.23 to 0.02)	CBM	0	Moderate
					−0.32 (−1.59 to 0.95)			
					−0.94 (−2.37 to 0.49)			
	3 (698)	Nabiximols (2), Nabilone (1)	Placebo	Spasticity NRS or VAS scores	WMD (95% CI), −0.76 (−1.38 to −0.14)	CBM	73	Low
	4 (1433)	Nabilone (2), Dronabinol (1), THC/CBD (1)	Placebo	ADLs Barthel Index of ADL	WMD (95% CI), −0.58 (−1.73 to 0.56)	Placebo	0	Moderate
					0.23 (−0.13 to 0.59)			
					−0.03 (−0.39 to 0.33)			
	2 (497)	Nabiximols (2)	Placebo	Walking speed as assessed by timing	WMD (95% CI), −0.86 (−3.08 to 1.36)	CBM	24	Moderate
	3 (461)	Nabiximols	Placebo	Global Impression Patient global impression of change	OR (95% CI), 1.44 (1.07 to 1.94)	CBM	0	Low

(continued)

Table 2. Summary Estimates From Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes With Associated GRADE Ratings (continued)

Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[b]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
Depression	1 (66)	Nabiximols	Placebo	Depression Hospital Anxiety and Depression Scale (0-52) Follow-up 5 weeks	Mean difference (95% CI), 0.15 (−1.0 to 1.31)	Placebo	NA	Very low
	1 (182)	Nabiximols	Placebo	Depression assessed using the Montgomery-Åsberg Depression Scale (0-54) Follow-up 9 weeks	Mean difference (95% CI), 1.90 (−0.22 to 4.02)	Placebo	NA	Very low
	1 (160)	Nabiximols	Placebo	Depression Beck Depression Inventory Scale (0-63) Follow-up 6 weeks	Mean difference (95% CI), 0.69 (−0.76 to 2.14)	Placebo	NA	Very low
Anxiety disorder	1 (24)	Cannabidiol	Placebo	Anxiety Visual Analogue Mood Scale (anxiety factor scale; 0-100) Follow-up 107 minutes	Mean difference, −16.52 *P* value = .01	CBM	NA	Very low
Sleep disorder	1 (22)	Nabilone	Placebo	Sleep apnea/hypopnea Apnea Hypopnea Index Follow-up 3 weeks	Mean difference, −19.64 *P* value = .02	CBM	NA	Low
	8 (539) In other indications	Nabiximols (7), THC/CBD (1)	Placebo	Sleep quality NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.58 (−0.87 to −0.29)	CBM	33	Very low
	3 (1637) In other indications	Nabiximols (3)	Placebo	Sleep disturbance NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.26 (−0.52 to 0.00)	CBM	64	Very low
Psychosis	1 (35)	Cannabidiol	Amisulpride	Mental health Brief Psychiatric Rating Scale Follow-up 4 weeks	Mean difference (95% CI), −0.10 (−9.20 to 8.90)	CBM	NA	Low
	1 (35)	Cannabidiol	Amisulpride	Mood Positive and Negative Syndrome Scale (30-210) Follow-up 4 weeks	Mean difference (95% CI), 1 (−12.60 to 14.60)	Amisulpride	NA	Low
Tourette syndrome	1 (17)	THC capsules	Placebo	Tic severity Shapiro Tourette Syndrome Severity Scale (0-6) Follow-up 6 weeks	Mean difference, −0.70 *P* value = .03	THC	NA	Low
	1 (17)	THC capsules	Placebo	Tic severity Tourette syndrome symptom list (tic rating) Follow-up 6 weeks	Mean difference, −16.2 *P* value < .05	THC	NA	Low
	1 (18)	THC capsules	Placebo	Tic severity Yale Global Tic Severity Scale (0-100) Follow-up 6 weeks	Mean difference, −12.03 *P* value = .061	THC	NA	Low
	1 (17)	THC capsules	Placebo	Tic severity Tourette Syndrome Clinical Global Impression Scale (0-6) Follow-up 6 weeks	Mean difference, −0.57 *P* value = .008	THC	NA	Low

Abbreviations: ADL, activities of daily living; CBM, cannabis based medicine; EQ-5D, EuroQol Five Dimension Scale; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not applicable; NRS, numerical rating scale; OR, odds ratio; THC, tetrahydrocannabinol; VAS, visual analog scale; WMD, weighted mean difference.

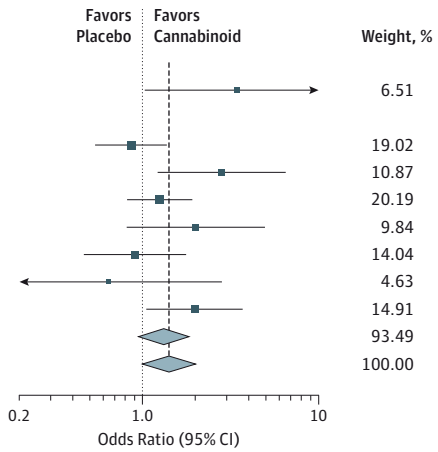
[a] No studies for glaucoma were included in the study estimate. The authors note that THC and cannabidiol were the interventions used in the reviewed glaucoma studies.

[b] Outcome includes the specific indication that was assessed, the means by which assessment was made, and folow-up (not shown for all studies).

[c] GRADE Working Group grades of evidence: (1) high quality, further research is very unlikely to change the group's confidence in the estimate of effect; (2) moderate quality, further research is likely to have an important impact on the group's confidence in the estimate of effect and may change the estimate; (3) low quality, further research is very likely to have an important impact on the group's confidence in the estimate of effect and is likely to change the estimate; (4) very low quality, the group is very uncertain about the estimate.

Figure 2. Improvement in Pain

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal I^2 = 44.5%, (P = .0.94)	241	660	209	660	1.32 (0.94-1.86)
Overall I^2 = 47.6%, (P = .0.64)	254	685	215	685	1.41 (0.99-2.00)



Odds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).

assessed patients with cancer pain, all other studies assessed patients with neuropathic pain. There were no clear differences based oncause of pain in the meta-analysis of NRS. Sensitivity analyses that included crossover trials showed results consistent with those based on parallel-group trials alone.

Spasticity Due to MS or Paraplegia

Fourteen studies (33 reports; 2280 participants) assessed spasticity due to MS or paraplegia.[17,19,65,87,91,122-149] Eleven studies (2138 participants) included patients with MS and 3 included patients with paraplegia (142 participants) caused by spinal cord injury. Six studies assessed nabiximols, 3 for dronabinol, 1 for nabilone, 4 for THC/CBD (2 of these also assessed dronabinol), and 1 each for ECP002A and smoked THC. All studies included a placebo control group; none included an active comparator. Two studies were at low risk of bias, 5 were at unclear risk of bias, and 7 were at high risk of bias. Studies generally suggested that cannabinoids were associated with improvements in spasticity, but this failed to reach statistical significance in most studies. There were no clear differences based on type of cannabinoid. Only studies in MS patients reported sufficient data to allow summary estimates to be generated. Cannabinoids (nabiximols, dronabinol, and THC/CBD) were associated with a greater average improvement on the Ashworth scale for spasticity compared with placebo, although this did not reach statistical significance (WMD, −0.12 [95% CI, −0.24 to 0.01]; 5 trials; **Figure 3**). Cannabinoids (nabilone and nabiximols) were also associated with a greater average improvement in spasticity assessed using numerical rating scales (mean difference, −0.76 [95% CI, −1.38 to −0.14]; 3 trials). There was no evidence of a difference in association according to type of cannabinoid for either analysis. Other measures of spasticity also suggested a greater benefit of cannabinoid but did not reach statistical significance (Table 2). The average number of patients who reported an improvement on a global impression of change score was also greater with nabiximols than placebo (OR, 1.44 [95% CI, 1.07 to 1.94]; 3 trials); this was supported by a further crossover trial of dronabinol and oral THC/CBD that provided continuous data for this outcome.[132] Sensitivity analyses that included crossover trials showed results consistent with those based on parallel group trials alone.

Depression

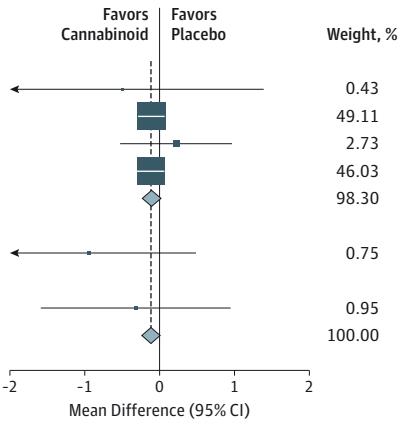
No studies evaluating cannabinoids for the treatment of depression fulfilled inclusion criteria. Five studies included for other indications reported depression as an outcome measure; 4 evaluated chronic pain and 1 evaluated spasticity in MS patients.[67,73,75,80,129] One trial assessed dronabinol (2 doses), 3 assessed nabiximols, and 1 assessed nabilone. Two studies were rated as having unclear risk of bias and 3 as having high risk of bias. Three studies suggested no difference between cannabinoids (dronabinol and nabiximols) and placebo in depression outcomes. One parallel-group trial that compared different doses of nabiximols with placebo reported a negative effect of nabiximols for the highest dose (11-14 sprays per day) compared with placebo (mean difference from baseline, 2.50 [95% CI, 0.38 to 4.62]) but no difference between placebo and the 2 lower doses.[67]

Anxiety Disorder

One small parallel-group trial, judged at high risk of bias, evaluated patients with generalized social anxiety disorder.[150] The trial reported that cannabidiol was associated with a greater improvement on the anxiety factor of a visual analogue mood scale (mean difference from baseline, −16.52; P value = .01) compared with placebo during a simulated public speaking test. Additional data about anxiety outcomes provided by 4 studies (1 parallel group) in patients with chronic pain also sug-

Figure 3. Change in Ashworth Score for Cannabinoid Compared With Placebo, Stratified According to Cannabinoid

Score Change With Cannabinoid vs Placebo by Study	Cannabinoid No. of Patients	Cannabinoid Mean (SD) Score Change	Placebo No. of Patients	Placebo Mean (SD) Score Change	Mean Difference (95% CI)	Weight, %
Nabiximols						
Collin,[125] 2010	156	-3.3 (9.25)	160	-2.8 (7.81)	-0.50 (-2.39 to 1.39)	0.43
Collin,[127] 2007	114	-.64 (.56)	63	-.53 (.58)	-0.11 (-0.29 to 0.07)	49.11
Wade,[129] 2004	73	-.37 (2.51)	70	-.59 (2.04)	0.22 (-0.53 to 0.97)	2.73
Berman,[87] 2007	40	-.13 (.43)	44	-.01 (.42)	-0.12 (-0.30 to 0.06)	46.03
Subtotal I^2 = 0.0%, (P = .82)	383		337		-0.11 (-0.23 to 0.02)	98.30
Dronabinol						
Zajicek,[131] 2003	197	-1.86 (7.95)	207	-.92 (6.56)	-0.94 (-2.37 to 0.49)	0.75
Tetrahydrocannabinol/cannabidiol						
Zajicek,[131] 2003	207	-1.24 (6.6)	207	-.92 (6.56)	-0.32 (-1.59 to 0.95)	0.95
Overall I^2 = 0.0%, (P = .80)	590		544		-0.12 (-0.24 to 0.01)	100.00



The square data markers indicate mean differences from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal line indicate, 95% CIs. The blue diamond data markers represent the subtotal and overall weighted mean difference and 95% CI. The vertical dashed line shows the summary effect estimate, the solid vertical line shows the line of no effect (mean difference = 0).

gested a greater benefit of cannabinoids (dronabinol, nabilone, and nabiximols) than placebo but these studies were not restricted to patients with anxiety disorders.[73-75,80]

Sleep Disorder

Two studies (5 reports; 54 participants) evaluated cannabinoids (nabilone) specifically for the treatment of sleep problems. One was a parallel-group trial judged at high risk of bias. This reported a a greater benefit of nabilone compared with placebo on the sleep apnea/hypopnea index (mean difference from baseline, −19.64; P value = .02). The other was a crossover trial judged at low risk of bias in patients with fibromyalgia and compared nabilone with amitriptyline. This suggested that nabilone was associated with improvements in insomnia (mean difference from baseline, −3.25 [95% CI, −5.26 to −1.24]) and with greater sleep restfulness (mean difference from baseline, 0.48 [95% CI, 0.01 to 0.95]). Nineteen placebo-controlled studies included for other indications (chronic pain and MS) also evaluated sleep as an outcome.* Thirteen studies assessed nabiximols, 1 for nabilone, 1 for dronabinol, 2 for THC/CBD capsules, and two assessed smoked THC (one at various doses). Two of the studies that assessed nabiximols also assessed oral THC and the trial of dronabinol also assessed oral THC/CBD. There was some evidence that cannabinoids may improve sleep in these patient groups. Cannabinoids (mainly nabiximols) were associated with a greater average improvement in sleep quality (WMD, −0.58 [95% CI, −0.87 to −0.29]; 8 trials) and sleep disturbance (WMD, −0.26 [95% CI, −0.52 to 0.00]; 3 trials). One trial assessed THC/CBD, all others assessed nabiximols, results were similar for both cannabinoids.

Psychosis

Psychosis was assessed in 2 studies (9 reports; 71 participants) judged at high risk of bias, which evaluated cannabidiol compared with amisulpride or placebo.[21,151-158] The trials found no difference in mental health outcomes between treatment groups.

Glaucoma

One very small crossover trial (6 participants)[159] judged at unclear risk of bias compared tetrahydrocannabinol (THC; 5 mg), cannabidiol (20 mg), cannabidiol (40 mg) oromucosal spray, and placebo. This trial found no difference between placebo and cannabinoids on measures of intraocular pressure in patients with glaucoma.

Movement Disorders Due to Tourette Syndrome

Two small placebo-controlled studies (4 reports; 36 participants)[160-163] suggested that THC capsules may be associated with a significant improvement in tic severity in patients with Tourette syndrome.

Adverse Events

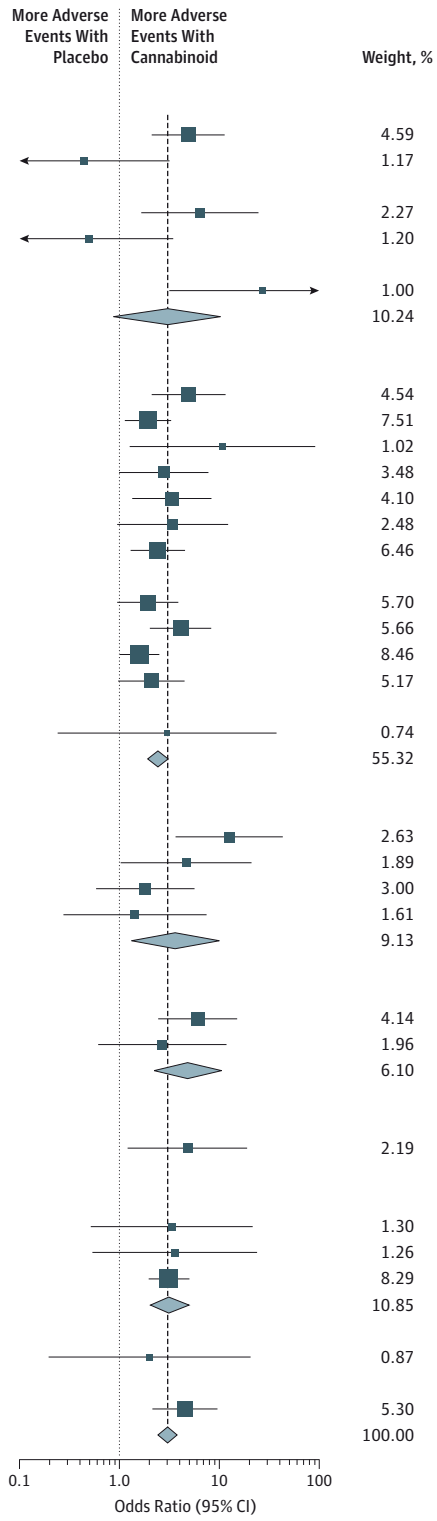
Data about AEs were reported in 62 studies (127 reports). Meta-regression and stratified analysis showed no evidence for a difference in the association of cannabinoids with the incidence of "any AE" based on type of cannabinoid, study design, indication, comparator, or duration of follow-up†; further analyses were conducted for all studies combined. **Figure 4** shows the results of the meta-analyses for the number of participants experiencing any AE compared when compared with controls, stratified according to cannabinoid. Cannabinoids were associated with a much greater risk of any AE, serious AE, withdrawals due to AE, and a number of specific AEs (**Table 3**). No studies evaluating the long-term AEs of cannabinoids were identified, even when searches were extended to lower levels of evidence.

*References 22, 23, 65, 67-69, 75, 76, 79-81, 87, 88, 123-125, 129-131

†References 15, 16, 18, 22-26, 28-31, 33-38, 41, 42, 44-47, 51, 57, 58, 60, 62, 64-69, 72-85, 87, 88, 123-127, 129-131, 159, 160, 162

Figure 4. Odds of Having Any Adverse Event With Cannabinoids Compared With Placebo, Stratified According to Cannabinoid

Adverse Events With Cannabinoid vs Placebo by Cannabinoid, Indication, and Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)	Weight, %
Dronabinol						
HIV						
Beal et al,[62] 1995	31	72	9	67	4.87 (2.10-11.32)	4.59
Timpone et al,[60] 1997	7	11	8	10	0.44 (0.06-3.16)	1.17
Nausea and vomiting						
Lane et al,[26] 1991	16	21	7	21	6.40 (1.65-24.77)	2.27
Meiri et al,[25] 2007	2	17	3	14	0.49 (0.07-3.44)	1.20
Pain						
Svendsen et al,[82] 2004	23	24	11	24	27.18 (3.14-235.02)	1.00
Subtotal I^2 = 69.1%, (P = .01)	79	145	38	136	3.01 (0.87- 10.43)	10.24
Nabiximols						
Pain						
Berman et al,[87] 2007	46	56	29	60	4.92 (2.10-11.52)	4.54
GW Pharmaceuticals et al,[22] 2005	120	149	101	148	1.93 (1.13-3.28)	7.51
GW Pharmaceuticals et al,[23] 2012	35	36	26	34	10.77 (1.27-91.52)	1.02
Nurmikko et al,[76] 2007	57	63	48	62	2.77 (0.99-7.77)	3.48
Portenoy et al,[67] 2012	83	90	71	91	3.34 (1.33- 8.36)	4.10
Rog et al,[80] 2005	30	34	22	32	3.41 (0.94-12.30)	2.48
Serpell et al,[88] 2014	109	128	83	118	2.42 (1.29-4.53)	6.46
Multiple sclerosis						
Collin et al,[127] 2007	102	124	46	65	1.92 (0.95-3.88)	5.70
Collin et al,[125] 2010	156	167	132	170	4.08 (2.01-8.30)	5.66
Langford et al,[65] 2013	120	167	106	172	1.59 (1.01-2.51)	8.46
Wade et al,[129] 2004	67	80	57	80	2.08 (0.97-4.47)	5.17
Nausea and vomiting						
Duran et al,[24] 2010	6	7	6	9	3.00 (0.24-37.67)	0.74
Subtotal I^2 = 8.3%, (P = .36)	931	1101	727	1041	2.41 (1.91-3.05)	55.32
Nabilone						
Nausea and vomiting						
Chan et al,[28] 1987	32	36	14	36	12.57 (3.65-43.30)	2.63
George et al,[35] 1983	17	20	11	20	4.64 (1.02-21.00)	1.89
Johansson et al,[38] 1982	14	26	9	23	1.81 (0.58-5.66)	3.00
Pomeroy et al,[29] 1986	16	19	15	19	1.42 (0.27-7.44)	1.61
Subtotal I^2 = 54.9%, (P = .08)	79	101	49	98	3.63 (1.31-10.02)	9.13
Levonantradol						
Nausea and vomiting						
Heim et al,[33] 1984	32	45	13	45	6.06 (2.43-15.08)	4.14
Hutcheon et al,[34] 1983	23	26	20	27	2.68 (0.61-11.78)	1.96
Subtotal I^2 = 0.0%, (P = .36)	55	71	33	72	4.84 (2.23-10.52)	6.10
Ajulemic acid (CT3)						
Pain						
Karst et al,[83] 2003	12	19	5	19	4.80 (1.20-19.13)	2.19
Tetrahydrocannabinol capsules						
Tourette						
Müller-Vahl et al,[160] 2003	5	9	3	11	3.33 (0.51-21.58)	1.30
Müller-Vahl et al,[162] 2001	5	12	2	12	3.57 (0.53-23.95)	1.26
Ungerleider et al,[146] 1982	136	172	99	181	3.13 (1.96-5.00)	8.29
Subtotal I^2 = 0.0%, (P = .99)	146	193	104	204	3.16 (2.03-4.93)	10.85
Tetrahydrocannabinol oromucosal spray						
Tomida et al,[159] 2006	3	6	2	6	2.00 (0.19-20.61)	0.87
Tetrahydrocannabinol/cannabidiol capsules						
Zajicek et al,[123] 2012	133	143	100	134	4.52 (2.13-9.59)	5.30
Overall I^2 = 31.2%, (P = .057)	1438	1779	1058	1710	3.03 (2.42-3.80)	100.00



The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted line shows the line of no effect (OR = 1).

Table 3. Summary Estimates From Meta-analyses for Each AE Assessed: Odds of Participants Experiencing AE With Cannabinoid vs Placebo or Active Comparison

	No. of Studies (No. of Patients)	Summary OR (95% CI)	I^2, %
General AE categories			
Any	29 (3714)	3.03 (2.42-3.80)	31
Serious	34 (3248)	1.41 (1.04-1.92)	0
Withdrawal due to AE	23 (2755)	2.94 (2.18-3.96)	2
MedDRA high-level grouping[164]			
Gastrointestinal disorders	10 (1960)	1.78 (1.43-2.22)	0
Infections and infestations	7 (1681)	1.13 (0.87-1.46)	0
Psychiatric disorders	8 (1672)	3.10 (1.81-5.29)	55
Nervous system disorders	10 (1521)	3.17 (2.20-4.58)	46
Musculoskeletal and connective tissues disorders	7 (1310)	1.32 (0.75-2.32)	34
General disorders and administration site conditions	6 (1208)	1.78 (1.34-2.36)	0
Death	5 (929)	1.01 (0.51-2.00)	0
Ear and labyrinth disorders	3 (922)	2.72 (1.55-4.75)	0
Respiratory, thoracic, and mediastinal disorders	5 (851)	0.80 (0.46-1.39)	0
Cardiac disorders	7 (833)	1.42 (0.58-3.48)	0
Blood disorders	3 (543)	1.42 (0.20-10.25)	18
Injury, poisoning and procedural complications	3 (543)	1.18 (0.48-2.93)	0
Renal and urinary disorders	3 (470)	2.45 (2.27-2.65)	0
Investigations	2 (427)	1.55 (0.36-6.71)	0
Metabolism and nutrition	2 (427)	2.37 (1.00-5.61)	0
Neoplasms, benign, malignant, and unspecified	2 (427)	0.99 (0.47-2.08)	0
Skin and subcutaneous	3 (405)	0.85 (0.34-2.13)	0
Eye disorders	1 (339)	1.42 (0.46-4.33)	NA
Reproductive system	1 (246)	1.55 (0.20-11.92)	NA
Hepatobiliary disorders	1 (181)	3.07 (0.12-76.29)	NA
Mental status change	3 (106)	2.49 (0.49-12.64)	0
Other body systems	1 (42)	2.59 (0.34-19.47)	NA
Injection site pain	1 (32)	2.49 (0.92-6.68)	NA
Individual AEs			
Dizziness	41 (4243)	5.09 (4.10-6.32)	18
Dry mouth	36 (4181)	3.50 (2.58-4.75)	28
Nausea	30 (3579)	2.08 (1.63-2.65)	0
Fatigue	20 (2717)	2.00 (1.54-2.62)	0
Somnolence	26 (3168)	2.83 (2.05-3.91)	27
Euphoria	27 (2420)	4.08 (2.18-7.64)	49
Depression	15 (2353)	1.32 (0.87-2.01)	0
Vomiting	17 (2191)	1.67 (1.13-2.47)	0
Diarrhea	17 (2077)	1.65 (1.04-2.62)	15
Disorientation	12 (1736)	5.41 (2.61-11.19)	0
Asthenia	15 (1717)	2.03 (1.35-3.06)	0
Drowsiness	18 (1272)	3.68 (2.24-6.01)	44
Anxiety	12 (1242)	1.98 (0.73-5.35)	54
Confusion	13 (1160)	4.03 (2.05-7.97)	0
Balance	6 (920)	2.62 (1.12-6.13)	0
Hallucination	10 (898)	2.19 (1.02-4.68)	0
Dyspnea	4 (375)	0.83 (0.26-2.63)	0
Paranoia	4 (492)	2.05 (0.42-10.10)	0
Psychosis	2 (37)	1.09 (0.07-16.35)	25
Seizures	2 (42)	0.91 (0.05-15.66)	0

Abbreviations: AE, adverse event; I^2, measures of heterogeneity; NA, not applicable; OR, odds ratio; MedDRA, medical dictionary for regulatory activities.

Discussion

We conducted an extensive systematic review of the benefits and AEs associated with medical cannabinoids across a broad range of conditions. We included 79 RCTs (6462 participants), the majority of which evaluated nausea and vomiting due to chemotherapy or chronic pain and spasticity due to MS and paraplegia. Other patient categories were evaluated in fewer than 5 studies.

Most studies suggested that cannabinoids were associated with improvements in symptoms, but these associations did not reach statistical significance in all studies. Based on the GRADE approach, there was moderate-quality evidence to suggest that cannabinoids may be beneficial for the treatment of chronic neuropathic or cancer pain (smoked THC and nabiximols) and spasticity due to MS (nabiximols, nabilone, THC/CBD capsules, and dronabinol). There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy (dronabinol and nabiximols), weight gain in HIV (dronabinol), sleep disorders (nabilone, nabiximols), and Tourette syndrome (THC capsules); and very low-quality evidence for an improvement in anxiety as assessed by a public speaking test (cannabidiol). There was low-quality evidence for no effect on psychosis (cannabidiol) and very low-level evidence for no effect on depression (nabiximols). There was an increased risk of short-term AEs with cannabinoid use, including serious AEs. Common AEs included asthenia, balance problems, confusion, dizziness, disorientation, diarrhea, euphoria, drowsiness, dry mouth, fatigue, hallucination, nausea, somnolence, and vomiting. There was no clear evidence for a difference in association (either beneficial or harmful) based on type of cannabinoids or mode of administration. Only 2 studies evaluated cannabis.[59,77] There was no evidence that the effects of cannabis differed from other cannabinoids.

Strengths and Weaknesses

This review followed recommendations for rigorous systematic reviews.[7,8] In order to identify as many relevant studies as possible and reduce the risk of publication bias, a highly sensitive search strategy was used and an extensive range of resources were searched including electronic databases, guidelines, and systematic reviews. Both published and unpublished trials were eligible for inclusion. There were no date or language restrictions. In order to minimize bias and errors, the main Embase strategies were peer reviewed by a second independent information specialist[165] and all stages of the review process were performed independently by 2 reviewers. We used the Cochrane risk of bias tool[11] to assess the included RCTs. This highlighted a number of methodological weaknesses in the included trials including failure to appropriately handle withdrawals, selective outcome reporting, and inadequate description of methods of randomization, allocation concealment, and blinding. An additional limitation of many included studies was their very small sample sizes. This was particularly the case for the trial of glaucoma (N = 6), Tourette syndrome (average N = 18), sleep disorder (average N = 27), and anxiety disorder (N = 24), which means these studies may have lacked the power to detect differences between treatment groups.

The synthesis combined a narrative discussion of individual study results with meta-analysis (for studies in which suitable data were available), supplemented by interpretation (following guidance of the GRADE Working Group).[14] The data analysis was complicated by a number of issues. The included studies used a large variety of measures to evaluate outcomes, and even very similar outcomes were often assessed using different measures. Furthermore, a wide range of time points were reported in the included trials, which limited the applicability of the findings of these studies. Multiple different cannabinoids were evaluated in the included studies. We stratified analyses based on type of cannabinoid to investigate whether there were differences in associations based on type of cannabinoid. The majority of the studies were 2-group trials with a placebo control group; however, some studies included active comparisons and multiple groups comparing more than 1 form of cannabinoid, different doses of cannabinoids, or active and placebo comparator groups. This necessitated selecting a single result from each trial to contribute to the meta-analysis to avoid double counting of studies. Where possible, we selected the result for the treatment or dose most similar to the other studies contributing to that meta-analysis and for placebo-controlled comparisons rather than active comparisons. For the short-term AE analysis, we selected the highest-reported cannabinoids dose because we hypothesized that this would be most likely to be associated with AEs—additionally, this analysis would present a worst-case scenario. Studies evaluated various forms of cannabis administered via various routes (oral capsules, smoked, vaporized, oromucosal spray, intramuscular injection) and active comparators differed across trials. These differences in form, combined with the variety of outcome measures and the broad indication groupings considered by this review, resulted in a very heterogeneous set of included studies, which meant that meta-analysis was not always possible or appropriate. Many studies reported insufficient information to allow meta-analysis (eg, reporting only *P* values for group differences) or no information on the analysis performed. A further difficulty with the continuous data were that even for the same outcomes, some studies reported results as difference between groups at follow-up and others reported results for difference in change from baseline. As advised by the *Cochrane Handbook for Systematic Reviews of Interventions*, we combined both types of data when estimating summary mean differences.[7] A potential problem with RCTs using crossover designs is the possible unblinding due to strong treatment or AEs. Additionally, studies of this design were rarely analyzed appropriately and none reported the required data accounting for their crossover design to permit appropriate inclusion in meta-analyses.[166] Primary analyses were therefore based on parallel-group studies, with crossover trials included as sensitivity analyses.

Our search identified a number of existing reviews that assessed the use of medical cannabinoids for MS,[167-170] nau-

sea and vomiting due to chemotherapy,[171-175] pain,[176-191] psychosis,[192-194] and Tourette syndrome.[195,196] Almost all previous reviews focused on single indications and all but one (which evaluated cannabinoids in 4 trials in patients with pain due to rheumatoid arthritis)[188] did not use the GRADE approach to rating the quality of the evidence. As far as we are aware, our review is the first comprehensive review to evaluate the safety and efficacy of cannabinoids across a broad range of indications. A key strength of review was that it allowed us to conduct pooled analysis for the AEs associated with medicinal cannabinoids, adding considerable power to this analysis.

Unanswered Questions and Future Research

Further large, robust, RCTs are needed to confirm the effects of cannabinoids, particularly on weight gain in patients with HIV/AIDS, depression, sleep disorders, anxiety disorders, psychosis, glaucoma, and Tourette syndrome are required. Further studies evaluating cannabis itself are also required because there is very little evidence on the effects and AEs of cannabis. Future trials should adhere to the CONSORT (Consolidated Standards of Reporting Trials) reporting standards[197] and ensure that appropriate methods are used for randomization, allocation concealment, patient and outcome assessor blinding, handling of withdrawals, and avoiding selective outcome reporting. Future studies should assess patient-relevant outcomes (including disease-specific end points, quality of life, and AEs) using standardized outcome measures at similar time points to ensure inclusion in future meta-analyses.

Conclusions

There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

ARTICLE INFORMATION

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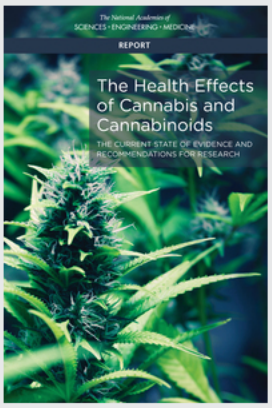

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DETAILS

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THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Eric B. Larson,** Group Health Research Institute, and **Bobbie A. Berkowitz,** Columbia University Medical Center. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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To begin, the committee would like to thank the sponsors of this study for their guidance and support. Support for the committee's work was generously provided by the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention; The Colorado Health Foundation; Mat-Su Health Foundation; National Highway Traffic Safety Administration; National Institutes of Health/National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; the Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and Washington State Department of Health.

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Contents

Preface

At the time of this report's release in January 2017, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions. Eight of these states and the District of Columbia have also legalized cannabis for recreational use. In addition to the growing availability of legalized cannabis, there has also been a rapid expansion in the types of available cannabis products, including edibles, oils, and a variety of inhaled substances. The growing acceptance, accessibility, and use of cannabis raise important public health concerns, and there is a clear need to establish what is known and what needs to be known about the health effects of cannabis use.

The committee was tasked with conducting a comprehensive review of the current evidence regarding the health effects of using cannabis and cannabis-derived products. The study was conducted in a limited time frame in order to respond to a quickly moving landscape, but as described in the report's methods section, the amount of work that this report entailed and the volume of literature reviewed clearly indicates the substantial effort involved and the importance of this issue to the committee.

In the current report, the committee presents a rigorous and thoughtful summary of the landscape of cannabis and health and puts forth recommendations to help advance the research field and better inform public health decisions. I wish to express my deepest gratitude to my fellow committee members who worked so hard and with good grace to accomplish this task. As with other National Academies of Sciences, Engineering, and Medicine reports, the work of the committee would have been

far more difficult, if not impossible, without the support of a dedicated, knowledgeable, and very hardworking National Academies staff.

Marie C. McCormick, *Chair*
Committee on the Health Effects of Marijuana:
An Evidence Review and Research Agenda

Summary

Over the past 20 years there have been substantial changes to the cannabis policy landscape. To date, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions (NCSL, 2016). Eight of these states and the District of Columbia have also legalized cannabis for recreational use. These landmark changes in policy have markedly changed cannabis use patterns and perceived levels of risk. Based on a recent nationwide survey, 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days, and between 2002 and 2015 the percentage of past month cannabis users in this age range has steadily increased (CBHSQ, 2016).

Despite the extensive changes in policy at the state level and the rapid rise in the use of cannabis both for medical purposes and for recreational use, conclusive evidence regarding the short- and long-term health effects (harms and benefits) of cannabis use remains elusive. A lack of scientific research has resulted in a lack of information on the health implications of cannabis use, which is a significant public health concern for vulnerable populations such as pregnant women and adolescents. Unlike other substances whose use may confer risk, such as alcohol or tobacco, no accepted standards exist to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeutic uses, effectively.

Within this context, in March 2016, the Health and Medicine Division

BOX S-1
Statement of Task

The Nat ona Academ es of Sc ences, Eng neer ng, and Med c ne (the Nat ona Academ es) w appo nt an ad hoc comm ttee to deve op a comprehens ve, n-depth rev ew of ex st ng ev dence regard ng the hea th effects of us ng mar juana and/or ts const tuents.

The comm ttee w deve op a consensus report w th two pr mary sect ons: (1) a sect on of the report w summar ze what can be determ ned about the hea th effects of mar juana use and, (2) a sect on of the report w summar ze potent a therapeut c uses of mar juana. The report w a so prov de a background overv ew of the cannab no d/endocannab no d system, h story of use n the Un ted States, and the regu at on and po cy andscape. In add t on, the report w out ne and make recommendat ons regard ng a research agenda dent fy ng the most cr t ca research quest ons regard ng the assoc at on of mar juana use w th hea th outcomes (both r sks and therapeut c) that can be answered n the short term (.e., w th n a 3-year t me frame) as we as any steps that shou d be taken n the short term to ensure that suffic ent data are be ng gathered to answer ong-term quest ons (e.g., appropr ate quest ons on arge popu at on surve ance surveys, c n ca data co ect on or other data capture, and reso ut on of barr ers to nkage between survey data and death/morb d ty reg str es to enab e popu at on- eve mor-b d ty and morta ty effects est mates). The comm ttee shou d focus on quest ons and consequences w th the potent a for the greatest pub c hea th mpact, wh e shedd ng ght on the character st cs of mar juana use that mpact both short- and ong-term hea th.

In conduct ng ts work, the comm ttee w conduct a comprehens ve rev ew of the ev dence, us ng accepted approaches of terature search, ev dence rev ew, grad ng, and synthes s. Stud es rev ewed regard ng hea th r sks shou d be as broad as poss b e, nc ud ng but not m ted to ep dem o ogy and c n ca stud es, and tox co ogy and an ma stud es when determ ned appropr ate by the comm ttee. The comm ttee w prov de summary determ nat ons regard ng causa ty based on strength of ev dence. Both U.S. and nternat ona stud es may be rev ewed based upon re evance and methodo og ca r gor.

(formerly the Institute of Medicine [IOM][1]) of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was asked to convene a committee of experts to conduct a comprehensive review of the literature regarding the health effects of using cannabis and/or its constituents that had appeared since the publication of the 1999 IOM report

[1] As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

Marijuana and Medicine. The resulting Committee on the Health Effects of Marijuana consisted of 16 experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, respiratory disease, pediatric and adolescent health, immunology, toxicology, preclinical research, epidemiology, systematic review, and public health. The sponsors of this report include federal, state, philanthropic, and nongovernmental organizations, including the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention (CDC); The Colorado Health Foundation; Mat-Su Health Foundation; National Highway Traffic Safety Administration; National Institutes of Health/National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; the Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and Washington State Department of Health.

In its statement of task, the committee was asked to make recommendations for a research agenda that will identify the most critical research questions regarding the association of cannabis use with health outcomes (both harms and benefits) that can be answered in the short term (i.e., within a 3-year time frame), as well as steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions. Of note, throughout the report the committee has attempted to highlight research conclusions that affect certain populations (e.g., pregnant women, adolescents) that may be more vulnerable to potential harmful effects of cannabis use. The committee's full statement of task is presented in Box S-1.

STUDY CONTEXT AND APPROACH

Over the past 20 years the IOM published several consensus reports that focused on the health effects of marijuana or addressed marijuana within the context of other drug or substance abuse topics.[2] The two IOM reports that most prominently informed the committee's work were *Marijuana and Health,* published in 1982, and the 1999 report *Marijuana and Medicine: Assessing the Science Base.* Although these reports differed in scope, they were useful in providing a comprehensive body of evidence upon which the current committee could build.

The scientific literature on cannabis use has grown substantially since the 1999 publication of *Marijuana and Medicine.* The committee conducted an extensive search of relevant databases, including Medline, Embase,

[2] See https://www.nap.edu/search/?year=1995&rpp=20&ft=1&term=marijuana (accessed January 5, 2017).

BOX S-2
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects

- Chron c pa n; cancer, chemotherapy- nduced nausea/vom t ng; anorex a and we ght oss; rr tab e bowe syndrome; ep epsy; spast c ty re ated to mu t p e sc eros s or sp na cord njury; Tourette syndrome; amyotroph c atera sc eros s; Hunt ngton's d sease; Park nson's d sease; dyston a; de-ment a; g aucoma; traumat c bra n njury; add ct on; anx ety; depress on; s eep d sorders; posttraumat c stress d sorder; sch zophren a and other psychoses

Cancer

- Lung cancer; head and neck cancer; test cu ar cancer; esophagea cancer; other cancer

Cardiometabolic risk

- Acute myocard a nfarct on; stroke; metabo c dysregu at on, metabo c syndrome, pred abetes, and d abetes me tus

Respiratory disease

- Pu monary funct on; chron c obstruct ve pu monary d sorder; resp ratory symptoms (nc ud ng chron c bronch t s); asthma

Immunity

- Immune funct on; nfect ous d sease

the Cochrane Database of Systematic Reviews, and PsycINFO, and they initially retrieved more than 24,000 abstracts that could have potentially been relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by "anonymous" authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report.

Given the large scientific literature on cannabis, the breadth of the statement of task, and the time constraints of the study, the committee developed an approach that resulted in giving primacy to recently published systematic reviews (since 2011) and high-quality primary research for 11 groups of health endpoints (see Box S-2). For each health endpoint,

Injury and death

- A -cause morta ty; occupat ona njury; motor veh c e crash; overdose njury and death

Prenatal, perinatal, and postnatal exposure to cannabis

- Pregnancy comp cat ons for the mother; feta growth and deve opment; neonata cond t ons; ater outcomes for the nfant

Psychosocial

- Cogn t on (earn ng, memory, attent on, nte gence); academ c ach eve-ment and educat ona outcomes; emp oyment and ncome; soc a re at on-sh ps and other soc a ro es

Mental health

- Sch zophren a and other psychoses; b po ar d sorders, depress on; su -c de; anx ety; posttraumat c stress d sorder

Problem cannabis use

- Cannab s use d sorder

Cannabis use and abuse of other substances

- Abuse of other substances

systematic reviews were identified and assessed for quality using published criteria; only fair- and good-quality reviews were considered by the committee. The committee's conclusions are based on the findings from the most recently published systematic review and all relevant fair- and good-quality primary research published after the systematic review. Where no systematic review existed, the committee reviewed all relevant primary research published between January 1, 1999, and August 1, 2016. Primary research was assessed using standard approaches (e.g., Cochrane Quality Assessment, Newcastle–Ontario scale) as a guide.

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited time frame while adhering to the National

Academies' high standards for the quality and rigor of committee reports. Readers of this report should recognize two important points. First, the committee was not tasked to conduct multiple systematic reviews, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search; assessments by more than one person of the quality (risk of bias) of key literature and the conclusions; prespecification of the questions of interest before conclusions were formulated; standard language to allow comparisons between conclusions; and declarations of conflict of interest via the National Academies conflict-of-interest policies. Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the time frame available to the committee. Furthermore, very good research may not be reflected in this report because it did not directly address the health endpoint research questions that were prioritized by the committee.

This report is organized into four parts and 16 chapters. Part I: Introduction and Background, Part II: Therapeutic Effects (Therapeutic Effects of Cannabis and Cannabinoids), Part III: Other Health Effects, and Part IV: Research Barriers and Recommendations. In Part II, most of the evidence reviewed in Chapter 4 derives from clinical and basic science research conducted for the specific purpose of answering an a priori question of whether cannabis and/or cannabinoids are an effective treatment for a specific disease or health condition. The evidence reviewed in Part III derives from epidemiological research that primarily reviews the effects of smoked cannabis. It is of note that several of the prioritized health endpoints discussed in Part III are also reviewed in Part II, albeit from the perspective of effects associated with using cannabis for primarily recreational, as opposed to therapeutic, purposes.

Several health endpoints are discussed in multiple chapters of the report (e.g., cancer, schizophrenia); however, it is important to note that the research conclusions regarding potential harms and benefits discussed in these chapters may differ. This is, in part, due to differences in the study design of the reviewed evidence, differences in characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across the report's chapters. In drafting the report's conclusions, the committee made an effort to be as specific as possible about the type and/or duration of cannabis or cannabinoid exposure and, where relevant, cross-referenced findings from other report chapters.

REPORT CONCLUSIONS ON THE ASSOCIATION BETWEEN CANNABIS USE AND HEALTH

From their review, the committee arrived at nearly 100 different research conclusions related to cannabis or cannabinoid use and health. Informed by the reports of previous IOM committees,[3] the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoid use (for therapeutic purposes) is an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) is statistically associated with the prioritized health

[3] *Adverse Effects of Vaccines: Evidence and Causality* (IOM, 2012); *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence* (IOM, 2008); *Veterans and Agent Orange: Update 2014* (NASEM, 2016).

BOX S-3
Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeut c effects: There s strong ev dence from random zed contro ed tr a s to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s strong ev dence from random zed contro ed tr a s to support or refute a stat st ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are many support ve find ngs from good-qua ty stud es w th no cred b e oppos ng find ngs. A firm conc us on can be made, and the m tat ons to the ev dence, nc ud ng chance, b as, and confound ng factors, can be ru ed out w th reasonab e confidence.

SUBSTANTIAL EVIDENCE

For therapeut c effects: There s strong ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s strong ev dence to support or refute a stat st - ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are severa support ve find ngs from good-qua ty stud es w th very few or no cred b e oppos ng find ngs. A firm conc us on can be made, but m nor m tat ons, nc ud ng chance, b as, and confound ng factors, cannot be ru ed out w th reasonab e confidence.

continued

BOX S-3 Continued

MODERATE EVIDENCE

For therapeut c effects: There s some ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s some ev dence to support or refute a stat st - ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are severa support ve find ngs from good- to fa r-qua ty stud es w th very few or no cred b e oppos ng find ngs. A genera conc u- s on can be made, but m tat ons, nc ud ng chance, b as, and confound ng factors, cannot be ru ed out w th reasonab e confidence.

LIMITED EVIDENCE

For therapeut c effects: There s weak ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s weak ev dence to support or refute a stat st - ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are support ve find ngs from fa r-qua ty stud es or m xed find ngs w th most favor ng one conc us on. A conc us on can be made, but there s s gn ficant uncerta nty due to chance, b as, and confound ng factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeut c effects: There s no or nsuffic ent ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s no or nsuffic ent ev dence to support or re- fute a stat st ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are m xed find ngs, a s ng e poor study, or hea th endpo nt has not been stud ed at a . No conc us on can be made because of substant a uncerta nty due to chance, b as, and confound ng factors.

endpoints of interest. Box S-3 describes these categories and the general parameters for the types of evidence supporting each category. For a full listing of the committee's conclusions, please see this chapter's annex.

REPORT RECOMMENDATIONS

This is a pivotal time in the world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. The committee has put forth a substantial number of research conclusions on the health effects of cannabis and cannabinoids. Based on their research conclusions, the committee members formulated four recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers. The report's full recommendations are described below.

Address Research Gaps

***Recommendation 1*: To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), public agencies,[4] philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:**

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or under-researched populations, such as children and youth (often described as less than 18 years of age) and older populations (generally over 50 years of age), pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and THC or other cannabinoids.
- Determine the harms and benefits associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential beneficial and harmful health effects of using different forms of cannabis, such

[4] Agencies may include the CDC, relevant agencies of the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA).

as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.
- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other high-priority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.
- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

Improve Research Quality

***Recommendation 2*: To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), agencies of the U.S. Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention, should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research. Workshop objectives should include, but need not be limited to:**

- The development of a minimum dataset for observational and clinical studies, standards for research methods and design, and guidelines for data collection methods.

- Adaptation of existing research-reporting standards to the needs of cannabis research.
- The development of uniform terminology for clinical and epidemiological cannabis research.
- The development of standardized and evidence-based question banks for clinical research and public health surveillance tools.

Improve Surveillance Capacity

***Recommendation 3*: To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts. Potential efforts should include, but need not be limited to:**

- The development of question banks on the beneficial and harmful health effects of therapeutic and recreational cannabis use and their incorporation into major public health surveys, including the National Health and Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System, National Survey on Drug Use and Health, Youth Risk Behavior Surveillance System, National Vital Statistics System, Medical Expenditure Panel Survey, and the National Survey of Family Growth.
- Determining the capacity to collect and reliably interpret data from diagnostic classification codes in administrative data (e.g., *International Classification of Diseases-10*).
- The establishment and utilization of state-based testing facilities to analyze the chemical composition of cannabis and products containing cannabis, cannabinoids, or THC.
- The development of novel diagnostic technologies that allow for rapid, accurate, and noninvasive assessment of cannabis exposure and impairment.
- Strategies for surveillance of harmful effects of cannabis for therapeutic use.

Address Research Barriers

***Recommendation 4*: The Centers for Disease Control and Prevention, National Institutes of Health, U.S. Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda. Committee objectives should include, but need not be limited to:**

- Proposing strategies for expanding access to research-grade marijuana, through the creation and approval of new facilities for growing and storing cannabis.
- Identifying nontraditional funding sources and mechanisms to support a comprehensive national cannabis research agenda.
- Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products.

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ANNEX

Report Conclusions[5]

Chapter 4 Conclusions—Therapeutic Effects of Cannabis and Cannabinoids

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) (4-20)

[5] Numbers in parentheses correspond to chapter conclusion numbers.

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-4b)
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

Chapter 5 Conclusions—Cancer

There is moderate evidence of *no* statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:

- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

Chapter 6 Conclusions—Cardiometabolic Risk

There is limited evidence of a statistical association between cannabis use and:

- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

There is no evidence to support or refute a statistical association between *chronic effects* of cannabis use and:

- The increased risk of acute myocardial infarction (6-1b)

Chapter 7 Conclusions—Respiratory Disease

There is substantial evidence of a statistical association between cannabis smoking and:

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:

- Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

Chapter 8 Conclusions—Immunity

There is limited evidence of a statistical association between cannabis smoking and:

- A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

There is limited evidence of *no* statistical association between cannabis use and:

- The progression of liver fibrosis or hepatic disease in individuals with viral hepatitis C (HCV) (daily cannabis use) (8-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)
- Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) (8-2)
- Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)

Chapter 9 Conclusions—Injury and Death

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- All-cause mortality (self-reported cannabis use) (9-1)
- Occupational accidents or injuries (general, nonmedical cannabis use) (9-2)
- Death due to cannabis overdose (9-4a)

Chapter 10 Conclusions—Prenatal, Perinatal, and Neonatal Exposure

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother (10-1)
- Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

- Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

Chapter 11 Conclusions—Psychosocial

There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impaired academic achievement and education outcomes (11-2)
- Increased rates of unemployment and/or low income (11-3)
- Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

There is limited evidence of a statistical association between *sustained abstinence from* cannabis use and:

- Impairments in the cognitive domains of learning, memory, and attention (11-1b)

Chapter 12 Conclusions—Mental Health

There is substantial evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

There is moderate evidence of *no* statistical association between cannabis use and:

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)

- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

Chapter 13 Conclusions—Problem Cannabis Use

There is substantial evidence that:

- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use (13-2e)
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

There is substantial evidence of a statistical association between:

- Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)
- Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)

There is moderate evidence that:

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors for the development of problem cannabis use (13-2b)
- Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)
- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)

- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

Chapter 14 Conclusions—Cannaabis Use and the Abuse of Other Substances

There is moderate evidence of a statistical association between cannabis use and:

- The development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The initiation of tobacco use (14-1)
- Changes in the rates and use patterns of other licit and illicit substances (14-2)

Chapter 15 Conclusions—Challenges and Barriers in Conducting Cannabis Research

There are several challenges and barriers in conducting cannabis and cannabinoid research, including

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use (15-3)
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)

Part I

Introduction and Background

1

Introduction

Over the past 20 years, significant changes have taken place in the policy landscape surrounding cannabis legalization, production, and use. To date, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions (NCSL, 2016). Eight of these states and the District of Columbia have also legalized cannabis for recreational use. These landmark changes in policy have markedly changed cannabis use patterns and perceived levels of risk. Based on a recent nationwide survey, 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days, and between 2002 and 2015 the percentage of past month cannabis users in this age range has steadily increased (CBHSQ, 2016).

Despite this reported rapid rise in the use of cannabis, both for medical purposes and for recreational use, conclusive evidence regarding the short- and long-term health effects of cannabis use remains elusive. While a myriad of studies have examined cannabis use in all its various forms (Calabria et al., 2010; Whiting et al., 2015, 2016; WHO, 2016), often these research conclusions are not appropriately synthesized, translated for, or communicated to policy makers, health care providers, state health officials, or other stakeholders who have been charged with influencing and enacting policies, procedures, and laws related to cannabis use. Unlike other substances whose use may confer risk, such as alcohol or tobacco, no accepted standards for the safe use or appropriate doses are available to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeu-

tic uses, effectively (Freeman et al., 2014; Marsot et al., 2016). Moreover, studying the potential health impacts of cannabis presents its own set of unique challenges. Current challenges include the existence of certain regulations and policies that restrict access to cannabis products suited for research purposes (e.g., Schedule 1 status; regulatory approvals), the limited availability of funding for comprehensive cannabis research, and crosscutting methodological challenges. Additionally, researchers are often unable to obtain the necessary quantity, quality, or type of cannabis product to address cutting-edge public health research questions.

STUDY CHARGE

Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. In March 2016 the Health and Medicine Division[1] of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was asked to convene a committee of experts to conduct a comprehensive review of literature regarding the health consequences of using cannabis or its constituents that had appeared since the publication of the 1999 Institute of Medicine (IOM) report *Marijuana and Medicine* (IOM, 1999). In addition, the committee was asked to make recommendations for a research agenda that will identify the most critical research questions regarding the association of cannabis use with health outcomes (both harms and benefits) that can be answered in the short term (i.e., within a 3-year time frame), as well as steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions. Of note, throughout this report the committee has attempted to highlight research conclusions that affect certain populations (e.g., pregnant women, adolescents) that may be at greater risk for potential adverse effects of cannabis use. The committee's full statement of task is presented in Box 1-1.

The resulting Committee on the Health Effects of Marijuana included experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, pulmonary, pediatric and adolescent health, immunology, toxicology, preclinical research, epidemiology, systematic review, and public health. (See Appendix E for the biographical sketches of committee members.)

In conducting its work, the committee met six times from March 2016 through December 2016. In conjunction with two of those meet-

[1] As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

BOX 1-1
Statement of Task

The Nat ona Academ es of Sc ences, Eng neer ng, and Med c ne (the Nat ona Academ es) w appo nt an ad hoc comm ttee to deve op a comprehens ve, n-depth rev ew of ex st ng ev dence regard ng the hea th effects of us ng mar juana and/or ts const tuents.

The comm ttee w deve op a consensus report w th two pr mary sect ons: (1) a sect on of the report w summar ze what can be determ ned about the hea th effects of mar juana use and, (2) a sect on of the report w summar ze potent a therapeut c uses of mar juana. The report w a so prov de a background overv ew of the cannab no d/endocannab no d system, h story of use n the Un ted States and the regu at on and po cy andscape. In add t on, the report w out ne and make recommendat ons regard ng a research agenda dent fy ng the most cr t ca research quest ons regard ng the assoc at on of mar juana use w th hea th outcomes (both r sks and therapeut c) that can be answered n the short term (.e., w th n a 3-year t me frame) as we as any steps that shou d be taken n the short term to ensure that suffic ent data are be ng gathered to answer ong-term quest ons (e.g., appropr ate quest ons on arge popu at on surve ance surveys, c n ca data co ect on or other data capture, and reso ut on of barr ers to nkage between survey data and death/morb d ty reg str es to enab e popu at on- eve mor-b d ty and morta ty effects est mates). The comm ttee shou d focus on quest ons and consequences w th the potent a for the greatest pub c hea th mpact, wh e shedd ng ght on the character st cs of mar juana use that mpact both short- and ong-term hea th.

In conduct ng ts work, the comm ttee w conduct a comprehens ve rev ew of the ev dence, us ng accepted approaches of terature search, ev dence rev ew, grad ng and synthes s. Stud es rev ewed regard ng hea th r sks shou d be as broad as poss b e, nc ud ng but not m ted to ep dem o ogy and c n ca stud es, and tox co ogy and an ma stud es when determ ned appropr ate by the comm ttee. The comm ttee w prov de summary determ nat ons regard ng causa ty based on strength of ev dence. Both U.S. and nternat ona stud es may be rev ewed based upon re evance and methodo og ca r gor.

ings, the committee held half-day public information-gathering sessions which allowed the committee to hear from study sponsors, experts, and other stakeholders. These discussions helped to inform the committee's deliberations.

Sponsors of this report include federal, state, philanthropic, and non-governmental organizations. These include the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention (CDC); The Colorado Health Foundation; Mat-Su Health Foundation; National Highway Traffic Safety Administration;

National Institutes of Health/National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; the Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and the Washington State Department of Health.

STUDY CONTEXT AND APPROACH

Over the past 20 years the IOM has published several consensus reports that focused on the health effects of marijuana or addressed marijuana within the context of other drug or substance abuse topics.[2] Two IOM reports that most prominently informed the committee's work were *Marijuana and Health* (IOM, 1982), and the 1999 report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999). Although these reports differed in scope, they were useful in providing a comprehensive body of evidence upon which the current committee could build.

Marijuana and Health (IOM, 1982) was commissioned by the former Secretary of Health and Human Services and the former director of the National Institutes of Health, Joseph Califano, Jr., and Donald S. Fredrickson, respectively. The study's committee was appointed to (1) analyze the potential hazards of marijuana use on user safety and health, (2) analyze data concerning the therapeutic value of marijuana, (3) assess the federal research programs, (4) identify new research directions, and (5) draw conclusions that would assist future policy decision making. The authoring committee concluded that there was evidence indicating that marijuana has a broad range of psychological and biological effects, some of which under certain conditions are harmful to human health, but there was a substantial lack of definitive evidence to characterize the seriousness of harm. The committee's major conclusion was that "what little we know for certain about the effects of marijuana on human health—and all that we have reason to suspect—justifies serious national concern" (IOM, 1982, p. 5). The committee's major recommendation called for an intensification and more comprehensive research effort into the effects of marijuana on the health of the American people.

In 1997 the White House Office of National Drug Control Policy contracted with the IOM to conduct a scientific review of available literature to determine the potential health benefits and risks of marijuana and its constituent cannabinoids. The resulting report, *Marijuana and Medicine* (IOM, 1999), offered several conclusions and recommendations (see Box 1-2) on the effects of isolated cannabinoids, the efficacy of cannabinoid drugs, the influence of psychological effects on therapeutic effects,

[2] See https://www.nap.edu/search/?year=1995&rpp=20&ft=1&term=marijuana (accessed July 2016).

BOX 1-2
***Marijuana and Medicine: Assessing the Science Base* (1999)**
Conclusions and Recommendations

Conclusions:

- At th s po nt, our know edge about the b o ogy of mar juana and cannab - no ds a ows us to make some genera conc us ons:
  - Cannab no ds ke y have a natura ro e n pa n modu at on, contro of movement, and memory.
  - The natura ro e of cannab no ds n mmune systems s ke y mu t - faceted and rema ns unc ear.
  - The bra n deve ops to erance to cannab no ds.
  - An ma research demonstrates the potent a for dependence, but th s potent a s observed under a narrower range of cond t ons than w th benzod azep nes, op ates, coca ne, or n cot ne.
  - W thdrawa symptoms can be observed n an ma s but appear to be m d compared to op ates or benzod azep nes, such as d azepam (Va um).
- The d fferent cannab no d receptor types found n the body appear to p ay d fferent ro es n norma human phys o ogy. In add t on, some effects of cannab no ds appear to be ndependent of those receptors. The var ety of mechan sms through wh ch cannab no ds can nfluence human phys o ogy under es the var ety of potent a therapeut c uses for drugs that m ght act se ect ve y on d fferent cannab no d systems.
- Sc ent fic data nd cate the potent a therapeut c va ue of cannab no d drugs, pr mar y tetrahydrocannab no (THC), for pa n re ef, contro of nau- sea and vom t ng, and appet te st mu at on; smoked mar juana, however, s a crude THC de very system that a so de vers harmfu substances.
- The psycho og ca effects of cannab no ds, such as anx ety reduct on, se- dat on, and euphor a, can nfluence the r potent a therapeut c va ue. Those effects are potent a y undes rab e for certa n pat ents and s tuat ons and benefic a for others. In add t on, psycho og ca effects can comp cate the nterpretat on of other aspects of the drug's effect.
- Numerous stud es suggest that mar juana smoke s an mportant r sk factor n the deve opment of resp ratory d sease. A d st nct ve mar juana w th- drawa syndrome has been dent fied, but t s m d and short ved. The syndrome nc udes rest essness, rr tab ty, m d ag tat on, nsomn a, s eep d sturbance, nausea, and cramp ng.
- Present data on drug use progress on ne ther support nor refute the sug- gest on that med ca ava ab ty wou d ncrease drug abuse. However, th s quest on s beyond the ssues norma y cons dered for med ca uses of drugs and shou d not be a factor n eva uat ng the therapeut c potent a of mar juana or cannab no ds.

continued

BOX 1-2 Continued

Recommendations:

- Research shou d cont nue nto the phys o og ca effects of synthet c and p ant-der ved cannab no ds and the natura funct on of cannab no ds found n the body. Because d fferent cannab no ds appear to have d fferent effects, cannab no d research shou d nc ude, but not be restr cted to, effects attr butab e to THC a one.
- C n ca tr a s of cannab no d drugs for symptom management shou d be conducted w th the goa of deve op ng rap d-onset, re ab e, and safe de- very systems.
- Psycho og ca effects of cannab no ds such as anx ety reduct on and seda- t on, wh ch can nfluence med ca benefits, shou d be eva uated n c n ca tr a s.
- Stud es to define the nd v dua hea th r sks of smok ng mar juana shou d be conducted, part cu ar y among popu at ons n wh ch mar juana use s preva ent.
- C n ca tr a s of mar juana use for med ca purposes shou d be conducted under the fo ow ng m ted c rcumstances: tr a s shou d nvo ve on y short- term mar juana use (ess than 6 months), shou d be conducted n pat ents w th cond t ons for wh ch there s reasonab e expectat on of efficacy, shou d be approved by nst tut ona rev ew boards, and shou d co ect data about efficacy.
- Short-term use of smoked mar juana (ess than 6 months) for pat ents w th deb tat ng symptoms (such as ntractab e pa n or vom t ng) must meet the fo ow ng cond t ons:
  - fa ure of a approved med cat ons to prov de re ef has been documented,
  - the symptoms can reasonab y be expected to be re eved by rap d- onset cannab no d drugs,
  - such treatment s adm n stered under med ca superv s on n a manner that a ows for assessment of treatment effect veness,
  - and nvo ves an overs ght strategy comparab e to an nst tut ona rev ew board process that cou d prov de gu dance w th n 24 hours of a subm s- s on by a phys c an to prov de mar juana to a pat ent for a spec fied use.

SOURCE: IOM, 1999.

physiological risks, marijuana dependence and withdrawal, marijuana as a "gateway drug," and the use of smoked marijuana.

The scientific literature on cannabis use has grown substantially since the publication of *Marijuana and Medicine* in 1999. The current committee conducted an extensive search of relevant databases, including Medline, Embase, the Cochrane Database of Systematic Reviews, and PsycINFO,

FIGURE 1-1 Summary of the committee's process.

and they initially retrieved more than 24,000 abstracts for articles published since the 1999 report that could potentially be relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by "anonymous" authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report. (See Appendix B for details.)

The methodological approach taken by the committee to conduct this comprehensive literature review and meet the objectives outlined in the Statement of Task is detailed in Appendix B and briefly described here. Given the large scientific literature on cannabis, the breadth of the statement of task, and the time constraints of the study, the committee developed an approach that resulted in giving primacy to recently published systematic reviews (since 2011) and high-quality primary research that studied 1 or more of 11 groups of health endpoints (see Figure 1-1 and Box 1-3). For each health endpoint, systematic reviews were identified and assessed for quality using methods adapted from published criteria (Whiting et al., 2016); only reviews that were assessed by the committee as being of good or fair quality were considered in this comprehensive review. The committee's conclusions are based on the findings from the most recently published systematic review and all relevant primary literature that was determined to be fair and good quality that was published after the most recent systematic review. Where no systematic review existed, the committee reviewed all relevant primary research from January 1, 1999, through August 1, 2016. Primary research was evaluated using global assessments of the quality of available studies guided by standard approaches and methodologies (Cochrane Quality Assessment [Higgins et al., 2011], Newcastle–Ontario scale [Wells et al., 2014]). Any deviations from this approach are noted in the relevant chapters. For a comprehensive description of the committee's approach to evaluating the available literature, please refer to Appendix B.

BOX 1-3
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects

- Chron c pa n; cancer, chemotherapy- nduced nausea/vom t ng; anorex a and we ght oss; rr tab e bowe syndrome; ep epsy; spast c ty re ated to mu t p e sc eros s or sp na cord njury; Tourette syndrome; amyotroph c atera sc eros s; Hunt ngton's d sease; Park nson's d sease; dyston a; de-ment a; g aucoma; traumat c bra n njury; add ct on; anx ety; depress on; s eep d sorders; posttraumat c stress d sorder; sch zophren a and other psychoses

Cancer

- Lung cancer; head and neck cancer; test cu ar cancer; esophagea cancer; other cancer

Cardiometabolic risk

- Acute myocard a nfarct on; stroke; metabo c dysregu at on, metabo c syndrome, pred abetes, and d abetes me tus

Respiratory disease

- Pu monary funct on; chron c obstruct ve pu monary d sorder; resp ratory symptoms (nc ud ng chron c bronch t s); asthma

Immunity

- Immune funct on; nfect ous d sease

Informed by the reports of previous IOM committees,[3] the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoid use (for therapeutic purposes) is an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) is statistically associated with the prioritized health endpoints of interest. Box 1-4 describes these categories and the general parameters for the types of evidence supporting each category. The committee used these weight-of-evidence categories in their conclusions.

[3] *Adverse Effects of Vaccines: Evidence and Causality* (IOM, 2012); *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence* (IOM, 2008); *Veterans and Agent Orange: Update 2014* (NASEM, 2016).

Injury and death

- A -cause morta ty; occupat ona njury; motor veh c e crash; overdose njury and death

Prenatal, perinatal, and postnatal exposure to cannabis

- Pregnancy comp cat ons for the mother; feta growth and deve opment; neonata cond t ons; ater outcomes for the nfant

Psychosocial

- Cogn t on (earn ng, memory, attent on, nte gence); academ c ach eve-ment and educat ona outcomes; emp oyment and ncome; soc a re at on-sh ps and other soc a ro es

Mental health

- Sch zophren a and other psychoses; b po ar d sorders, depress on; su -c de; anx ety; posttraumat c stress d sorder

Problem cannabis use

- Cannab s use d sorder

Cannabis use and abuse of other substances

- Abuse of other substances

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited time frame while adhering to the National Academies high standards for the quality and rigor of committee reports.

First, the committee was not tasked with conducting multiple systematic reviews, which would have implied a lengthy and robust series of processes. The committee adopted key features of that process; however, a comprehensive literature search; assessments by more than one person of the quality (risk of bias) of key literature and the conclusions; pre-specification of the questions of interest before conclusions were formulated; standard language to allow comparisons between conclusions; and

BOX 1-4
Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeut c effects: There s strong ev dence from random zed contro ed tr a s to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s strong ev dence from random zed contro ed tr a s to support or refute a stat st ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are many support ve find ngs from good-qua ty stud es w th no cred b e oppos ng find ngs. A firm conc us on can be made, and the m tat ons to the ev dence, nc ud ng chance, b as, and confound ng factors, can be ru ed out w th reasonab e confidence.

SUBSTANTIAL EVIDENCE

For therapeut c effects: There s strong ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s strong ev dence to support or refute a stat st - ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are severa support ve find ngs from good-qua ty stud es w th very few or no cred b e oppos ng find ngs. A firm conc us on can be made, but m nor m tat ons, nc ud ng chance, b as, and confound ng factors, cannot be ru ed out w th reasonab e confidence.

MODERATE EVIDENCE

For therapeut c effects: There s some ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

declarations of conflict of interest via the National Academies' conflict-of-interest policies.

Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the time frame available to the committee. Furthermore, some very good research may not have been reviewed in this report because it did not directly address the specific health endpoint questions formulated by the committee.

For other hea th effects: There s some ev dence to support or refute a stat st - ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are severa support ve find ngs from good- to fa r-qua ty stud es w th very few or no cred b e oppos ng find ngs. A genera conc u- s on can be made, but m tat ons, nc ud ng chance, b as, and confound ng factors, cannot be ru ed out w th reasonab e confidence.

LIMITED EVIDENCE

For therapeut c effects: There s weak ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s weak ev dence to support or refute a stat st - ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are support ve find ngs from fa r-qua ty stud es or m xed find ngs w th most favor ng one conc us on. A conc us on can be made, but there s s gn ficant uncerta nty due to chance, b as, and confound ng factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeut c effects: There s no or nsuffic ent ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s no or nsuffic ent ev dence to support or re- fute a stat st ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are m xed find ngs, a s ng e poor study, or hea th endpo nt has not been stud ed at a . No conc us on can be made because of substant a uncerta nty due to chance, b as, and confound ng factors.

Special Considerations for the Report

Biological Plausibility

After careful consideration, the committee chose not to attempt to review basic, nonhuman research in order to attempt to bolster evidence for identified health outcomes from cannabis exposure. This policy was, in part, dictated by the time constraints available for crafting this report. Also, while basic research is in the end critical for understanding health outcome mechanisms and suggesting new and innovative interventions,

it often cannot explain the large number of null findings, the frequent variation among human study outcomes, the adverse clinical effects seen in some studies, nor the diversity in host susceptibility to cannabis exposure. Given the methodologic variation in the studies reviewed, as well as potential deficiencies in study design and execution, the committee focused its attention and energy on identifying high-quality studies with the best information and lowest risk of bias as the way to ensure that report findings and conclusions were as informative and relevant as possible. In those instances where cannabis-disease associations seemed relatively secure and evidence-based, the committee believed that the findings would have clinical and public health importance even in the absence of supporting basic studies. Similarly, for those experimental studies where causation could be more explicitly determined—mostly in the area of therapeutics—these findings, if sufficiently robust and replicable, were deemed to stand on their own whether or not bolstered with mechanistic or biologically plausible underpinnings.

Considerations of Observational Studies

The vast majority of the systematic reviews, meta-analyses, and primary literature reviewed in Part III: Other Health Effects consists of observational studies. This is in contrast to the literature base in other fields such as therapeutics (discussed in Part II: Therapeutic Effects). As such, it was not possible to restrict the literature reviews to those that synthesized evidence from randomized clinical trials (RCTs). The methodology used for systematic reviews and meta-analysis originates in the synthesis of data from RCTs, where methodology is highly standardized and structured. The synthesis of observational studies presents some challenges that have not been fully met, arising, in part, out of the greater variety in study design.

Exposure measurement is always an additional concern when evaluating comprehensive reviews of observational studies. Assessment of cannabis exposure is particularly challenging because of its illegal status (in most settings) and the reliance on self-report. Inherent difficulties in accurately assessing the exposure in terms of dose, specific type of cannabis product used, mode of intake, duration, frequency, and other variables result in the variability in definitions used to operationalize cannabis exposure. Additionally, observational studies often have to contend with confounders related to polysubstance use, which obscures the ability to answer questions about the effects of "cannabis only" on the health effects. Moreover, in some cases, samples included different populations (i.e., adolescents versus adults), cannabis-use history (i.e., chronic versus

acute), and patterns of use (i.e., frequency, dose, quantity)—all of which provide mixed or inconsistent evidence as to the effects of cannabis on a specific outcome. Additional limitations include a lack of longitudinal assessments and small study cohorts.

There is also a concern about the broad reporting standards across cannabis research fields. For example, several systematic reviews on cognition discussed in the report's Psychosocial chapter did not consistently describe the methods for scoring the evidence for each endpoint. That is, the reviews include scores of the strength and consistency of the evidence for each outcome, but they provided less information about issues such as study design and statistical analyses. As a result, the committee found that the reviews did not include the conventional data generally found within quantitatively-based systematic examinations of a topic, or such as would be found in meta-analytic reviews. Reasons for this may include variations in study methodologies, instrumentation, populations, or research designs.

Despite these special considerations regarding the use of systematic reviews, meta-analyses, and primary literature of observational studies, the committee determined that using recent good- or fair-quality systematic reviews was the most appropriate approach to adequately address the committee's broad statement of task and comprehensive, prioritized research questions while maintaining a high standard for quality and rigor. For additional information on these considerations, please see Box 11-2 in Chapter 11 (Psychosocial) and Box 12-2 in Chapter 12 (Mental Health).

Comparing Harms and Benefits of Cannabis Use

Several health endpoints are discussed in multiple chapters of the report (e.g., cancer, schizophrenia); however, it is important to note that the research conclusions regarding potential harms and benefits discussed in these chapters may differ. This is, in part, due to differences in the study design of the reviewed evidence, differences in characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across the report's chapters. In drafting the report's conclusions, the committee made an effort to be as specific as possible about the type and/or duration of cannabis or cannabinoid exposure and, where relevant, cross-referenced findings from other report chapters.

Key Definitions

The terms "marijuana" and "cannabis" are often used interchangeably, particularly within the United States; however, these are two separate entities. Cannabis is a broad term that can be used to describe organic products (e.g., cannabinoids,[4] marijuana,[5] hemp[6]) derived from the *Cannabis sativa* plant. These products exist in various forms and are used for a number of different purposes (e.g., medical, industrial, recreational). Given its broad potential, the all-encompassing word "cannabis" has been adopted as the standard terminology within scientific and scholarly communities. The committee uses the term "cannabis" rather than "marijuana" throughout this report.

The committee notes the existence of "cannabimimetic agents" (often referred to as "K2" or "Spice") which are made up of dried plant matter sprayed with synthetic chemicals that mimic the effect of THC by interacting with cannabinoid receptors in the brain (King, 2014). At the request of the study sponsors, nontherapeutic synthetic cannabinoids are not considered in this study.

REPORT ORGANIZATION

This report is organized into four parts and 16 chapters. Part I: Introduction and Background (Chapters 1–3) provides an overview of the origin, purpose, and organization of the report, as well as essential information on cannabis and cannabis-derived medications and products, and the history and current state of federal and state cannabis policy. In addition to this Introduction (Chapter 1), Chapter 2 (Cannabis) reviews the biology of cannabis and its constituent compounds, exploring the biochemistry of the marijuana plant, its derivatives, and the different routes of administration. Additionally, this chapter provides an overview of synthetic versions of cannabis, including U.S. Food and Drug Administration–approved medicinal synthetics and manufactured cannabis (street drugs such as K2, Spice). Chapter 3 (Cannabis: Prevalence of Use, Regulation, and Current Policy Landscape) provides an overview of cannabis use in the United States and reviews policy related to cannabis legislation.

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[4] Cannabinoids are a group of active chemical compounds found in cannabis. Among the more than 100 different types of cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD) (Small, 2015).

[5] In general, marijuana refers only to parts of the plant or derivative products that contain substantial levels of tetrahydrocannabinol (THC), the chemical compound that is found in the highest concentrations in the cannabis plant and which is primarily responsible for the plant's intoxicative qualities (Small, 2015).

[6] Under U.S. law, cannabis plants with very low levels of THC (not more than 0.3 percent) are not considered marijuana but instead "industrial hemp" (Small, 2015).

Part II: Therapeutic Effects (Chapter 4—Therapeutic Effects of Cannabis and Cannabinoids) discusses the health effects of cannabis and cannabinoids used for therapeutic purposes in relation to the most commonly reported conditions for medical cannabis use (in states where usage is legal), as well as the current qualifying ailments recognized by state medical marijuana programs. Most of the evidence reviewed in this chapter derives from clinical and basic science research conducted for the specific purpose of answering an a priori question of whether cannabis and/or cannabinoids are an effective treatment for a specific disease or health condition. The vast majority of these studies examined the potential therapeutic effect of cannabinoids (e.g., FDA-approved synthetics) rather than smoked cannabis.

Part III: Other Health Effects (Chapters 5–14) discusses the health effects of cannabis and/or cannabis-derived products used for primarily recreational and other nontherapeutic purposes. Most of the evidence reviewed in Part III derives from epidemiological research primarily focusing on smoked cannabis. It is of note that several of the prioritized health conditions discussed in Part III are also reviewed in Part II, albeit from the perspective of effects associated with using cannabis for primarily recreational, as opposed to therapeutic, purposes. A bulleted list of chapter highlights are included in the introduction of the chapters in Part II and Part III of the report.

Within Part III, the effects of cannabis use on cancer incidence are discussed in Chapter 5. Chapter 6 addresses cardiometabolic risks of cannabis use, including effects on acute myocardial infarction, stroke, and metabolic effects—metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes mellitus. Respiratory disease—pulmonary function, chronic obstructive pulmonary disease, respiratory symptoms including chronic bronchitis, and asthma—are discussed in Chapter 7. Immunity and infection are discussed in Chapter 8. The effects of cannabis use on overall mortality, overdose death, employment injuries, and motor vehicle crashes are reviewed in Chapter 9 (Injury and Death). Prenatal, perinatal, and neonatal effects are discussed in Chapter 10. Psychosocial effects, including the effects of cannabis on learning, memory, attention, academic achievement, employment and income, and social relationships and social roles are discussed in Chapter 11, and mental health conditions, including schizophrenia and other psychosis, bipolar disorder, depression, suicide, anxiety, and posttraumatic stress disorder are discussed in Chapter 12. Chapter 13 discusses problem cannabis use, including cannabis use disorder, and the abuse of other substances is discussed in Chapter 14.

Part IV: Research Barriers and Recommendations (Chapters 15–16) reviews the regulatory barriers and methodological challenges that hinder cannabis research, and recommends the actions necessary to successfully

implement a comprehensive cannabis research agenda. Chapter 15 provides an overview of barriers to studying cannabis, including regulatory, policy, and financial, as well as of methodological challenges, and Chapter 16 outlines the committee's proposed research agenda, detailing both short-term and long-term objectives.

Appendixes A–E contain the report glossary, details about the committee's search strategy, systematic reviews considered in this report, open session agendas, and biographical sketches of committee and staff members.

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2

Cannabis

HISTORY OF CANNABIS

Cannabis sativa is one of the world's oldest cultivated plants (Russo, 2007). Although the earliest written records of the human use of cannabis date from the 6th century B.C. (ca. 2,600 cal BP), existing evidence suggests that its use in Europe and East Asia started in the early Holocene (ca. 8,000 cal BP) (Long et al., 2016). Many 19th-century practitioners ascribed medicinal properties to cannabis after the drug found its way to Europe during a period of colonial expansion into Africa and Asia. For example, William B. O'Shaughnessy, an Irish physician working at the Medical College and Hospital in Calcutta, first introduced cannabis (Indian hemp) to Western medicine as a treatment for tetanus and other convulsive diseases (O'Shaughnessy, 1840). At approximately the same time, French physician Jean-Jacques Moreau de Tours experimented with the use of cannabis preparations for the treatment of mental disorders (Moreau de Tours, 1845). Soon after, in 1851, cannabis was included in the 3rd edition of the *Pharmacopoeia of the United States* (USP). Subsequent revisions of the USP described in detail how to prepare extracts and tinctures of dried cannabis flowers to be used as analgesic, hypnotic, and anticonvulsant (Russo, 2007; U.S. Pharmacopoeial Convention, 1916). Growing concerns about cannabis resulted in the outlawing of cannabis in several states in the early 1900s and federal prohibition of the drug in 1937 with the passage of the Marihuana Tax Act. In response to these concerns, in 1942 the American Medical Association removed cannabis from the 12th edition of *U.S. Pharmacopeia* (IOM, 1999).

THE CANNABIS PLANT

Cannabis cultivars are considered as part of one genus, *Cannabis*, family Cannabaceae, order Urticales (Kuddus et al., 2013). Two accepted genera of Cannabaceae are Cannabis and Humulus (hops). There is, however, an ongoing debate concerning the taxonomic differentiation within the *Cannabis* genus (Laursen, 2015). On the basis of genetic variations, a multitypic genus with at least two putative species, *Cannabis sativa* and *Cannabis indica*, has been proposed by some researchers (Clarke and Merlin, 2015; Hillig, 2005). Other researchers have suggested a unique species *Cannabis sativa* with the genetic differences explained by variations at both the subspecies and the variety level or at a biotype level of putative taxa (Small, 2015).

Chemical Constituents of Cannabis

To date, more than 104 different cannabinoids[1] have been identified in cannabis (ElSohly and Gul, 2014). Other compounds identified include terpenoids, flavonoids, nitrogenous compounds, and more common plant molecules (American Herbal Pharmacopoeia, 2013). Among these, Δ^9-tetrahydrocannabinol (THC) has received the most attention for being responsible for the intoxicated state sought after by recreational cannabis users, owing to its ability to act as a partial agonist[2] for type-1 cannabinoid (CB_1) receptors. Cannabinoids exist mainly in the plant as their carboxylic precursors (Δ^9-tetrahydrocannabinolic acid [THCA] and cannabidiolic acid [CBDA]) and are decarboxylated by light or heat while in storage or when combusted (Grotenhermen, 2003). Δ^9-THC is synthesized within the glandular trichomes present in the flowers, leaves, and bracts of the female plant. It shares a common precursor, olivetoic acid, with another quantitatively important constituent of *Cannabis sativa*, cannabidiol (CBD), which is the most abundant cannabinoid in hemp (see Figure 2-1). For this reason, the genetic profile and relative level of expression of the enzymes responsible for their synthesis (genotype), namely THCA synthase and CBDA synthase, determine the chemical composition of a particular cultivar (chemotype).

Cannabis plants typically exhibit one of the three main different chemotypes based on the absolute and relative concentrations of Δ^9-THCA and CBDA (see Table 2-1), which makes it possible to distinguish among the Δ^9-THC-type, or drug-type; the intermediate-type; and the CBD-type

[1] Cannabinoids are a group of psychoactive chemical compounds found in the cannabis plant.

[2] Partial agonists are ligands that interact with their receptors to produce a level of response that is less than the response to full agonists.

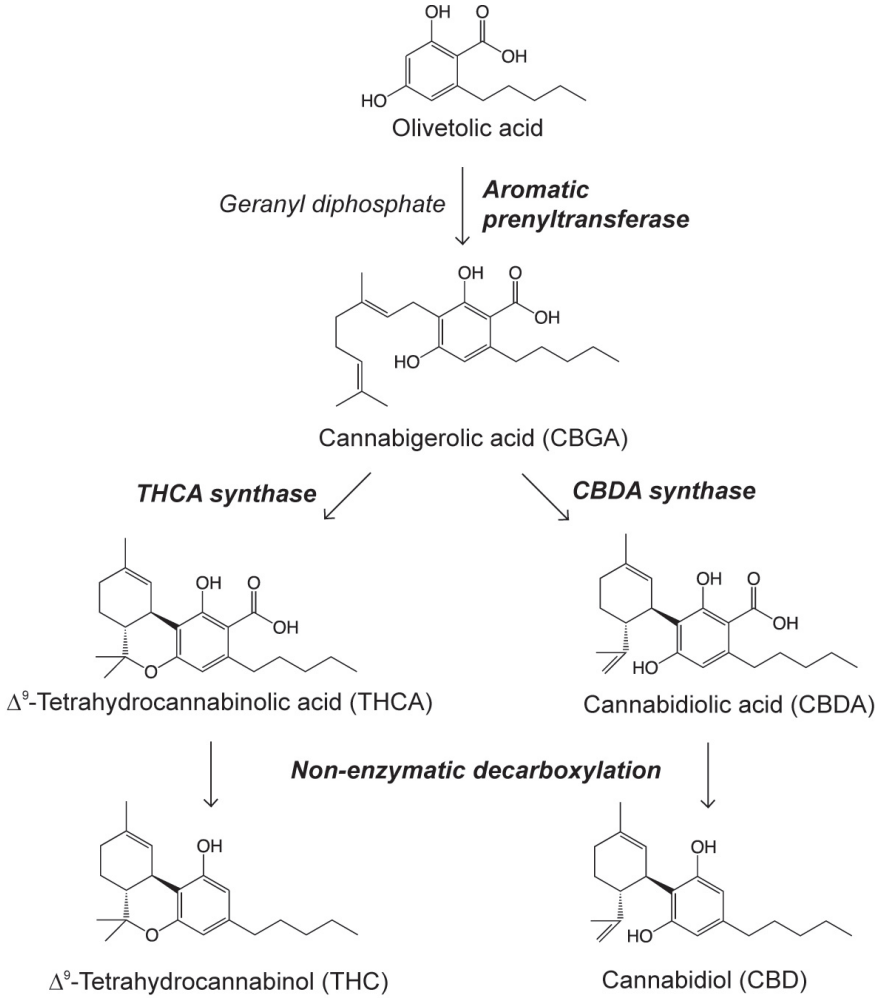

FIGURE 2-1 Synthetic pathway of the main cannabinoids, Δ^9-THC and CBD, from the common precursor, olivetol.

cannabis plants grown for fiber (industrial hemp) or seed oil in which the content of Δ^9-THC does not exceed 0.3 percent on a dry-weight basis (Chandra et al., 2013). CBD is pharmacologically active, however, and, therefore, classifying cannabis in terms of drug- and fiber-producing seems inaccurate. Both THC- and CBD-types are considered drug-types, and both cultivars could theoretically be exploited to produce fiber.

TABLE 2-1 Cannabis Phenotypes

Chemotype	Δ^9-THC	CBD	CBD: Δ^9-THC ratio
THC-type	0.5–15%	0.01–0.16%	<0.02
Hybrid	0.5–5%	0.9–7.3%	0.6–4
CBD-type	0.05–0.7%	1.0–13.6%	>5

NOTE: THCA-predominant strains can yield more than 25 percent Δ^9-THC; specifically selected CBDA clones can yield up to 20 percent CBD.
SOURCE: Modified from Galal et al., 2009.

Pharmacological Properties of Δ^9-THC

In a series of studies conducted in the late 1930s and early 1940s, Roger Adams and coworkers isolated cannabinol and CBD from hemp oil and then isomerized CBD into a mixture of two tetrahydrocannabinols with "marihuana-like" physiological activity in dogs, proving their structure except for the final placement of one double bond (Adams et al., 1940a,b). Two years later, tetrahydrocannabinol was first isolated from cannabis resin (Wollner et al., 1942). In 1964, thanks to the development of such potent analytical techniques as nuclear magnetic resonance imaging, Gaoni and Mechoulam were able to identify the position of this elusive double bond, thus resolving the final structure of Δ^9-THC (Gaoni and Mechoulam, 1964).

In the late 1980s William Devane and Allyn Howlett first postulated the existence of cannabinoid receptors by showing how synthetic molecules designed to mimic the actions of Δ^9-THC were able to bind a selective site in brain membranes, thus inhibiting the intracellular synthesis of cyclic adenosine monophosphate (cAMP) through a G protein–mediated mechanism (Devane et al., 1988). The mapping of cannabinoid-binding sites in the rat brain (Herkenham et al., 1990) and the molecular cloning of the first cannabinoid receptor gene (Matsuda et al., 1990) subsequently corroborated this hypothesis. Three years later, a second G protein–coupled cannabinoid receptor was cloned from a promyelocytic cell line and termed CB_2 (Munro et al., 1993).

Both CB_1 and CB_2 signal through the transducing G proteins, G_i and G_o, and their activation by Δ^9-THC or other agonists causes the inhibition of adenylyl cyclase activity, the closing of voltage-gated calcium channels, the opening of inwardly rectifying potassium channels, and the stimulation of mitogen-activated protein kinases such as extracellular signal–regulated kinases (ERKs) and focal adhesion kinases (FAKs) (Mackie, 2006).

The expression pattern of CB_1 receptors in brain structures correlates with the psychoactive effects of cannabis. In mammals, high concen-

trations of CB_1 are found in areas that regulate appetite, memory, fear extinction, motor responses, and posture such as the hippocampus, basal ganglia, basolateral amygdala, hypothalamus, and cerebellum (Mackie, 2006). CB_1 is also found in a number of nonneural tissues, including the gastrointestinal tract, adipocytes, liver, and skeletal muscle. In addition to CB_1, the brain also contains a small number of CB_2 receptors, although this subtype is mainly expressed in macrophages and macrophage-derived cells such as microglia, osteoclasts, and osteoblasts (Mackie, 2006).

Pharmacological Properties of Cannabidiol

Cannabidiol was first isolated from hemp oil in 1940 (Adams et al., 1940a) and its structure predicted by chemical methods (Adams et al., 1940b); its fine structure was determined in later studies (Mechoulam and Shvo, 1963). CBD lacks the cannabis-like intoxicating properties of Δ^9-THC and, for this reason, has been traditionally considered non-psychoactive. CBD displays very low affinity for CB_1 and CB_2 cannabinoid receptors (Thomas et al., 2007), but it might be able to negatively modulate CB_1 via an allosteric mechanism (Laprairie et al., 2015)[3]; however, CBD can interfere with the deactivation of the endocannabinoid molecule anandamide, by targeting either its uptake or its enzymatic degradation, catalyzed by fatty-acid amide hydrolase (FAAH), which could indirectly activate CB_1 (De Petrocellis et al., 2011; Elmes et al., 2015) (see Box 2-1).

CBD is also a known agonist of serotonin 5-HT1A receptors (Russo et al., 2005) and transient receptor potential vanilloid type 1 (TRPV1) receptors (Bisogno et al., 2001). It can also enhance adenosine receptor signaling by inhibiting adenosine inactivation, suggesting a potential therapeutic role in pain and inflammation (Carrier et al., 2006). The antioxidant and anti-inflammatory properties of this compound may explain its potential neuroprotective actions (Scuderi et al., 2009). Irrespective of the mechanism of action, there is evidence that CBD could potentially be exploited in the treatment and symptom relief of various neurological disorders such as epilepsy and seizures (Hofmann and Frazier, 2013; Jones et al., 2010), psychosis (Leweke et al., 2016), anxiety (Bergamaschi et al., 2011), movement disorders (e.g., Huntington's disease and amyotrophic lateral sclerosis) (de Lago and Fernandez-Ruiz, 2007; Iuvone et al., 2009), and multiple sclerosis (Lakhan and Rowland, 2009).

[3] Allosteric modulators are ligands that indirectly influence the effects of an agonist or inverse agonist at a target receptor. Allosteric modulators bind to a site distinct from that of the orthosteric agonist binding site.

BOX 2-1
Endocannabinoids and Their Signaling Systems

There are two endocannab no ds, 2-arch donoy g ycero (2-AG) and anandam de.

2-AG

2-AG s generated by the enzymat c act v ty of a membrane-assoc ated d acy - g ycero pase (DGL), wh ch converts Sn2-arach don c ac d conta n ng d acy g yc- ero s nto 2-AG (see F gure 2-2). Two soforms of DGL, a pha and beta, have been dent fied. The a pha soform generates 2-AG ut zed dur ng neurona deve opment and for synapt c commun cat on between neurons, wh e the beta soform may contr bute to both bra n deve opment and nflammat on. The act v ty of DGL-α s regu ated by ntrace u ar ca c um, g utath one, and ce u ar oca zat on, and v a posttrans at ona mod ficat on. Once produced, 2-AG can act v a both CB_1 and CB_2 receptors to exert a range of b o og ca effects n centra and per phera ce s.

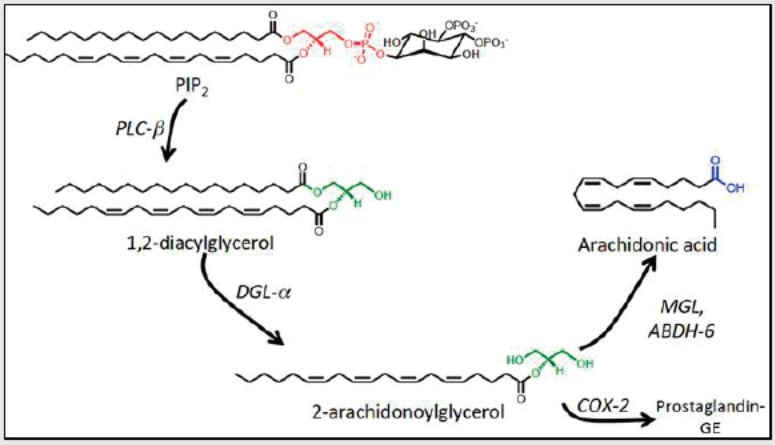

FIGURE 2-2 Pathways of 2 AG formation and deactivation

2-AG s pr mar y degraded by monoacy g ycero pase (MGL) nto free arach - don c ac d and g ycero . In the centra nervous system (CNS), the free arach don c ac d generated by MGL-med ated hydro ys s of 2-AG may serve as a precursor for the generat on of prostag and ns by cyc ooxygenases. The act v ty of MGL can be regu ated by posttrans at ona mod ficat on (e.g., su feny at on). There s a so ev dence that 2-AG can be oxygenated by cyc ooxygenase-2 to generate prostag and n g ycero s.

Anandamide

The format on of anandam de nvo ves two steps (see F gure 2-3). The first cons sts of the transfer of arach don c ac d from phosphat dy cho ne (PC) to phosphat dy ethano am ne (PE). Th s react on s cata yzed by the *N*-acy transferase PLA2G4E and y e ds a d verse group of *N*-arach donoy -subst tuted PE spec es (NAPEs). The second step s the c eavage of NAPEs to produce anandam de and may be med ated by e ther NAPE-spec fic phospho pase D (NAPE-PLD) or a pha/beta-hydro ase doma n-4 (ABHD-4). PLA2G4E may represent the rate- m t ng step for anandam de format on, though add t ona work s needed to confirm th s poss b ty. After re ease nto the extrace u ar m eu, anandam de s captured by neurons and g a through carr er-med ated transport and s subsequent y hydro- yzed to arach don c ac d by fatty ac d am de hydro ase (FAAH), a postsynapt c ser ne hydro ase expressed throughout the CNS. In m crog a, anandam de m ght be a so degraded by the ysosoma cyste ne hydro ase, *N*-acy ethano am ne ac d am dase (NAAA).

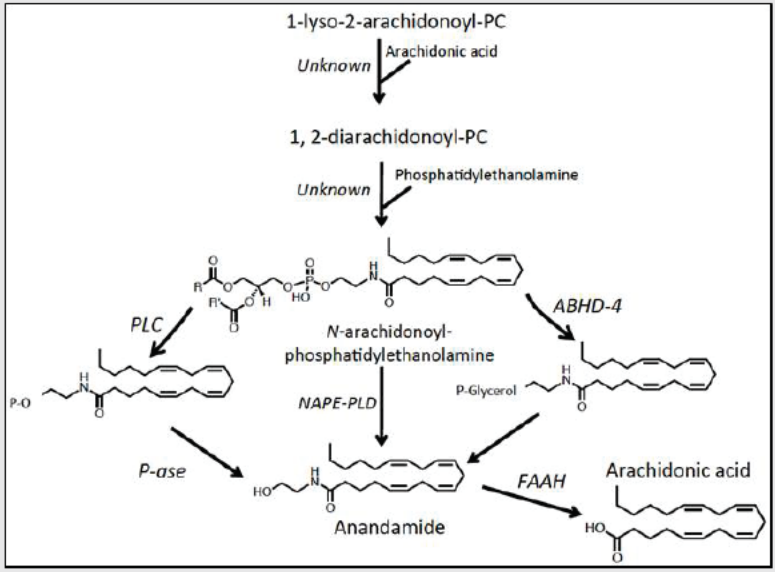

FIGURE 2-3 Pathways of anandamide formation and deactivation

Endocannabinoid Synaptic Signaling (CB_1) (A Central Example)

One of the best-stud ed forms of endocannab no d s gna ng occurs at CNS synapses. There are severa un que features of endocannab no d s gna ng re at ve to am no ac d and pept de-based neurotransm tters. F rst, endocannab no d s gna - ng occurs n a retrograde d rect on, .e., the s gna ng s n t ated n postsynapt c neurons and acts upon presynapt c term na s. Th s s n stark contrast to trad t ona

continued

BOX 2-1 Continued

anterograde chem ca neurotransm ss on, wh ch s n t ated at the axon term na and conveys s gna s to postsynapt c neurons w th n a connected neurona c rcu t or system. A second un que feature of th s system s that, n contrast to c ass ca neurotransm tters, endocannab no ds are not preformed and stored n ves c es pend ng re ease. In contrast, they are produced "on demand" upon st mu at on of postsynapt c ce s through a var ety of s gna s.

The ro e of 2-AG n med at ng endocannab no d synapt c s gna ng has been we estab shed dur ng the past decade. Indeed, at exc tatory synapses, a key components of 2-AG-med ated s gna ng (DGL-α, MGL, CB_1 receptor) are dea y oca zed to fac tate retrograde contro of neurotransm tter re ease. Spec fica y, DGL-α s found n postsynapt c sp nes wh e MGL and CB_1 are ocated n axon term na s. The act v ty of DGL-α can be ncreased by st mu at on of Gq-coup ed-neurotransm tter receptors (e.g., metabotrop c g utamate receptors) or by a ca - c um nflux. Once act ve, DGL-α generates 2-AG at the ce membrane, wh ch trave s n a retrograde d rect on to the presynapt c term na to nteract w th CB_1. The act vat on of CB_1 by 2-AG resu ts n a reduct on n presynapt c re ease probab ty predom nant y v a G /o-dependent s gna transduct on cascades. Th s synapt c depress on can ast for seconds to m nutes or onger, depend ng on the durat on of receptor st mu at on and the spec fic types of downstream s gna ng cascades n t ated. After nteract ng w th the receptor, 2-AG s hydro yzed pr mar y by MGL ocated n the cytoso of the presynapt c axon term na . MGL n astrocytes may a so contr bute to the term nat on of 2-AG-med ated synapt c s gna ng.

There s a so ev dence that anandam de can act as a retrograde modu ator of neurotransm tter re ease n a manner s m ar to 2-AG, but w th some d st nct d fferences that are suggest ve of a broader paracr ne mode of act on.

SOURCE: Piomelli, 2015.

CANNABIS-DERIVED PRODUCTS

In the United States, cannabis-derived products are consumed for both medical and recreational purposes in a variety of ways. These include smoking or inhaling from cigarettes (joints), pipes (bowls), water pipes (bongs, hookahs), and blunts (cigars filled with cannabis); eating or drinking food products and beverages; or vaporizing the product. These different modes are used to consume different cannabis products, including cannabis "buds" (dried cannabis flowers); cannabis resin (hashish, bubble hash); and cannabis oil (butane honey oil, shatter, wax, crumble). The oil, which may contain up to 75 percent Δ^9-THC—versus 5 to 20 percent in the herb or resin (Raber et al., 2015)—is extracted from plant material using organic solvents, such as ethanol, hexane, butane, or supercritical

(or subcritical) CO_2, and can be either smoked or vaporized by pressing the extracted oil against the heated surface of an oil rig pipe (dabbing). Cannabinoids can also be absorbed through the skin and mucosal tissues, so topical creams, patches, vaginal sprays, and rectal suppositories are sometimes employed and used as a form of administering Δ^9-THC (Brenneisen et al., 1996). A broad selection of cannabis-derived products are also available in the form of food and snack items, beverages, clothing, and health and beauty aid products.

Potency of Cannabis

In the 1990s and early 2000s, the bulk of cannabis consumed in the United States was grown abroad and illicitly imported. The past decade has seen an influx of high-potency cannabis produced within the United States—for example, "sinsemilla"—which is grown from clones rather than from seeds. Data from the U.S. Drug Enforcement Administration (DEA) seizures record a substantial increase in average potency, from 4 percent in 1995 to roughly 12 percent in 2014, both because high-quality U.S.-grown cannabis has taken market share from Mexican imports and because cannabis from both sources has grown in potency (ElSohly et al., 2016; Kilmer, 2014).

Route of Administration

The route of administration of cannabis can affect the onset, intensity, and duration of the psychotropic effects, the effects on organ systems, and the addictive potential and negative consequences associated with its use (Ehrler et al., 2015). The consumption of cannabis causes a particular combination of relaxation and euphoria, commonly referred to as a "high." When cannabis is smoked, Δ^9-THC quickly diffuses to the brain, eliciting a perceived high within seconds to minutes. Blood levels of Δ^9-THC reach a maximum after about 30 minutes and then rapidly subside within 1 to 3.5 hours (Fabritius et al., 2013; Huestis et al., 1992). Vaping has an onset, peak, and duration that are similar to those of smoking and produces a similar high (Abrams et al., 2007). "Dabbing," a term for flash-vaporizing butane hash oil-based concentrates, has been reported to offer a different and stronger intoxicating effect than smoking/vaping (Loflin and Earleywine, 2014). By contrast, eating does not produce effects for 30 minutes to 2 hours, and the perceived high is relatively prolonged, lasting 5 to 8 hours or even longer. The slow action of orally ingested cannabis is due to Δ^9-THC being absorbed by the intestine and transported to the liver (hepatic first pass) where it is converted into 11-OH-THC, an equipotent and longer-lasting metabolite (Huestis et al., 1992). Edibles make

it harder to titrate the intoxicating effects due to the delayed and variable onset. Consequently, edibles have been tied to the ingestion of excessive amounts of cannabis under the misperception that the initial dose had not produced the desired effect (Ghosh and Basu, 2015; MacCoun and Mello, 2015). The availability of edibles has also been associated with increased rates of accidental pediatric ingestion of cannabis (Wang et al., 2014).

Trends in Routes of Administration

There are no high-quality nationally representative data on the prevalence of the non-herbal forms of cannabis (e.g., edibles, oils, and other concentrates), but evidence suggests that they are more commonly used by medical cannabis patients in states with recreational or lenient medical cannabis policies (Daniulaityte et al., 2015; Pacula et al., 2016). Forty percent of 12th-grade past-year users reported using cannabis in edible form in medical cannabis states, versus 26 percent in states without medical cannabis laws (NIDA, 2014). In Washington State, an online survey from 2013 found that, among daily and near-daily cannabis users, 27.5 percent had used edibles, 22.8 percent had used hash resin, and 20.4 percent had "dabbed" in the past week (Kilmer et al., 2013).

Data from recreational cannabis sales in Washington and Colorado provide a glimpse of trends that are specific to markets that have legalized cannabis. In Washington State, herbal cannabis remains dominant, having accounted for two-thirds of all sales revenues in June 2016, but it is losing market share as "cannabis extracts for inhalation" become more popular, at 21 percent in June 2016 as compared with 12 percent 1 year prior. The sales of liquid and solid edibles (9 percent) combined account for most of the remaining sales.[4] Non-herbal varieties are even more popular on Colorado's recreational market, where herbal cannabis accounts for a narrow majority (56 percent) and sales of solid concentrates (24 percent) and edibles (13 percent) are on the rise (Castle, 2016).

Partly to provide a guide for the responsible use of non-herbal varieties of cannabis, states that have legalized the recreational cannabis have defined a standard "dose" of THC. Washington State and Colorado have set the standard "dose" of THC as 10 mg, while Oregon chose a lower limit of 5 mg. For perspective, the typical joint size in the United States is 0.66 g (Mariani et al., 2011) and the average potency is 8 percent THC (Fabritius et al., 2013), resulting in an average dose of 8.25 mg THC per joint; higher THC levels ranging from 15–20 percent or higher would yield

[4] Author's calculations from Washington State Liquor and Cannabis Board's publicly available August 2016 "traceability" dataset ("biotrackthc_dispensing.csv"). Data requests available at: http://lcb.wa.gov/records/public-records (accessed January 5, 2017).

a THC dose between 9.9–13.2 mg. Occasional users report feeling "high" after consuming only 2–3 mg of THC (Hall and Pacula, 2010); however, users who have developed tolerance to the effects of THC via frequent use may prefer much larger quantities.

CLINICAL FEATURES OF CANNABIS INTOXICATION

During acute cannabis intoxication, the user's sociability and sensitivity to certain stimuli (e.g., colors, music) may be enhanced, the perception of time is altered, and the appetite for sweet and fatty foods is heightened. Some users report feeling relaxed or experiencing a pleasurable "rush" or "buzz" after smoking cannabis (Agrawal et al., 2014). These subjective effects are often associated with decreased short-term memory, dry mouth, and impaired perception and motor skills. When very high blood levels of Δ^9-THC are attained, the person may experience panic attacks, paranoid thoughts, and hallucinations (Li et al., 2014). Furthermore, as legalized medical and recreational cannabis availability increase nationwide, the impairment of driving abilities during acute intoxication has become a public safety issue.

In addition to Δ^9-THC dosage, two main factors influence the intensity and duration of acute intoxication: individual differences in the rate of absorption and metabolism of Δ^9-THC, and the loss of sensitivity to its pharmacological actions. Prolonged CB_1 receptor occupation as a consequence of the sustained use of cannabis can trigger a process of desensitization, rendering subjects tolerant to the central and peripheral effects of Δ^9-THC and other cannabinoid agonists (Gonzalez et al., 2005). Animals exposed repeatedly to Δ^9-THC display decreased CB_1 receptor levels as well as impaired coupling between CB_1 and its transducing G-proteins (Gonzalez et al., 2005). Similarly, in humans, imaging studies have shown that chronic cannabis use leads to a down-regulation of CB_1 receptors in the cortical regions of the brain and that this effect can be reversed by abstinence (Hirvonen et al., 2012).

CANNABINOID-BASED MEDICATIONS

The U.S. Food and Drug Administration (FDA) has licensed three drugs based on cannabinoids (see Table 2-2). Dronabinol, the generic name for synthetic Δ^9-THC, is marketed under the trade name of Marinol® and is clinically indicated to counteract the nausea and vomiting associated with chemotherapy and to stimulate appetite in AIDS patients affected by wasting syndrome. A synthetic analog of Δ^9-THC, nabilone (Cesamet®), is prescribed for similar indications. Both dronabinol and nabilone are given orally and have a slow onset of action. In July 2016 the

TABLE 2-2 Cannabinoid-Based Medications

	CANNABINOID-BASED MEDICATIONS		
	Substance	Route of Administration	**Description**
Natural Product Derived Compounds	Cannabidiol (CBD)	Oral capsule Oromucosal spray	Cannabinoid extracted from *Cannabis* plant
	Cannabis	Multiple	Multiple active cannabinoids
	Cannador	Oral capsule	THC and CBD from *Cannabis* extract
	Epidiolex® (FDA Fast Track)	Oil	Concentrated CBD from *Cannabis* extract
	Nabiximol (Sativex®) (FDA Fast Track)	Oromucosal spray	THC and CBD extract from two *Cannabis* plant varieties
	Tetrahydrocannabinol (THC)	Oral capsule Smoked Oromucosal spray	Active cannabinoid of *Cannabis* plant
	THC/CBD	Oral capsule	Combination of cannabinoids
Synthetic Compounds	Ajulemic acid (AjA) (FDA PHASE II Active)	Oral capsule	Synthetic nonpsychoactive cannabinoid
	Dronabinol (Marinol®; Syndros®) (FDA approved)	Oral capsule	Synthetic THC
	Nabilone (Cesamet®) (FDA approved)	Oral capsule	Synthetic cannabinoid—THC analogue

FDA approved Syndros®, a liquid formulation of dronabinol, for the treatment of patients experiencing chemotherapy-induced nausea and vomiting who have not responded to conventional antiemetic therapies. The agent is also indicated for treating anorexia associated with weight loss in patients with AIDS. Two additional cannabinoid-based medications have been examined by the FDA. Nabiximols (Sativex®) is an ethanol cannabis extract composed of Δ^9-THC and CBD in a one-to-one ratio. Nabiximols is administered as an oromucosal spray and is indicated in the symptomatic relief of multiple sclerosis and as an adjunctive analgesic treatment in cancer patients (Pertwee, 2012). As of September 2016, nabiximols has

been launched in 15 countries, including Canada, Germany, Italy, Spain, the United Kingdom, and has been approved in a further 12, but not in the United States.[5] In response to the urgent need expressed by parents of children with intractable epilepsy, in 2013 the FDA allowed investigational new drug studies of Epidiolex®, a concentrated CBD oil (>98 percent CBD), also developed by GW Pharmaceuticals, as an anti-seizure medication for Dravet and Lennox-Gastaut syndromes.

SYNTHETIC CANNABINOIDS AS RECREATIONAL DRUGS

In addition to nabilone, many other synthetic cannabinoids agonists have been described and widely tested on experimental animals to investigate the consequences of cannabinoid receptor activation[6] (e.g., CP-55940, WIN-55212-2, JWH-018) (Iversen, 2000; Pertwee, 2012). The therapeutic application of these highly potent molecules is limited by their CB_1-mediated psychotropic side effects, which presumably provide the rationale for the illicit use of some of them as an alternative to cannabis (Wells and Ott, 2011). Preclinical and clinical data in support of this claim remain very limited, however. Internet-marketed products such as Spice, K2, and Eclipse are a blend of various types of plant material (typically herbs and spices) that have been sprayed with one of these synthetic cannabinoids (as well as other non-cannabinoid psychoactive drugs). Since 2009 more than 140 different synthetic cannabinoids have been identified in herbal mixtures consumed as recreational drugs. The synthetic cannabinoids used in "herbal mixtures" are chemically heterogeneous, most of them being aminoalkylindole derivatives such as naphthoylindoles (e.g., JWH-018 and JWH-210), cyclopropylindoles (e.g., UR-144, XLR-11), or quinoline esters (e.g., PB-22). They seem to appeal especially to young cannabis and polydrug users because they are relatively inexpensive, easily available through the Internet, and difficult to identify with standard immunoassay drug screenings. In contrast to Δ^9-THC, which is a partial agonist of the CB_1 receptor, many of the synthetic cannabinoids bind to CB_1 receptors with high affinity and efficacy, which may also be associated with higher potential of toxicity (Hermanns-Clausen et al., 2016). According to the National Institute on Drug Abuse (NIDA, 2012, p. 2), people using these various blends have been admitted to Poison Control Centers reporting "rapid heart rate, vomiting, agitation, confusion, and hallucinations." Synthetic cannabinoids can also raise blood pressure and cause a reduced blood supply to the heart (myocardial ischemia), and in a

[5] For additional information see: http://www.gwpharm.com (accessed January 5, 2017).

[6] Due to the determined scope of this report, nontherapeutic synthetic cannabinoids will not be discussed in the forthcoming chapters of the report.

few cases they have been associated with heart attacks. Regular users may experience withdrawal and symptoms of dependence (Tait et al., 2016).

CANNABIS CONTAMINANTS AND ADULTERANTS

The large economic potential and illicit aspect of cannabis has given rise to numerous potentially hazardous natural contaminants or artificial adulterants being reported in crude cannabis and cannabis preparations. Most frequent natural contaminants consist of degradation products, microbial contamination (e.g., fungi, bacteria), and heavy metals. These contaminants are usually introduced during cultivation and storage (McLaren et al., 2008). Growth enhancers and pest control chemicals are the most common risks to both the producer and the consumer. Cannabis can also be contaminated for marketing purposes. This usually entails adding substances (e.g., tiny glass beads, lead) to increase the weight of the cannabis product (Busse et al., 2008; Randerson, 2007) or adding psychotropic substances (e.g., tobacco, calamus) and cholinergic compounds to either enhance the efficacy of low-quality cannabis or to alleviate its side effects (McPartland et al., 2008). Additionally, some extraction and inhalation methods used for certain dosing formulations (tinctures, butane hash oil, "dabs") can result in substantial pesticide and solvent contamination (Thomas and Pollard, 2016).

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3

Cannabis: Prevalence of Use, Regulation, and Current Policy Landscape

PREVALENCE OF CANNABIS USE IN THE UNITED STATES (1975–2014)

The popularity of cannabis has ebbed and flowed over the past century. Despite being outlawed in several states in the early 1900s and being federally prohibited in 1937, cannabis remained relatively obscure until the 1960s, when an upsurge in use among adolescents and young adults brought the drug into the mainstream. Since the early 1970s, two surveys, the National Survey on Drug Use and Health (NSDUH) and Monitoring the Future, have provided nationally representative data on self-reported use of cannabis. The NSDUH (called the National Household Survey on Drug Abuse until 2002) has polled Americans 12 years of age and older since 1971, and Monitoring the Future has polled high school seniors since 1976, adding 8th- and 10th-graders in 1991 (CBHSQ, 2014; ICPSR, 2016). Both national surveys include questions that ask respondents whether they have ever used cannabis and if they have used cannabis within the past year or within the past 30 days. These data have been used to categorize users, with those reporting use within the past month often considered to be "active" or "current" users. Monitoring the Future also asks youth about how easily they could access cannabis, whether they approve of its use, and how risky they perceive it to be. Other national surveys of interest include the Centers for Disease Control and Prevention's (CDC's) Youth Risk Behavior Survey, which surveys the health-risk behaviors of

9th- through 12th-grade students on a biannual basis,[1] and the CDC's Behavioral Risk Factor Surveillance System,[2] which collects state and local data regarding health-related risk behaviors, chronic health conditions, and the use of preventive services. It is of note that many surveillance surveys differ in their design and methodology, which often limits the ability to compare and compile data across studies.

The prevalence of cannabis use peaked in the late 1970s, when more than one-third of high school seniors (37 percent in 1976) and one in eight Americans over 12 years old (12.8 percent in 1979) reported past-month use (Johnston et al., 2016). Self-reported past-month use declined throughout the 1980s and by 1992 was just one-third of the 1970s peak, both among high school seniors (12.1 percent) and the general population (4.4 percent). The recorded decline in use did not last long. The mid-1990s saw rapid increases, with use by high school seniors nearly doubling within just the 5 years from 1992 (11.9 percent) to 1997 (23.7 percent). Throughout the late 1990s and early 2000s, the rates of use largely stagnated, with trends among youth and the general population moving roughly in parallel (Johnston et al., 2016).

The years since 2007 have seen steady year-over-year increases in general population past-month use, rising from 5.8 percent to 8.4 percent in 2014 (a 45 percent increase). There is no single clear explanation for the post-2007 increases in use. Hypothesized causes include declining potency-adjusted prices on the illicit market; the proliferation of medical cannabis laws, especially those that allow for sale at brick-and-mortar dispensaries; and changing public perceptions about the harms of cannabis use (Sevigny et al., 2014).

Today, cannabis is the most popular illicit drug in the United States (in terms of past-month users), trailed by prescription-type drugs used for nonmedical purposes, such as pain relievers (3.8 million), tranquilizers (1.9m), and stimulants (1.7m), and by prohibited drugs such as cocaine (1.9m), hallucinogens (1.2m), and heroin (0.3m) (CBHSQ, 2016a). A recent survey showed that the primary use of cannabis in the United States remains recreational (89.5 percent of adult cannabis users), with only 10.5 percent reporting use solely for medical purposes, and 36.1 percent reporting a mixed medical/recreational use (Schauer et al., 2016).

In 2015, an estimated 22.2 million of more than 265 million Americans 12 years of age or older reported having used cannabis in the past month (8.3 percent) (CBHSQ, 2016a). Cannabis use is most prevalent among

[1] For additional information see: http://www.cdc.gov/healthyyouth/data/yrbs/results.htm (accessed January 6, 2017).

[2] For additional information see: http://www.cdc.gov/brfss/about/index.htm (accessed January 6, 2017).

young people ages 18 to 25 (19.8 percent using in the past month) (CBHSQ, 2016a). Interestingly, since 2002 the use of cannabis has decreased among 12- to 17-year-olds, while it has markedly increased in the senior population, that is, those over 55 years (Azofeifa et al., 2016).

Males are nearly twice as likely (10.6 percent) to use cannabis as females (6.2 percent) (see Table 3-1). Black Americans use cannabis at the highest rate among major ethnic groups (10.7 percent), followed by whites (8.4 percent) and Hispanics (7.2 percent) (CBHSQ, 2016b). Use is also more common among lower-income Americans and those without college degrees (Davenport and Caulkins, 2016).

Different demographics have different rates of cannabis use. For example, dividing the population by age yields stark differences. Data from the Monitoring the Future survey show that more than one-fifth (21.3 percent) of high school seniors reported past-month use in 2015

TABLE 3-1 Past-Month Use Rates by Demographic

	Past-Month Use Rate (%)
Ethnicity	
White, Non-Hispanic	8.4
African American, Non-Hispanic	10.7
Hispanic	7.2
Asian Non-Hispanic	3.0
Gender	
Male	10.6
Female	6.2
Education	
Less Than High School	8.2
High School Graduate	9.1
Some College	10.5
College Grad	5.9
Family Income[a]	
Less than $10k	13.6
$20k–$29.9k	9.7
$50k–$74.9k	7.8
$75k +	6.6
Age[a]	
12–17	7.1
18–25	20.1
26–34	13.0
35–49	7.1
50+	3.9

[a] Calculated with the Substance Abuse and Mental Health Services Administration's (SAMHSA's) public online data analysis system (PDAS). Crosstab: IRMJRC × CATAG3 (CBHSQ, 2016b).

SOURCE: Derived from CBHSQ, 2016b.

(Johnston et al., 2016). According to NSDUH data, past-month use is highest among 18- to 25-year-olds (19.8 percent) and lower in older groups. All age groups have shown increases in past-month cannabis use since 2002, with the sole exception of adolescents between agees 12 and 17, whose use in 2015 (7.0 percent) was lower than that reported in 2002 (8.2 percent) (CBHSQ, 2016a).

Volume and Intensity of Cannabis Use Today

A different and often overlooked picture of cannabis use is painted when it is measured in terms of volume or intensity of use rather than the prevalence of current users. The NSDUH survey asks past-month cannabis users how many days in the past 30 they have used "marijuana or hashish," allowing researchers to measure the volume of use by aggregating reported use-days or by tracking the number of users who report use on more than 20 days in the past 30, termed heavy or "daily/near-daily" users.

Today, 22.2 million Americans 12 years of age and older report current cannabis use (defined as "users in the past 30 days") (CBHSQ, 2016a). As a proportion of past-month users, heavy users have grown from roughly one in nine in 1992 to more than one in three (35.4 percent) in 2014, indicating an increased intensity of use among current users.[3] Furthermore, the population of heavy users has not only become larger, it has also become older. Burns et al. note an inversion of the ratio of youth (ages 12–17) to older adults (ages 50 and older): in 2002, more than three times as many youths as older adults were using cannabis on a daily or near-daily basis; by 2011, 2.5 times as many adults as youth were daily or near-daily cannabis users (Burns et al., 2013).

Generally, the intensity of use correlates with use prevalence: groups with high prevalence tend to be the same as those with high intensity. But some groups are noticeable exceptions. For example, Americans with less than a high school education are less likely to report past-month use than Americans with a high school diploma or with a partial college education, but in terms of past-month use, those with less than a high school education are most likely to report daily/near-daily use (44.8 percent). Likewise, among age demographics, 26- to 34-year-olds report less past-month use than 18- to 25-year-olds do, but they report substantially more

[3] Computed by NSDUH cross-tabs for 1992 and 2014. For 1992: https://www.icpsr.umich.edu/icpsrweb/ICPSR/series/64/studies/6887?archive=ICPSR&sortBy=7 (accessed January 6, 2017). Compute "MRJMON" against "MJDAY30A," recoded as "MJDAY30A(r: 0-20;21-30)." For 2014: http://www.icpsr.umich.edu/cgi-bin/SDA/NAHDAP/hsda?nahdap+36361-0001 (accessed January 6, 2017). Compute "IRMJRC" against "MJDAY30A," recoded as "MJDAY30A (r: 0-20;21-30)."

heavy use among current users (42.2 percent). Heavy use among past-month users is lowest among 12- to 17-year-olds (7.4 percent). Younger users tend to have lighter habits. According to Monitoring the Future data, in 2015, 6 percent of high school seniors who used cannabis in the past month reported use on a *daily* basis, as did 3 percent of 10th-graders and 1.1 percent of 8th-graders (Johnston et al., 2016).

One result of the increased intensity of use among past-month users is that the bulk of cannabis consumption is increasingly concentrated among a small number of heavy users. By one estimate, the one-third of current cannabis users that use daily or near daily accounted for two-thirds of the reported days of past-month use and three-quarters of expenditures (Davenport and Caulkins, 2016).

CANNABIS REGULATION IN THE UNITED STATES

In the United States at the turn of the 20th century, cannabis was generally used for medical rather than recreational purposes. As such, the production and use of cannabis was regulated by consumer safety laws such as the Pure Food and Drug Act of 1906, which required producers to disclose and label the quantity of cannabis present in any product sold as food or medicine. Although several U.S. states enacted bans on cannabis between 1911 and 1930, it escaped early federal prohibitions, such as the Harrison Act of 1914, which regulated opium and derivatives of the coca plant (Musto, 1999).

Fear of "marihuana," as cannabis was beginning to be called, grew during the 1920s and 1930s as immigration from Mexico steadily increased in southwestern states. In the mid-1930s, the federal government, through the Federal Bureau of Narcotics, endorsed state-level actions and encouraged states to adopt the Marihuana Tax Act as a means to criminalize the unregistered and untaxed production and use of cannabis. National prohibition did not take shape, however, until Congress passed the Marihuana Tax Act of 1937, which regulated the production, distribution, and use of cannabis via Congress's power to tax commerce. The act required those dealing with cannabis to register with federal authorities and pay a tax (Booth, 2005; Musto, 1999). The supply and use of the drug was not criminalized, but nonmedical supply or use was a violation and subject to a fine and imprisonment.

Today, cannabis is regulated by local, state, federal, and international law. State laws often mirror federal law, enshrined in the Comprehensive Drug Abuse Prevention and Control Act of 1970, which includes the Controlled Substances Act (CSA). The CSA modernized and consolidated earlier federal drug laws, making them consistent with international drug control conventions, specifically the United Nations Single Convention

on Narcotic Drugs of 1961, which the United States ratified (Caulkins et al., 2016). The CSA placed cannabis in Schedule I, the most restrictive category reserved for substances that have no currently accepted medical use, alongside heroin and lysergic acid diethylamide (LSD). The federal government does not recognize the medical use of cannabis, citing no evidence of the accepted medical use of herbal cannabis. It bears mentioning that pharmaceutical-grade cannabinoids have been isolated and are scheduled apart from cannabis. For example, tetrahydrocannabinol (THC) is sold as Marinol®, available with prescription (a Schedule III drug). That THC, which is the principal active ingredient in cannabis, in its pure form is listed in Schedule III indicates that the placement of botanical or whole cannabis in Schedule 1 may be driven by the lack of recognition of medical use for the whole plant.

Federal criminal law prohibits the supply and use of cannabis with exceptions for medical and scientific purposes. The enforcement of cannabis prohibition by federal authorities has focused on international smuggling and domestic crop eradication as well as violations on federal lands. The federal government has relied on state and local authorities to enforce criminal prohibitions on cannabis retail and use. In 2014 there were more than 1.5 million arrests for drug law violations,[4] approximately 30,000 of which were made by the U.S. Drug Enforcement Administration (DEA).[5] However, federal law remains an important factor in regulating cannabis. While the National Institutes of Health (NIH) have funded cannabis research—$111 million on 281 cannabinoid research projects in 2015 alone (NIH, 2016)—the federal government has restricted research on cannabis by licensing a single producer under contract with the National Institute on Drug Abuse (NIDA) and requiring multiple administrative reviews on research proposals (Caulkins et al., 2016) (see Chapter 15—Challenges and Barriers in Conducting Cannabis Research for additional information).[6] Federal law also prohibits the importation of and intra- and interstate trade in cannabis. Tangentially, federal banking and commercial laws impede the development of commercial cannabis businesses. Though

[4] As a noteworthy caveat, within the United States there is evidence of racial, social, and economic status–based disparities in the enforcement and issued penalties related to cannabis sale and use (Austin and Ressler, 2016). Within this context, it is important to acknowledge the potential impact of these laws on the health outcomes of disenfranchised communities.

[5] See https://ucr.fbi.gov/crime-in-the-u.s/2014/crime-in-the-u.s.-2014/tables/table-29 (accessed January 6, 2017) and https://www.dea.gov/resource-center/statistics.shtml#arrests (accessed January 6, 2017).

[6] In August 2016, NIDA announced a policy change intended to support an increase in the number of DEA-registered marijuana manufacturers. This change was designed to ensure a larger and more diverse supply of marijuana for U.S. Food and Drug Administration (FDA)-authorized research purposes (DEA, 2016).

legal at the state level, the federal prohibition on cannabis prevents businesses from accessing the banking sector, precluding entrepreneurs from accessing lines of credit, electronic funds transfer, checking accounts, and other financial goods and services available to contemporary businesses. Federal tax code also prohibits cannabis businesses from deducting typical costs of business (Caulkins et al., 2015; Oglesby, 2015). In summary, the legal changes in cannabis policy during the past 50 years have been characterized primarily by three types of policies, each implemented by various states, beginning with (1) decriminalization throughout the 1970s, which preceded (2) medical cannabis laws and (3) regulated and licensed recreational cannabis.

Decriminalization of Possession and Use

States and localities perform most of the legwork involved in enforcing the criminal prohibition on cannabis as they arrest and convict the vast majority of offenders. Each state maintains its own set of laws that regulate the supply and use of the drug. In most cases, acts involving cannabis are subject to criminal prohibition, but sanctions vary considerably by state, each of which is constitutionally entitled to establish its own criminal codes and penalties.

The reduction of statutory penalties for use-related acts, including personal possession, is referred to as *decriminalization* or *depenalization*. About a dozen U.S. states are often described as having decriminalized possession in the 1970s (Pacula et al., 2005), beginning with Oregon in 1973. This move to reduce penalties on cannabis use halted until 2001 when Nevada decriminalized possession of small amounts of cannabis. Today, 21 states and the District of Columbia have decriminalized possession of small amounts of cannabis (Caulkins et al., 2016).

During the 1970s, the federal government briefly considered abolishing criminal sanctions for use-related acts. The 1972 National Commission on Marihuana and Drug Abuse, appointed by President Nixon, recommended that federal law be amended to decriminalize cannabis possession, use, and low-level retail (Shafer Commission, 1972). Those recommendations were rejected by the Nixon administration. President Carter raised the issue again in a 1977 speech to Congress, calling for federal decriminalization of cannabis possession, but his administration did not succeed in changing policies (Musto, 1999).

Medical Cannabis Laws

The next major shift in state cannabis policy in the United States was the enactment of medical cannabis laws. Starting in 1996 California

passed a popular referendum (Proposition 215) to allow individuals suffering from various illnesses to use herbal, whole plant cannabis, making California the first jurisdiction in the Western Hemisphere to legalize medical cannabis in some form. The law generally provides an affirmative defense for individuals using cannabis for medical purposes. Reforms at the state level continued in the waning years of the 20th century, with a handful of states passing laws to allow doctors to prescribe medical cannabis or allow for a legal defense for use of medical cannabis. The permission of use of the flower or products derived from the cannabis flower has now spread to 28 states and the District of Columbia. Another 16 states allow limited access to low-tetrahydrocannabinol (THC)/high-cannabidiol (CBD) products (NCSL, 2016). Figure 3-1 demonstrates that low-THC/high-CBD laws are a recent phenomenon.

Medical cannabis laws and policies vary greatly in terms of the regulations governing supply and use. Some are more restrictive than others, limiting the access of the drug to a certain class of individuals who suffer from certain illnesses or conditions, or establishing stricter limits on the production and distribution of the substance to at-home cultivation by patients and caregivers. Some states legally protect and regulate the

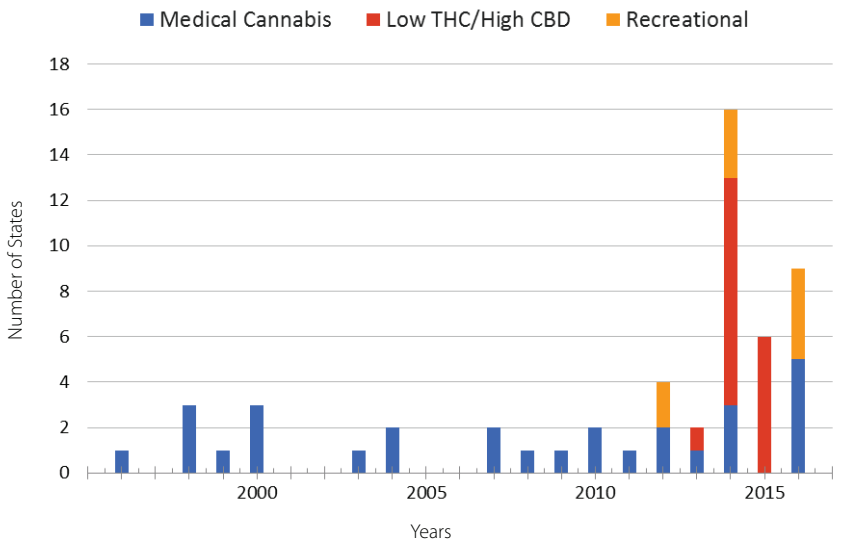

FIGURE 3-1 Passage of state cannabis laws (figure includes the District of Columbia).
SOURCE: Adapted from NCSL, 2016.

operation of storefronts known as dispensaries. In these states, patients with a recommendation can enter stores and obtain a wide array of cannabis and cannabis products. Some dispensaries openly advertise their wares and services to patients at point of sale, with others aggressively promoting their business to the general public.

When it comes to the distribution of medical cannabis, some states, such as New York, restrict the sale of medical cannabis to non-smokable forms of the drug. Others require that patients register with the state and identify their source of cannabis. Even within states regulations may vary. Some states allow for local bans and municipal ordinances to help regulate additional aspects of the supply of cannabis.

Nonmedical, Adult Recreational Use

In 2010 California voted on legalizing recreational cannabis—in effect, permitting and regulating the supply and distribution of cannabis for adults to use nonmedically. Proposition 19 sought to repeal the state's criminal prohibitions on cannabis, regulating it for recreational purposes for those over 21 years of age. The initiative failed, with 54 percent voting against. Two years later residents of Colorado, Oregon, and Washington went to the polls to vote on legalizing the adult recreational use of cannabis. Oregon's initiative failed, with 53 percent of voters rejecting the measure[7]; however, Colorado and Washington State, after passing ballot initiatives in November 2012, became the first jurisdictions to legalize the large-scale commercial production of cannabis for recreational use for adults over 21, with Colorado also permitting home cultivation. In November 2014 similar initiatives were approved by voters in Alaska[8] and Oregon. The District of Columbia took a narrower approach by legalizing only possession and home cultivation. The DC City Council subsequently attempted to permit and regulate a commercial market but was blocked by the U.S. Congress.

The liberalization of cannabis laws has been a gradual process. Early steps included medical cannabis, including the allowance and, sometimes, legal protection of dispensaries. Later, Alaska, Colorado, Oregon, and Washington State regulated the production and distribution of recreational cannabis by private, for-profit commercial actors along similar lines. Besides the general commercial design of these initiatives, the details of the regulations vary. Table 3-2 describes a few of the regula-

[7] Oregon temporarily allowed sales of recreational cannabis through existing medical dispensaries beginning in October 2015, though licensed recreational stores are not expected to open until late 2016.

[8] Alaska is expected to allow recreational cannabis sales in licensed stores by late 2016.

tory differences between Alaska, Colorado, Oregon, Washington, and the District of Columbia. With the exception of Washington State, all permit at-home cultivation. The District of Columbia follows a "grow and give" noncommercial model. None impose potency limits or require users to register.

In November 2016, California, Maine, Massachusetts, and Nevada voted to legalize adult measures related to recreational cannabis use

TABLE 3-2 Regulatory Differences Across Four States and the District of Columbia That Have Legalized Recreational Cannabis

	Alaska	Colorado
Legal Process	Voter initiative, state statute	Voter initiative, amendment to state constitution
When Passed	November 2014	November 2012
When Implemented	February 2015: Personal possession, consumption, cultivation Late 2016 (expected): Retail sales	December 2012: Personal possession, consumption, cultivation January 2014: Retail sales
Regulatory Authority	Marijuana Control Board (Alcoholic Beverage Control Board)	Marijuana Enforcement Division (Department of Revenue)
Minimum Age	21	21
Residency Requirement	None	None
Personal Possession Quantity	28.5 g	28.5 g
Home Cultivation	6 plants, 3 of which can be flowering	6 plants, 3 of which can be flowering
Interpersonal Sharing	28.5 g	28.5 g
Retail Transaction Limit	28.5 g	Residents: 28.5 g Non-residents: 7 g
Retail Pricing Structure	Market	Market
Average Retail Price per Gram After Tax	No retail stores currently	$11.50
Maximum THC Content	None	None

and possession (NORML, 2016). Arkansas, Florida, Montana, and North Dakota voted in favor of medical marijuana initiatives. In order to develop and enforce regulations for a recreational cannabis industry, each state has appointed a regulatory agency. Alaska, Oregon, and Washington State delegated this responsibility to existing alcohol authorities, while Colorado expanded the responsibilities of the Medical Marijuana Enforcement Division under the Department of Revenue. To aid in drafting rules fol-

Oregon	Washington	District of Columbia
Voter initiative, state statute	Voter initiative, state statute	Voter initiative
November 2014	November 2012	November 2014
July 2015: Personal possession, consumption, cultivation October 1, 2015: Retail sales via medical dispensaries Late-2016 (expected): retail sales through licensed retailers	December 2012: Personal possession, consumption July 2014: Retail sales	February 2015: Personal possession, consumption, cultivation
Oregon Liquor Control Commission	Liquor and Cannabis Board (formerly the Liquor Control Board)	Not applicable
21	21	21
None	None	None
In public: 28.5 g At home: 228 g	28.5 g	57 g
4 plants in flower	Not allowed	6 plants per person 12 plants per household, 3 of which can be flowering
28.5 g	Not allowed	28.5 g
7 g	28.5 g	Not applicable
Market	Market	Not applicable
$10.00	$10.00	Not applicable
None	None	None

continued

TABLE 3-2 Continued

	Alaska	Colorado
Registration Requirements	None	None
Advertising	Final advertising regulations to be determined by the Alaska Department of Health and Social Services Division of Public Health	Restricted to media with no more than 30 percent of the audience under the age of 21
Taxation	$50 excise tax per ounce on sales or transfers from cultivation facility to retail store or product manufacturer	15 percent excise tax on cultivation; 10 percent retail marijuana sales tax; 2.9 percent state sales tax; local sales taxes
Cannabis Clubs	Not explicitly allowed or prohibited; ban on in-store consumption repealed in November 2015	Not allowed
Medical Cannabis	2000: Patient registry, possession, home cultivation	2000: Patient registry, possession, consumption 2010: Commercial production and sales

SOURCE: Adapted from UNODC World Drug Report 2016 (UNODC, 2016).

lowing the passage of their initiatives, state agencies held public hearings and working groups to solicit public input (Pardo, 2014).

The federal government has not challenged these state laws by invoking the supremacy clause of the U.S. Constitution. However, under the 10th Amendment, as reaffirmed by U.S. jurisprudence, the federal government cannot force a state to criminalize an act under state law (Garvey and Yeh, 2014). When the voters of these states passed initiatives to legalize, regulate, and tax recreational cannabis, they simultaneously repealed the penal provisions and sanctions prohibiting and criminalizing unauthorized cultivation, trafficking, and possession of cannabis. Under the Obama administration, the federal government seems to have opted for a more pragmatic solution which allows for a rules-based cannabis industry, as dictated by state regulations, while maintaining the future option to preempt.

Oregon	Washington	District of Columbia
None	None	None
Entry sign required on exterior of dispensaries; Oregon Liquor Control Commission has authority to further regulate or prohibit advertising	Limited to one sign for retailers at business location	Not applicable, no commercial market
October–December 2015: No tax on retail sales; after January 5, 2016: 25 percent sales tax	July–June 2014: 25 percent tax at each stage (production, processing, retail) July 2015: 37 percent sales tax	Not applicable, no commercial market
Not allowed	Not allowed	Not allowed; currently under investigation by city task force.
1999: Patient registry, possession, home cultivation	1999: Possession 2012: Home cultivation, no patient registry	2011: Patient registry

POLICY LANDSCAPE

Most researchers recognize that a growing general public acceptance of the drug for medical and recreational purposes has been encouraging the changes at the state level. It remains to be seen if cannabis will be legalized at the national level or if such public opinion will continue. In 2015, according to a Gallup tracker poll, 58 percent of Americans favored legalizing cannabis, marking the third straight year that cannabis legalization found majority support (Gallup, 2015). Given that a large percentage of the U.S. population lives in states that permit some degree of access to THC-containing compounds via either the medical or the recreational market, it is important to examine the current policy landscape, which may shape future state and federal regulations of cannabis.

State-Level Changes

State-Regulated Use

Cannabis policy change has occurred at the state level in large part due to changing public sentiment. Many states have reformed their cannabis laws, not from a deliberative legislative process but through popular referendums. As discussed earlier, states have passed laws to allow qualifying individual's access to medical cannabis. These laws can be broadly divided into three distinct categories: loose medical, restricted access, and non-THC.

Some of the earliest laws passed—and the laws generally found in most states west of the Mississippi River—are referred to as *loose medical*. In states with these policies, access to medical cannabis is not strictly limited to provable qualifying ailments, such as terminal cancer, HIV/AIDS, or glaucoma. A patient may access medical cannabis when his or her physician deems it necessary, and in some jurisdictions this amounts to little more than de facto legalization of recreational use. One study that surveyed more than 4,000 individuals seeking access to medical cannabis in California concluded that the typical patient was a white male in his early 30s who started using cannabis in his teens with fewer reported disabilities than the national average (O'Connell and Bou-Matar, 2007). Under *restricted access*, patients must meet certain qualifying criteria (such as a qualifying medical condition) or are restricted to what types of medical products are available, or both. For example, New York prohibits the use of smokable herbal cannabis, allowing only tinctures, oils, concentrates, and other forms of products. *Non-THC* laws permit the use of no-THC or low-THC/high-CBD products, such as CBD oil, to treat a short list of qualifying conditions, such as refractory epilepsy. This category is by far the most restrictive, and states that adopt these non-THC policies generally prohibit the supply and distribution of such products, granting only a legal defense for their use.

That said, 28 states and the District of Columbia fall in one or the other of the first two categories and allow for loose or restricted medical use, where patients may access some form of THC-containing compound. Sixteen states fall in the non-THC category. A total of 44 states and the District of Columbia have amended their laws to allow for some form of medical cannabis (NCSL, 2016) (see Figure 3-2).

Of all the jurisdictions that allow for some sort of access to THC-containing compounds, cancer, HIV/AIDS, multiple sclerosis, and glaucoma are among the most recognized qualifying ailments (NCSL, 2016). And examination of all jurisdictions shows that most list seizures and epileptic seizures within their statutes (NCSL, 2016). However, several states are open in their interpretation, allowing for medical cannabis to

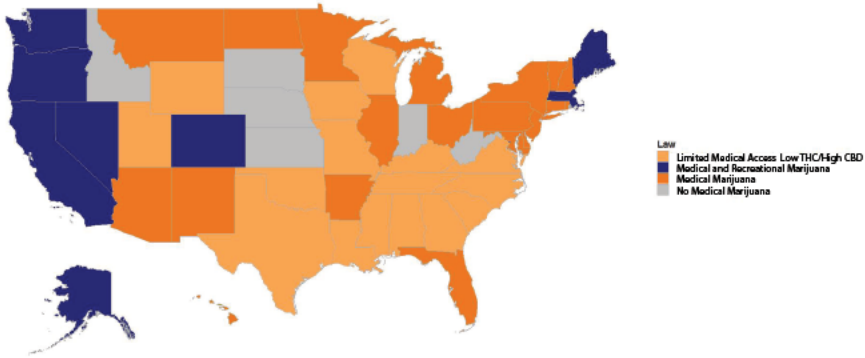

FIGURE 3-2 Cannabis laws by state, November 2016.
SOURCE: Adapted from NCSL, 2016.

be used to treat any illness for which the drug provides relief. Since few states maintain medical cannabis patient registries, the committee relied on data on the percentage of patients reporting certain qualifying illnesses in Oregon and Colorado (see Figure 3-3). As can be seen in the figure, the overwhelming majority obtained a recommendation on the basis of a claimed need to treat pain.

State Research on Therapeutic Effects

In addition to state-level legal changes that regulate cannabis for either medical or recreational purposes, a few states have sought to expand research into cannabis's therapeutic effects. The Center for Medicinal Cannabis Research (CMCR) at the University of California was created in 2000 to conduct clinical and preclinical studies of cannabinoids, including smoked cannabis, for conditions for which cannabis may be beneficial. With state funding, the CMCR approved 21 federally approved studies: 13 have been completed, and 6 have been discontinued (CMCR, 2016).

Departing from this, Colorado has started to conduct research into the medicinal value of cannabis that is neither federally funded nor federally approved. In 2014 Colorado passed legislation to promote research into cannabis's medical benefits, creating the Medical Marijuana Scientific Advisory Council and appropriating $9 million in research grants. The advisory council approves research grants and evaluates research. As of early 2015, nine research grants have been approved, with six studies cur-

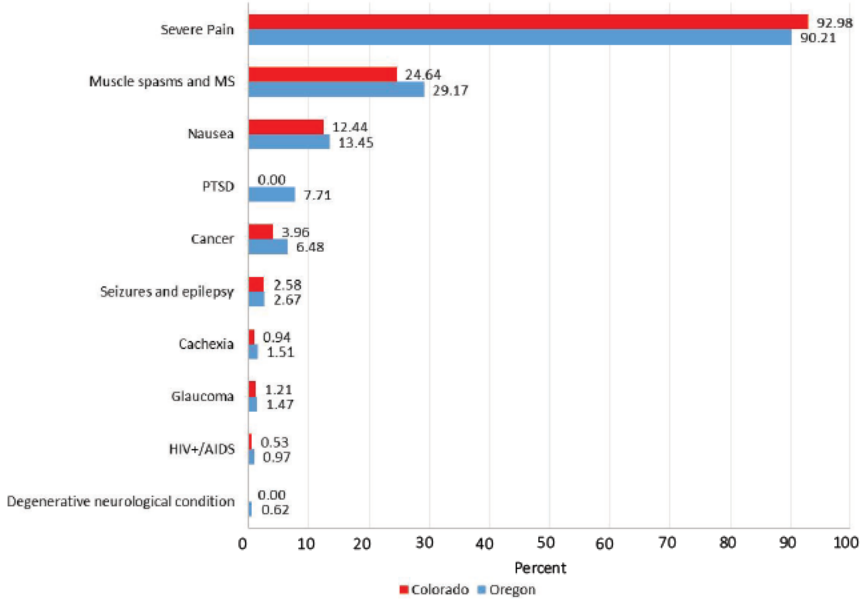

FIGURE 3-3 Percentage of medical cannabis patients reported by condition in Colorado and Oregon, July 2016.
NOTE: Patients may report multiple qualifying ailments.
SOURCES: Adapted from CDPHE, 2016; OHA, 2016.

rently under way.[9] Also in 2015, NIH provided $111 million in funding for 281 cannabinoid-related research efforts nationwide (NIH, 2016).

EXECUTIVE BRANCH POLICIES

Federal Regulated Use

As discussed earlier, the executive branch of the federal government has extensive influence and impact when it comes to regulating cannabis. Despite the complex domestic arrangements established by the U.S. Constitution and the current political climate, the executive branch has not challenged state-level laws that are in violation with federal drug laws. The Obama administration has issued a series of federal guidelines for

[9] See the Colorado Department of Public Health and Environment's Medical Marijuana Scientific Advisory Council: https://www.colorado.gov/pacific/cdphe/approved-medical-marijuana-research-grants (accessed January 6, 2017).

states that are reforming cannabis laws, granting limited space for such policies.

In 2009 the U.S. Department of Justice issued a policy memo declaring that it was not the federal government's intent to prosecute individuals who abide by state medical cannabis laws (Ogden, 2009). That policy was later updated in August 2013 following the legalization of nonmedical cannabis in Colorado and Washington State. The current policy guidelines outline eight enforcement criteria whereby the federal government may intervene and prosecute an individual or group for violating the Controlled Substances Act (Cole, 2013). Furthermore, the U.S. Department of Justice stated that it expects states that have legalized cannabis to implement robust systems of enforcement and regulation to protect public health and safety; however, recent evaluations of the policy guidelines suggest that the U.S. Department of Justice has done little to evaluate how states comply with federal priorities (GAO, 2016).

Because cannabis is still federally prohibited, laws that govern other aspects of commerce—namely, banking and finance—have prevented businesses that deal in cannabis from accessing lines of credit or banking (McErlean, 2015). Money laundering laws and the CSA prevent many banks from interacting with cannabis businesses. In order to ease this conflict, the U.S. Department of the Treasury, through the Financial Crimes Enforcement Network (FinCEN), has issued a directive to financial establishments allowing them to deal with cannabis businesses that comply with state laws (FinCEN, 2014).

Federal Research

Despite ongoing federal funding for cannabinoid research ($111 million in 2015 alone), cannabis researchers have found federal research funds to be restricted and limited. Research proposals were required to undergo a thorough and rigorous assessment by the DEA, NIDA, the FDA, and the U.S. Department of Health and Human Services (HHS). If they were federally approved, researchers were limited in the type and quantity of cannabis available from the University of Mississippi, which was contracted by NIDA to act as the only licit supply of the drug for research. (See Chapter 15—Challenges and Barriers in Conducting Cannabis Research for additional information.) In 2015 the Obama administration, via HHS and the DEA, relaxed some regulatory restrictions, eliminating duplicative reviews of research proposals by the HHS as well as increasing the amount of cannabis available for research by raising the aggregate production quota of cannabis cultivated at the University of Mississippi (DEA, 2016).

In August 2016 the DEA denied a petition to reschedule cannabis to

Schedule II, citing that cannabis has no currently accepted medical use in treatment in the United States (DEA, 2016). The administration did, however, adopt a new policy to end the NIDA-contracted monopoly of research-grade cannabis by the University of Mississippi. Under new rules, the DEA will facilitate cannabis research by increasing the number of private entities allowed to cultivate and distribute research-grade cannabis (DEA, 2016).

CONGRESSIONAL BRANCH POLICIES

Recently the 113th Congress used its regulatory powers to shape cannabis policy at both the state and the subnational level. In the Consolidated and Further Continuing Appropriations Act of 2015 (Public Law No. 113-235), lawmakers precluded the U.S. Department of Justice from using fiscal year 2015 appropriated funds to enforce the Controlled Substances Act to prevent states from implementing their own laws that authorize the use, distribution, possession, or cultivation of medical cannabis (Sec 538). In the same piece of legislation, Congress precluded the District of Columbia from using appropriated funds to regulate, legalize, or otherwise reduce penalties for the possession, distribution, or use of any Schedule I substance, effectively blocking any citywide effort to regulate the trade in cannabis (Sec 908b). During the same session, Congress authorized the Secretary of Agriculture to promulgate rules to ensure that medical cannabis costs are not treated as a deduction in Supplemental Nutrition Assistance Program (SNAP) benefits as well as allowing universities and state departments of agriculture to cultivate industrial hemp for research purposes (Garvey et al., 2015).

Members of the current 114th Congress have proposed several pieces of legislation on cannabis. Some would remove cannabis from the Controlled Substances Act and treat the drug like alcohol. Others would end the civil asset forfeiture of real property of businesses that comply with state medical cannabis laws or authorize the U.S. Department of Veterans Affairs to offer recommendations regarding veterans' use of cannabis in compliance with state regimes. One bill in particular, the Medical Marijuana Research Act, has gained bipartisan support from proponents and opponents of cannabis reform in Congress. The bill would increase cannabis research by making the drug and plant more accessible to researchers.

PUBLIC OPINION

Public opinion toward cannabis seems to be driving many of the policy changes that have taken place to date. Cannabis found mainstream market appeal in the late 1960s and early 1970s, and, as a result, polling

agencies started surveying the public opinion about the drug. In 1969 the Gallup Poll began asking Americans if they thought that the "use of cannabis should be made legal," and the company has continued to ask Americans the same question for nearly 50 years.[10]

Gallup poll responses showed that support for legal cannabis use increased to 28 percent in 1977 (the same year President Carter called for national decriminalization). For about 20 years, support declined and then plateaued at around 24 percent, only to inch upward 4 years after California passed legislation in favor of medical cannabis. By 2000, 31 percent of respondents favored legal use. Over the past 6 years support has vacillated, but it averaged 48 percent from 2010 through 2012 and has averaged 56 percent since 2013. In 2015, 58 percent of respondents favored legal use.

Polling shows that the public is overwhelmingly in favor of the use of cannabis for medical purposes if prescribed by a doctor. No other company has tracked public opinion concerning medical cannabis over time in the same way as the Gallup Poll, but a collection of national surveys from ProCon indicate that since 1998, 60 to 85 percent of Americans have been supportive of the use of medical cannabis (ProCon, 2016). In a recent poll by Quinnipiac, 89 percent of respondents supported medical cannabis (Quinnipiac, 2016). However, it is of note that states attribute different medicinal value to different forms of the drug, restricting who can access what part of the plant. National surveys may not capture these distinctions that are made in state-level law or policy. Yet, the general shift over time suggests that the public is welcoming some changes in cannabis policy and law. There appears to be greater agreement that cannabis should be available as a medicine to those with certain qualifying conditions, but it is harder to find similar political agreement on recreational cannabis. It is unclear whether the wording of the Gallup Poll's public opinion question paints an accurate picture of the current and ongoing sentiment with respect to states that are legalizing recreational cannabis.

POLICY AND RESEARCH

The political landscape for the commercialization, decriminalization, and use of cannabis is constantly evolving. As federal and state agencies continue to grapple with these important public policy issues, it is important to consider that each political decision may have significant public health implications.

[10] It should be noted that the question is somewhat vague, implying "legalization" but referring to "use" of cannabis, not the legal production and distribution of the drug. This ambiguity may cloud respondents' answers.

As laws and policies continue to change, research must also. Unfortunately, research on the health effects and potential therapeutic potential of cannabis use has been limited in this country, despite enormous changes at the state level. As such, there is currently limited research evidence to guide policy. This lack of aggregated knowledge is a significant impediment not only to the scientific understanding of cannabis but also to the advancement of public policy and the nation's overall public health.

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Part II

Therapeutic Effects

4

Therapeutic Effects of Cannabis and Cannabinoids

Chapter Highlights

- In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics.
- In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms.
- In adults with multiple sclerosis (MS)-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
- For these conditions the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects.

Cannabis sativa has a long history as a medicinal plant, likely dating back more than two millennia (Russo et al., 2007). It was available as a licensed medicine in the United States for about a century before the American Medical Association removed it from the 12th edition of the *U.S. Pharmacopeia* (IOM, 1999). In 1985, pharmaceutical companies received approval to begin developing Δ^9-tetrahydrocannabinol (THC) preparations—dronabinol and nabilone—for therapeutic use, and as a result, cannabinoids were reintroduced into the armamentarium of willing health care providers (Grotenhermen and Müller-Vahl, 2012). Efforts

are now being put into the trials of cannabidiol as a treatment for conditions such as epilepsy and schizophrenia,[1] although no such preparations have come to market at this time. Nabiximols, an oromucosal spray of a whole cannabis plant extract with a 1:1 ratio of THC to cannabidiol (CBD), was initially licensed and approved in Europe, the United Kingdom, and Canada for the treatment of pain and spasticity associated with multiple sclerosis (GW Pharmaceuticals, 2016; Pertwee, 2012), but it continues to undergo evaluation in Phase III clinical trials in the United States.[2] Efforts are under way to develop targeted pharmaceuticals that are agonists or antagonists of the cannabinoid receptors or that modulate the production and degradation of the endocannabinoids, although such interventions have not yet demonstrated safety or effectiveness. Nonetheless, therapeutic agents targeting cannabinoid receptors and endocannabinoids are expected to become available in the future.

The renewed interest in the therapeutic effects of cannabis emanates from the movement that began 20 years ago to make cannabis available as a medicine to patients with a variety of conditions. It was in 1996 that Arizona and California first passed medicinal cannabis legislation, although Arizona later rescinded the approval, so it would be California that paved the way. At the time that this report was written, in 2016, 28 states and the District of Columbia had legalized the medical use of cannabis; 8 states had legalized both medical and recreational use of cannabis; and another 16 states had allowed limited access to low-THC/high-CBD products (i.e., products with low levels of THC and high levels of CBD) (NCSL, 2016). A recent national survey showed that among current adult users, 10.5 percent reported using cannabis solely for medical purposes, and 46.6 percent reported a mixed medical/recreational use (Schauer et al., 2016). Of the states that allow for some access to cannabis compounds, cancer, HIV/AIDS, multiple sclerosis, glaucoma, seizures/epilepsy, and pain are among the most recognized qualifying ailments (Belendiuk et al., 2015; NCSL, 2016). There are certain states that provide more flexibility than others and that allow the use of medical cannabis for the treatment of any illness for which the drug provides relief for the individual. Given the steady liberalization of cannabis laws, the numbers of these states are likely to increase and therefore support the efforts to clarify the potential therapeutic benefits of medical cannabis on various health outcomes.

For example, the most common conditions for which medical cannabis is used in Colorado and Oregon are pain, spasticity associated with multiple sclerosis, nausea, posttraumatic stress disorder, cancer, epilepsy, cachexia, glaucoma, HIV/AIDS, and degenerative neurological

[1] ClinicalTrials.gov: NCT02447198, NCT02926859.
[2] ClinicalTrials.gov: NCT01361607.

conditions (CDPHE, 2016; OHA, 2016). We added to these conditions of interest by examining lists of qualifying ailments in states where such use is legal under state law. The resulting therapeutic uses covered by this chapter are chronic pain, cancer, chemotherapy-induced nausea and vomiting, anorexia and weight loss associated with HIV, irritable bowel syndrome, epilepsy, spasticity, Tourette syndrome, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dystonia, dementia, glaucoma, traumatic brain injury, addiction, anxiety, depression, sleep disorders, posttraumatic stress disorder, and schizophrenia and other psychoses. The committee is aware that there may be other conditions for which there is evidence of efficacy for cannabis or cannabinoids. In this chapter, the committee will discuss the findings from 16 of the most recent, good- to fair-quality systematic reviews and 21 primary literature articles that best address the committee's research questions of interest.

As a reminder to the reader, several of the prioritized health endpoints discussed here in Part II are also reviewed in chapters of Part III; however, the research conclusions within these chapters may differ. This is, in part, due to differences in the study design of the evidence reviewed (e.g., randomized controlled trials [RCTs] versus epidemiological studies), differences in the characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across chapters.

CHRONIC PAIN

Relief from chronic pain is by far the most common condition cited by patients for the medical use of cannabis. For example, Light et al. (2014) reported that 94 percent of Colorado medical marijuana ID cardholders indicated "severe pain" as a medical condition. Likewise, Ilgen et al. (2013) reported that 87 percent of participants in their study were seeking medical marijuana for pain relief. In addition, there is evidence that some individuals are replacing the use of conventional pain medications (e.g., opiates) with cannabis. For example, one recent study reported survey data from patrons of a Michigan medical marijuana dispensary suggesting that medical cannabis use in pain patients was associated with a 64 percent reduction in opioid use (Boehnke et al., 2016). Similarly, recent analyses of prescription data from Medicare Part D enrollees in states with medical access to cannabis suggest a significant reduction in the prescription of conventional pain medications (Bradford and Bradford, 2016). Combined with the survey data suggesting that pain is one of the primary reasons for the use of medical cannabis, these recent reports sug-

gest that a number of pain patients are replacing the use of opioids with cannabis, despite the fact that cannabis has not been approved by the U.S. Food and Drug Administration (FDA) for chronic pain.

Are Cannabis or Cannabinoids an Effective Treatment for the Reduction of Chronic Pain?

Systematic Reviews

Five good- to fair-quality systematic reviews were identified. Of those five reviews, Whiting et al. (2015) was the most comprehensive, both in terms of the target medical conditions and in terms of the cannabinoids tested. Snedecor et al. (2013) was narrowly focused on pain related to spinal cord injury, did not include any studies that used cannabis, and only identified one study investigating cannabinoids (dronabinol). Two reviews on pain related to rheumatoid arthritis did not contribute unique studies or findings (Fitzcharles et al., 2016; Richards et al., 2012). Finally, one review (Andreae et al., 2015) conducted a Bayesian analysis of five primary studies of peripheral neuropathy that had tested the efficacy of cannabis in flower form administered via inhalation. Two of the primary studies in that review were also included in the Whiting review, while the other three were not. It is worth noting that the conclusions across all of the reviews were largely consistent in suggesting that cannabinoids demonstrate a modest effect on pain. For the purposes of this discussion, the primary source of information for the effect on cannabinoids on chronic pain was the review by Whiting et al. (2015). Whiting et al. (2015) included RCTs that compared cannabinoids to usual care, a placebo, or no treatment for 10 conditions. Where RCTs were unavailable for a condition or outcome, nonrandomized studies, including uncontrolled studies, were considered. This information was supplemented by a search of the primary literature from April 2015 to August 2016 as well as by additional context from Andreae et al. (2015) that was specific to the effects of inhaled cannabinoids.

The rigorous screening approach used by Whiting et al. (2015) led to the identification of 28 randomized trials in patients with chronic pain (2,454 participants). Twenty-two of these trials evaluated plant-derived cannabinoids (nabiximols, 13 trials; plant flower that was smoked or vaporized, 5 trials; THC oramucosal spray, 3 trials; and oral THC, 1 trial), while 5 trials evaluated synthetic THC (i.e., nabilone). All but 1 of the selected primary trials used a placebo control, while the remaining trial used an active comparator (amitriptyline). The medical condition underlying the chronic pain was most often related to a neuropathy (17 trials); other conditions included cancer pain, multiple sclerosis, rheuma-

toid arthritis, musculoskeletal issues, and chemotherapy-induced pain. Analyses across 7 trials that evaluated nabiximols and 1 that evaluated the effects of inhaled cannabis suggested that plant-derived cannabinoids increase the odds for improvement of pain by approximately 40 percent versus the control condition (odds ratio [OR], 1.41, 95% confidence interval [CI] = 0.99–2.00; 8 trials). The effects did not differ significantly across pain conditions, although it was not clear that there was adequate statistical power to test for such differences.

Only 1 trial (n = 50) that examined inhaled cannabis was included in the effect size estimates from Whiting et al. (2015). This study (Abrams et al., 2007) also indicated that cannabis reduced pain versus a placebo (OR, 3.43, 95% CI = 1.03–11.48). It is worth noting that the effect size for inhaled cannabis is consistent with a separate recent review of 5 trials of the effect of inhaled cannabis on neuropathic pain (Andreae et al., 2015). The pooled ORs from these trials contributed to the Bayesian pooled effect estimate of 3.22 for pain relief versus placebo (95% CI = 1.59–7.24) tested across 9 THC concentrations. There was also some evidence of a dose-dependent effect in these studies.

Primary Literature

In the addition to the reviews by Whiting et al. (2015) and Andreae et al. (2015), the committee identified two additional studies on the effect of cannabis flower on acute pain (Wallace et al., 2015; Wilsey et al., 2016). One of those studies found a dose-dependent effect of vaporized cannabis flower on spontaneous pain, with the high dose (7 percent THC) showing the strongest effect size (Wallace et al., 2015). The other study found that vaporized cannabis flower reduced pain but did not find a significant dose-dependent effect (Wilsey et al., 2016). These two studies are consistent with the previous reviews by Whiting et al. (2015) and Andreae et al. (2015), suggesting a reduction in pain after cannabis administration.

Discussion of Findings

The majority of studies on pain cited in Whiting et al. (2015) evaluated nabiximols outside the United States. In their review, the committee found that only a handful of studies have evaluated the use of cannabis in the United States, and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse that was either vaporized or smoked. In contrast, many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States. For exam-

ple, in 2015 between 498,170 and 721,599 units of medical and recreational cannabis edibles were sold per month in Colorado (Colorado DOR, 2016, p. 12). Pain patients also use topical forms (e.g., transdermal patches and creams). Thus, while the use of cannabis for the treatment of pain is supported by well-controlled clinical trials as reviewed above, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States. Given the ubiquitous availability of cannabis products in much of the nation, more research is needed on the various forms, routes of administration, and combination of cannabinoids.

CONCLUSION 4-1 There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

CANCER

Cancer is a broad term used to describe a wide range of related diseases that are characterized by an abnormal, unregulated division of cells; it is a biological disorder that often results in tumor growth (NCI, 2015). Cancer is among the leading causes of mortality in the United States, and by the close of 2016 there will be an estimated 1.7 million new cancer diagnoses (NCI, 2016). Relevant to the committee's interest, there is evidence to suggest that cannabinoids (and the endocannabinoid system more generally) may play a role in the cancer regulation processes (Rocha et al., 2014). Therefore, there is interest in determining the efficacy of cannabis or cannabinoids for the treatment of cancer.

Are Cannabis or Cannabinoids an Effective Treatment for Cancer?

Systematic Reviews

Using the committee's search strategy only one recent review was found to be of good to fair quality (Rocha et al., 2014).[3] The review focused exclusively on the anti-tumor effects of cannabinoids on gliomas.[4] Of the 2,260 studies identified through December 2012, 35 studies met the inclusion criteria. With the exception of a small clinical trial, these studies

[3] Due to the lack of recent, high-quality reviews, the committee has identified that a research gap exists concerning the effectiveness of cannabis or cannabinoids in treating cancer in general.

[4] Glioma is a type of tumor that originates in the central nervous system (i.e., the brain or spine) and arises from glial cells.

were all preclinical studies. All 16 of the in vivo studies found an antitumor effect of cannabinoids.

Primary Literature

The committee did not identify any good-quality primary literature that reported on cannabis or cannabinoids for the treatment of cancer that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Clearly, there is insufficient evidence to make any statement about the efficacy of cannabinoids as a treatment for glioma. However, the signal from the preclinical literature suggests that clinical research with cannabinoids needs to be conducted.

CONCLUSION 4-2 There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers, including glioma.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Nausea and vomiting are common side effects of many cytotoxic chemotherapy agents. A number of pharmaceutical interventions in various drug classes have been approved for the treatment of chemotherapy-induced nausea and vomiting. Among the cannabinoid medications, nabilone and dronabinol were initially approved in 1985 for nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional antiemetic treatments (Todaro, 2012, pp. 488, 490).

Are Cannabis or Cannabinoids an Effective Treatment for the Reduction of Chemotherapy-Induced Nausea and Vomiting?

Systematic Reviews

Whiting et al. (2015) summarized 28 trials reporting on nausea and vomiting due to chemotherapy, most published before 1984, involving 1,772 participants. The cannabinoid therapies investigated in these trials included nabilone (14), tetrahydrocannabinol (6), levonantradol (4), dronabinol (3), and nabiximols (1). Eight studies were placebo controlled,

and 20 included active comparators (prochlorperazine 15; chlorpromazine 2; dromperidone 2; and alizapride, hydroxyzine, metoclopramide, and ondansetron 1 each). Two studies evaluated combinations of dronabinol with prochlorperazine or ondansetron. The average number of patients showing a complete nausea and vomiting response was greater with cannabinoids than the placebo (OR, 3.82, 95% CI = 1.55–9.42) in 3 trials of dronabinol and nabiximols that were considered low-quality evidence. Whiting et al. (2015) concluded that all trials suggested a greater benefit for cannabinoids than for both active agents and for the placebo, although these did not reach statistical significance in all trials.

Of the 23 trials summarized in a Cochrane review (Smith et al., 2015), 19 were crossover design and 4 were parallel-group design. The cannabinoids investigated were nabilone (12) or dronabinol (11), with 9 placebo-controlled trials (819 participants) and 15 with active comparators (prochlorperazine, 11; metoclopramide, 2; chlorpromazine, 1; domperidone, 1). In 2 trials, a cannabinoid added to a standard antiemetic was compared to the standard alone. While 2 of the placebo-controlled trials showed no significant difference in those reporting absence of nausea with cannabinoids (relative risk [RR], 2.0, 95% CI = 0.19–21), 3 showed a greater chance of having complete absence of vomiting with cannabinoids (RR, 5.7, 95% CI = 2.16–13) and 3 showed a numerically higher chance of complete absence of both nausea and vomiting (RR, 2.9, 95% CI = 1.8–4.7). There was no difference in outcome between patients who were cannabis-naïve and those who were not (P value = 0.4). Two trials found a patient preference for cannabinoids over the comparator. When compared to prochlorperazine, there was no significant difference in the control of nausea, vomiting, or both, although in 7 of the trials there was a higher chance of patients reporting a preference for the cannabinoid therapy (RR, 3.2, 95% CI = 2.2–4.7). In their review the investigators state that cannabinoids were highly effective, being more efficacious than the placebo and similar to conventional antiemetics in treating chemotherapy-induced nausea and vomiting. Despite causing more adverse events such as dizziness, dysphoria, euphoria, "feeling high," and sedation, there was weak evidence for a preference for cannabinoids over the placebo and stronger evidence for a preference over other antiemetics. Despite these findings, however, the authors concluded that there was no evidence to support the use of cannabinoids over current first-line antiemetic therapies and that cannabinoids should be considered as useful adjunctive treatment "for people on moderately or highly emetogenic chemotherapy that are refractory to other antiemetic treatments, when all other options have been tried" (Smith et al., 2015, p. 23).

Only 3 of the 28 trials in a systematic review of antiemetic therapies in children receiving chemotherapy involved cannabinoid therapies

(nabilone 2; THC 1) (Phillips et al., 2016). The comparators were prochlorperazine in the first nabilone trial, domperidone in the second, and prochlorperazine and metoclopramide in two separate randomizations in the THC trial. In 1 trial with unclear risk of bias, THC dosed at 10 mg/m^2 five times on the day of chemotherapy was superior to prochlorperazine in the complete control of acute nausea (RR, 20.7, 95% CI = 17.2–36.2) and vomiting (RR, 19.0, 95% CI = 13.7–26.3). Another trial reported better nausea severity scores for nabilone compared to domperidone (1.5 versus 2.5 on a 0 to 3 [none to worst] scale) ($p = 0.01$). The largest and most recent trial in this review compared THC to proclorperzine and found no benefit over the control on emesis (RR, 1.0, 95% CI = 0.85–1.17).

Primary Literature

An additional search of the primary literature since the review by Whiting et al. (2015) did not identify any additional studies. The primary literature was then searched in an effort to find studies of cannabinoids compared to the more widely used antiemetics. One trial conducted in 2007 investigated a cannabinoid therapy compared to the current generation of serotonin antagonist antiemetics, as opposed to the dopamine D2 receptor antagonists used in the earlier trials. This 64-patient study evaluated the frequently used antiemetic ondansetron versus dronabinol versus the combination of the two in delayed chemotherapy-induced nausea and vomiting (Meiri et al., 2007). The two agents appeared similar in their effectiveness, with no added benefit from the combination. Hence, the cannabinoid again fared as well as the current standard antiemetic in this more recent investigation.

Discussion of Findings

The oral THC preparations nabilone and dronabinol have been available for the treatment of chemotherapy-induced nausea and vomiting for more than 30 years (Grotenhermen and Müller-Vahl, 2012). They were both found to be superior to the placebo and equivalent to the available antiemetics at the time that the original trials were conducted. A more recent investigation suggests that dronabinol is equivalent to ondansetron for delayed nausea and vomiting, although no comparison to the currently more widely used neurokinin-1 inhibitors has been conducted. In the earlier trials, patients reported a preference for the cannabinoids over available agents. Despite an abundance of anecdotal reports of the benefits of plant cannabis, either inhaled or ingested orally, as an effective treatment for chemotherapy-induced nausea and vomiting, there are no good-quality randomized trials investigating this option. This is,

in part, due to the existing obstacles to investigating the potential therapeutic benefit of the cannabis plant. Nor have any of the reviewed trials investigated the effectiveness of cannabidiol or cannabidiol-enriched cannabis in chemotherapy-induced nausea and vomiting. Such information is frequently requested by patients seeking to control chemotherapy-induced nausea and vomiting without the psychoactive effects of the THC-based preparations. Resolving this identified research gap may be a future research priority.

CONCLUSION 4-3 There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting.

ANOREXIA AND WEIGHT LOSS

Anorexia and weight loss are common side effects of many diseases, especially cancer. And prior to the availability of highly active antiretroviral therapy, a wasting syndrome was a frequent clinical manifestation in patients with human immunodeficiency virus (HIV) infection and advanced acquired immune deficiency syndrome (AIDS). The labeled indications for dronabinol were expanded in 1992 to include treatment of anorexia associated with weight loss in patients with AIDS (IOM, 1999, p. 156).

Are Cannabis or Cannabinoids an Effective Treatment for Anorexia and Weight Loss Associated with HIV/AIDS, Cancer-Associated Anorexia-Cachexia Syndrome, and Anorexia Nervosa?

AIDS Wasting Syndrome

Systematic Reviews Two good-quality systematic reviews included trials investigating cannabinoid therapies in patients with HIV/AIDS. Four randomized controlled trials involving 255 patients were assessed by Whiting et al. (2015), who described all of the trials to be at high risk of bias (ROB) for reasons not elaborated.[5] All four studies included dronabinol, with one investigating inhaled cannabis as well. Three trials were placebo-controlled, and one used the progestational agent megestrol acetate as the comparator. The review authors concluded that there was some evidence suggesting that cannabinoids were effective in weight gain

[5] Key issues that led to high ROB ratings were: high (n = 1) or unclear (n = 3) ROB for allocation concealment; unclear ROB (n = 3) for blinded outcome assessments; high (n = 1) or unclear (n = 1) ROB for randomization.

in HIV. A second systematic review focused on morbidity and mortality in HIV/AIDS as the primary outcomes, with changes in appetite and weight as secondary endpoints (Lutge et al., 2013). Seven RCTs conducted between 1993 and 2009 were included in the qualitative analysis. The trials compared dronabinol or inhaled cannabis with a placebo or with each other. In one study the individuals' weights increased significantly more ($p < 0.01$) on higher doses of cannabis (3.9 percent THC) and dronabinol (10 mg) than on lower doses. In a second trial, median weight was increased with inhaled cannabis (3.5 percent) by 3.0 kg ($p = 0.021$) and dronabinol (2.5 mg) by 3.2 kg ($p = 0.004$) when compared with a placebo (a 1.1-kg increase over a 21-day exposure). In a study with 88 evaluable patients, the dronabinol group gained an average of 0.1 kg, while the placebo recipients lost a mean of 0.4 kg ($p = 0.14$). The proportion of patients gaining at least 2 kg was the same in both groups. Most of the weight gain was in the body fat compartment when this was investigated. Changes in appetite, food, and caloric intake were not deemed to be evaluable in any of the studies. These investigators concluded that the evidence for the efficacy and safety of cannabis and cannabinoids is lacking to support utility in treating AIDS-associated anorexia.

Primary Literature The committee did not identify any good-quality primary literature that reported on cannabis or cannabinoids as effective treatments for AIDS wasting syndrome that were published subsequently to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question. This is largely due to the virtual disappearance of the syndrome since effective antiretroviral therapies became available in the mid-1990s.

Cancer-Associated Anorexia-Cachexia Syndrome

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on cannabis or cannabinoids as effective treatments for cancer-associated anorexia-cachexia syndrome.

Primary Literature A Phase III multicenter, randomized, double-blind placebo-controlled trial was conducted by the Cannabis-In-Cachexia-Study-Group in patients with cancer-related anorexia-cachexia syndrome (Strasser et al., 2006). Patients with advanced cancer and weight loss of greater than 5 percent over 6 months were randomized 2:2:1 to receive treatment with a cannabis extract (standardized to THC 2.5 mg and cannabidiol 1.0 mg), THC 2.5 mg, or a placebo twice daily for 6 weeks. Appetite, mood, and nausea were monitored daily. Cancer-related quality of life and cannabinoid-related toxicity were also monitored. Only 164 of

the 243 patients who were randomized completed the trial. An intent-to-treat analysis yielded no difference between the groups in appetite, quality of life, or toxicity. Increased appetite was reported by 73 percent of the cannabis-extract, 58 percent of the THC group, and 69 percent of the placebo recipients. Recruitment was terminated early by the data review board because it was believed to be unlikely that differences would emerge between the treatment arms. The findings in this study reinforce the results from an earlier trial investigating dronabinol, megestrol acetate, or the combination in 469 advanced cancer patients with a loss of appetite and greater than 5 pounds weight loss over the prior 2 months (Jatoi et al., 2002). Megestrol acetate was superior to dronabinol for the improvement of both appetite and weight, with the combination therapy conferring no additional benefit. Seventy-five percent of the megestrol recipients reported an improvement in appetite compared to 49 percent of those receiving dronabinol ($p = 0.0001$). Of those in the combination arm, 66 percent reported improvement. A weight gain greater than or equal to 10 percent over their baseline at some point during the course of the trial was reported by 11 percent of those in the megestrol arm, compared with 3 percent of the dronabinol recipients ($p = 0.02$). The combination arm reported a weight gain in 8 percent. These findings confirm a similarly designed trial that was conducted in patients with AIDS wasting syndrome (Timpone et al., 1997).

Anorexia Nervosa

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for anorexia nervosa.

Primary Literature Pharmacological interventions in the treatment of anorexia nervosa have not been promising to date. Andries et al. (2014) conducted a prospective, randomized, double-blind, controlled crossover trial in 24 women with anorexia nervosa of at least 5 years' duration attending both psychiatric and somatic therapy as inpatients or outpatients. In addition to their standard psychotherapy and nutritional interventions, the participants received dronabinol 2.5 mg twice daily for 4 weeks and a matching placebo for 4 weeks, randomly assigned to two treatment sequences (dronabinol/placebo or placebo/dronabinol). The primary outcome was weight change assessed weekly. The secondary outcome was change in Eating Disorder Inventory-2 (EDI-2) scores. The participants had a significant weight gain of 1.00 kg (95% CI = 0.40–1.62) during dronabinol therapy and 0.34 kg (95% CI = −0.14–0.82) during the placebo ($p = 0.03$). No statistically different differences in EDI-2 score

changes were seen during treatment with dronabinol or the placebo, suggesting that there was no real effect on the participants' attitudinal and behavioral traits related to eating disorders. The authors acknowledged the small sample size and the short duration of exposure, as well as the potential psychogenic effects, but they concluded that low-dose dronabinol is a safe adjuvant palliative therapy in a highly selected subgroup of chronically undernourished women with anorexia nervosa.

Discussion of Findings

There is some evidence for oral cannabinoids being able to increase weight in patients with the HIV-associated wasting syndrome and anorexia nervosa. No benefit has been demonstrated in cancer-associated anorexia-cachexia syndrome. The studies have generally been small and of short duration and may not have investigated the optimal dose of the cannabinoid. In one study in HIV patients, both dronabinol and inhaled cannabis increased weight significantly compared to the placebo dronabinol. Cannabis has long been felt to have an orexigenic effect, increasing food intake (Abel, 1975). Small residential studies conducted in the 1980s found that inhaled cannabis increased caloric intake by 40 percent, with most of the increase occurring as snacks and not during meals (Foltin et al., 1988). Hence, the results of the clinical trials in AIDS wasting and cancer-associated anorexia-cachexia syndrome demonstrating little to no impact on appetite and weight were somewhat unexpected. One could postulate that perhaps other components of the plant in addition to THC may contribute to the effect of cannabis on appetite and food intake. There have not been any randomized controlled trials conducted studying the effect of plant-derived cannabis on appetite and weight with weight as the primary endpoint. This is, in part, due to existing obstacles to investigating the potential therapeutic benefit of the cannabis plant.

CONCLUSION 4-4

4-4(a) There is limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS.

4-4(b) There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder commonly associated with symptoms of abdominal cramping and changes in bowel movement patterns. Irritable bowel syndrome is classified into four types based on the types of bowel movements: IBS with diarrhea, IBS with constipation, IBS mixed, and IBS unclassified (NIDDK, 2015). Approximately 11 percent of the world's population suffers from at least one type of this disorder (Canavan et al., 2014).

Type 1 cannabinoid (CB_1) receptors are present in the mucosa and neuromuscular layers of the colon; they are also expressed in plasma cells and influence mucosal inflammation (Wright et al., 2005). In animal models, endocannabinoids acting on CB_1 receptors inhibit gastric and small intestinal transit and colonic propulsion (Pinto et al., 2002). Studies in healthy volunteers have shown effects on gastric motility and colonic motility (Esfandyari et al., 2006). Thus, cannabinoids have the potential for therapeutic effect in patients with IBS (Wong et al., 2012).

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms of Irritable Bowel Syndrome?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for symptoms of irritable bowel syndrome.

Primary Literature

We identified a single relevant trial (Wong et al., 2012) evaluating dronabinol in patients with irritable bowel syndrome with diarrhea (IBS-D). This low-risk-of-bias trial enrolled 36 patients between the ages of 18 and 69 with IBS-D. Patients were randomized to dronabinol 2.5 mg BID[6] (n = 10), dronabinol 5 mg BID (n = 13), or a placebo (n = 13) for 2 days. No overall treatment effects of dronabinol on gastric, small bowel, or colonic transit, as measured by radioscintigraphy, were detected.

Discussion of Findings

A single, small trial found no effect of two doses of dronabinol on gastrointestinal transit. The quality of evidence for the finding of no effect

[6] BID is an abbreviation for the Latin phrase *bis in die*, which means twice per day.

for irritable bowel syndrome is insufficient based on the short treatment duration, small sample size, short-term follow-up, and lack of patient-reported outcomes. Trials that evaluate the effects of cannabinoids on patient-reported outcomes are needed to further understand the clinical effects in patients with IBS.

CONCLUSION 4-5 There is insufficient evidence to support or refute the conclusion that dronabinol is an effective treatment for the symptoms of irritable bowel syndrome.

EPILEPSY

Epilepsy refers to a spectrum of chronic neurological disorders in which clusters of neurons in the brain sometimes signal abnormally and cause seizures (NINDS, 2016a). Epilepsy disorder affects an estimated 2.75 million Americans, across all age ranges and ethnicities (NINDS, 2016a). Although there are many antiepileptic medications currently on the market, about one-third of persons with epilepsy will continue to have seizures even when treated (Mohanraj and Brodie, 2006). Both THC and CBD can prevent seizures in animal models (Devinsky et al., 2014).

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms of Epilepsy?

Systematic Reviews

We identified two systematic reviews of randomized trials assessing the efficacy of cannabis or cannabinoids, used either as monotherapy or in addition to other therapies, in reducing seizure frequency in persons with epilepsy. Gloss and Vickrey (2014) published a systematic review of randomized controlled trials. They identified four reports (including one conference abstract and one letter to the editor) of cannabinoid trials, all of which they considered to be of low quality. Combined, the trials included a total of 48 patients. The systematic review's primary prespecified outcome was freedom from seizures for either 12 months or three times the longest previous seizure-free interval. None of the four trials assessed this endpoint. Accordingly, Gloss and Vickrey asserted that no reliable conclusions could be drawn regarding the efficacy of cannabinoids for epilepsy.

Koppel et al. (2014) published a fair-quality systematic review. They identified no high-quality randomized trials and concluded that the existing data were insufficient to support or refute the efficacy of cannabinoids for reducing seizure frequency.

Primary Literature

We identified two case series that reported on the experience of patients treated with cannabidiol for epilepsy that were published subsequent to the systematic reviews described above. The first of these was an open-label, expanded-access program of oral cannabidiol with no concurrent control group in patients with severe, intractable childhood-onset epilepsy that was conducted at 11 U.S. epilepsy centers and reported by Devinsky et al. (2016) and by Rosenberg et al. (2015). Devinsky et al. (2016) reported on 162 patients ages 1 to 30 years; Rosenberg et al. (2015) reported on 137 of these patients. The median monthly frequency of motor seizures was 30.0 (interquartile range [IQR] 11.0–96.0) at baseline and 15.8 (IQR 5.6–57.6) over the 12-week treatment period. The median reduction in motor seizures while receiving cannabidiol in this uncontrolled case series was 36.5 percent (IQR 0–64.7).

Tzadok et al. (2016) reported on the unblinded experience of Israeli pediatric epilepsy clinics treating 74 children and adolescents with intractable epilepsy with an oral formulation of cannabidiol and tetrahydrocannabinol at a 20:1 ratio for an average of 6 months. There was no concurrent control goup. Compared with baseline, 18 percent of children experienced a 75–100 percent reduction in seizure frequency, 34 percent experienced a 50–75 percent reduction, 12 percent reported a 25–50 percent reduction, 26 percent reported a reduction of less than 25 percent, and 7 percent reported aggravation of seizures that led to a discontinuation of the cannabinoid treatment.

The lack of a concurrent placebo control group and the resulting potential for regression to the mean and other sources of bias greatly reduce the strength of conclusions that can be drawn from the experiences reported by Devinsky et al. (2016), Rosenberg et al. (2015), and Tzadok et al. (2016) about the efficacy of cannabinoids for epilepsy. Randomized trials of the efficacy of cannabidiol for different forms of epilepsy have been completed,[7] but their results have not been published at the time of this report.

Discussion of Findings

Recent systematic reviews were unable to identify any randomized controlled trials evaluating the efficacy of cannabinoids for the treatment of epilepsy. Currently available clinical data therefore consist solely of uncontrolled case series, which do not provide high-quality evidence

[7] ClinicalTrials.gov: NCT02224560, NCT02224690, NCT02091375, NCT02324673.

of efficacy. Randomized trials of the efficacy of cannabidiol for different forms of epilepsy have been completed and await publication.

CONCLUSION 4-6 There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for epilepsy.

SPASTICITY ASSOCIATED WITH MULTIPLE SCLEROSIS OR SPINAL CORD INJURY

Spasticity is defined as disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles (Pandyan et al., 2005). It occurs in some patients with chronic neurological conditions such as multiple sclerosis (MS) and paraplegia due to spinal cord injury. Recent studies have shown that some individuals with MS are seeking alternative therapies, including cannabis, to treat symptoms associated with MS (Zajicek et al., 2012).

Are Cannabis or Cannabinoids an Effective Treatment for Spasticity Associated with Multiple Sclerosis or Spinal Cord Injury?

Systematic Reviews

We identified two recent systematic reviews that assessed the efficacy of cannabis or cannabinoids in treating muscle spasticity in patients with MS or paraplegia due to spinal cord injury—the systematic review by Whiting et al. (2015) that examined evidence for a broad range of medical uses of cannabis or cannabinoids and the systematic review by Koppel et al. (2014) that focused more narrowly on neurologic conditions. Both systematic reviews examined only randomized, placebo-controlled trials. Whiting et al. (2015) excluded from their primary analysis trials that did not use a parallel group design (i.e., they excluded crossover trials) and performed a quantitative pooling of results. In contrast, Koppel et al. (2014) included crossover trials but did not perform a quantitative pooling of results.

Whiting et al. (2015) searched for studies examining the efficacy of cannabinoids for spasticity due to MS or paraplegia. They identified 11 studies that included patients with MS and 3 that included patients with paraplegia caused by spinal cord injury. None of the studies in patients with paraplegia caused by spinal cord injury were reported as full papers or included sufficient data to allow them to be included in pooled estimates. Whiting et al. (2015) reported that in their pooled analysis of three

trials in patients with MS, nabiximols and nabilone were associated with an average change (i.e., improvement) in spasticity rating assessed by a patient-reported numeric rating scale of −0.76 (95% CI = −1.38 to −0.14) on a 0 to 10 scale that was statistically greater than for the placebo. They further reported finding no evidence for a difference according to type of cannabinoid (i.e., nabiximols versus nabilone). Whiting et al. (2015) also reported that the pooled odds of patient-reported improvement on a global impression-of-change score was greater with nabiximols than with the placebo (OR, 1.44, 95% CI = 1.07–1.94).

The review by Koppel et al. (2014) restricted its focus on spasticity to that due to MS. Their conclusions were broadly in agreement with corresponding conclusions from the review by Whiting et al. (2015). In particular, Koppel et al. (2014) concluded that in patients with MS, nabiximols and orally administered THC are "probably effective" for reducing patient-reported spasticity scores and that oral cannabis extract is "established as effective for reducing patient-reported scores" for spasticity (Koppel et al., 2014, p. 1558).

A commonly used scale for rating spasticity is the Ashworth scale (Ashworth, 1964). However, this scale has been criticized as unreliable, insensitive to therapeutic benefit, and reflective only of passive resistance to movement and not of other features of spasticity (Pandyan et al., 1999; Wade et al., 2010). Furthermore, no minimally important difference in the Ashworth scale has been established. Whiting et al. (2015) calculated a pooled measure of improvement on the Ashworth scale versus placebo based on five parallel-group-design trials. They reported that nabiximols, dronabinol, and oral THC/CBD were associated with a numerically greater average improvement on the Ashworth scale than with a placebo but that this difference was not statistically significant. This conclusion is in broad agreement with corresponding conclusions reached by Koppel et al. (2014), who concluded in particular that nabiximols, oral cannabis extract and orally administered THC are "probably ineffective" for reducing objective measures of spasticity in the short term (6–15 weeks), although oral cannabis extract and orally administered THC are "possibly effective" for objective measures at 1 year.

Primary Literature

An additional placebo-controlled crossover trial of nabiximols for the treatment of spasticity in patients with MS was published after the period covered by the Whiting and Koppel systematic reviews (Leocani et al., 2015). This study randomized 44 patients but analyzed only 34 because of post-randomization exclusions and dropouts. Such post-randomization exclusions and dropouts reduce the strength of the evidence that is pro-

vided by this study. Patient-reported measures of spasticity were not assessed. After 4 weeks of treatment, response on the modified Ashworth scale (defined as improvement of at least 20 percent) was more common in the THC/CBD group (50 percent) than in the placebo group (23.5 percent), p = 0.041.

Discussion of Findings

Based on evidence from randomized controlled trials included in systematic reviews, an oral cannabis extract, nabiximols, and orally administered THC are probably effective for reducing patient-reported spasticity scores in patients with MS. The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale. These agents have not consistently demonstrated a benefit on clinician-measured spasticity indices such as the modified Ashworth scale in patients with MS. Given the lack of published papers reporting the results of trials conducted in patients with spasticity due to spinal cord injury, there is insufficient evidence to conclude that cannabinoids are effective for treating spasticity in this population.

CONCLUSION 4-7

4-7(a) There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms, but limited evidence for an effect on clinician-measured spasticity.

4-7(b) There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury.

TOURETTE SYNDROME

Tourette syndrome is a neurological disorder characterized by sporadic movements or vocalizations commonly called "tics" (NINDS, 2014). While there is currently no cure for Tourette syndrome, recent efforts have explored whether cannabis may be effective in reducing symptoms commonly associated with the disorder (Koppel et al., 2014).

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms Associated with Tourette Syndrome?

Systematic Reviews

We identified two good-quality systematic reviews (Koppel et al., 2014; Whiting et al., 2015) that evaluated medical cannabis for Tourette syndrome. Both good-quality reviews identified the same trials, and we focus on the more recent review by Whiting et al. (2015). The two RCTs (four reports), conducted by the same research group (Müller-Vahl et al., 2001, 2002, 2003a,b), compared THC capsules (maximum dose 10 mg daily) to a placebo in 36 patients with Tourette syndrome. Tic severity, assessed by multiple measures, and global clinical outcomes were improved with THC capsules. On a 0 to 6 severity scale, symptoms were improved by less than 1 point. These outcomes were assessed at 2 days (unclear-risk-of-bias trial) and 6 weeks (high-risk-of-bias trial). Neither trial described randomization or allocation concealment adequately, and the 6-week trial was rated high risk of bias for incomplete outcome data.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for Tourette syndrome, and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

No clear link has been established between symptoms of Tourette syndrome and cannabinoid sites or mechanism of action. However, case reports have suggested that cannabis can reduce tics and that the therapeutic effects of cannabis might be due to the anxiety-reducing properties of marijuana rather than to a specific anti-tic effect (Hemming and Yellowlees, 1993; Sandyk and Awerbuch, 1988). Two small trials (assessed as being of fair to poor quality) provide limited evidence for the therapeutic effects of THC capsules on tic severity and global clinical outcomes.

CONCLUSION 4-8 There is limited evidence that THC capsules are an effective treatment for improving symptoms of Tourette syndrome.

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the motor neurons in the spinal cord, brain stem, and motor cortex, ultimately leading to complete paralysis (Rossi et al., 2010). The pathogenesis of ALS remains unclear, but the disease is thought to result from the interplay of a number of mechanisms, including neurofilament accumulation, excitotoxicity, oxidative stress, and neuroinflammation (Redler and Dokholyan, 2012), all of which may be amenable to manipulation of the endocannabinoid system and cannabinoid receptors.

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms Associated with Amyotrophic Lateral Sclerosis?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for symptoms associated with amyotrophic lateral sclerosis.

Primary Literature

On the basis of proposed pathogenesis and anecdotal reports of symptomatic benefit from the use of cannabis in patients with ALS, two small trials of dronabinol have been conducted. In a randomized, double-blind crossover study, 19 patients with ALS were treated with dronabinol doses of 2.5 to 10 mg daily for 4 weeks (Gelinas et al., 2002). Participants noted improvement in appetite and sleep but not in cramps or fasiculations (involuntary muscle twitches). The second study enrolled 27 patients with ALS who had moderate to severe cramps (greater than 4 on a 0–10 visual analogue scale) in a randomized, double-blind trial of dronabinol 5 mg twice daily or a placebo, each given for 2 weeks with an intervening 2-week washout period (Weber et al., 2010). The primary endpoint was a change in cramp intensity with secondary endpoints of change in cramp number, intensity of fasciculations, quality of life, sleep, appetite, and depression. There was no difference between dronabinol and the placebo seen in any of the endpoints. The investigators reported that the dronabinol was very well tolerated and postulated that the dronabinol dose may have been too low as well as suggesting that a carryover effect in the crossover design may have obfuscated any differences in the treatment arms. The sample size was too small to discern anything but a large effect.

Discussion of Findings

Two small studies investigated the effect of dronabinol on symptoms associated with ALS. Although there were no differences from placebo in either trial, the sample sizes were small, the duration of the studies was short, and the dose of dronabinol may have been too small to ascertain any activity. The effect of cannabis was not investigated.

CONCLUSION 4-9 There is insufficient evidence that cannabinoids are an effective treatment for symptoms associated with amyotrophic lateral sclerosis.

HUNTINGTON'S DISEASE

Huntington's disease is characterized by chorea (abnormal, involuntary movement) along with cognitive decline and psychiatric impairment (Armstrong and Miyasaki, 2012). Worsening chorea significantly impacts patient quality of life. The pathophysiology and neurochemical basis of Huntington's disease are incompletely understood. Neuroprotective trials often investigate agents that may decrease oxidative stress or glutamatergic changes related to excitotoxic stress. There is some preclinical evidence and limited clinical evidence that suggest that changes in the endocannabinoid system may be linked to the pathophysiology of Huntington's disease (Pazos et al., 2008; van Laere et al., 2010).

Are Cannabis or Cannabinoids an Effective Treatment for the Motor Function and Cognitive Performance Associated with Huntington's Disease?

Systematic Reviews

The systematic review from the American Academy of Neurology includes two studies on Huntington's disease (Koppel et al., 2014). A randomized, double-blind, placebo-controlled crossover pilot trial investigated nabilone 1 or 2 mg daily for 5 weeks followed by a placebo in 22 patients with symptomatic Huntington's disease (Curtis et al., 2009). An additional 22 patients were randomized to the placebo followed by nabilone. The primary endpoint was the total motor score of the Unified Huntington's Disease Rating Scale (UHDRS). Secondary endpoints included the chorea, cognitive performance, and psychiatric changes measured with the same instrument. No significant difference in the total motor score was seen in the 37 evaluable patients (treatment difference, 0.86, 95% CI = –1.8–3.52), with a 1-point change considered clinically significant. There was evidence of an improvement in the chorea subscore

with nabilone (treatment difference, 1.68, 95% CI = 0.44–2.92). There was no difference between treatments for cognition, but there was evidence of an improvement in the two neuropsychiatric outcome measures in the nabilone arm—UHDRS behavioral assessment (4.01, 95% CI = −0.11–8.13) and neuropsychiatric inventory (6.43, 95% CI = 0.2–12.66). The small estimated treatment effect with wide confidence intervals reduces the level of evidence for nabilone's effectiveness from this pilot study. However, based on this trial, the American Academy of Neurology guideline concluded that "nabilone possibly modestly improves Huntington's disease chorea" (Armstrong and Miyasaki, 2012, p. 601). The second study included in the systematic review was a lower-quality, 15-patient randomized, double-blind, placebo-controlled trial investigating the effect of cannabidiol capsules at a dose of 10 mg/kg/day in two divided doses (Consroe et al., 1991). The endpoints in this study involving patients with Huntington's disease who were not on neuroleptics were chorea severity, functional limitations, and side effects. There were no statistically significant differences between cannabidiol and placebo in any outcomes, although the American Academy of Neurology considered the study to be underpowered.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the declines in motor function and cognitive performance associated with Huntington's disease that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Two small studies have investigated the potential benefit of cannabinoids in patients with Huntington's disease. Although nabilone appeared to have some potential benefit on chorea, cannabidiol appeared to be equal to placebo in ameliorating symptoms. Both studies were of short duration and likely underpowered because of their small sample sizes. Cannabis has not been investigated in Huntington's disease.

CONCLUSION 4-10 There is insufficient evidence to support or refute the conclusion that oral cannabinoids are an effective treatment for chorea and certain neuropsychiatric symptoms associated with Huntington's disease.

PARKINSON'S DISEASE

Parkinson's disease is a motor system disorder attributed to the loss of dopamine-producing brain cells. It is characterized clinically by tremor, rigidity, bradykinesia (slowness of movement), and impaired balance and coordination (PDF, 2016a). An estimated 60,000 Americans are diagnosed with this disorder each year (PDF, 2016b).

Although the disease is progressive and without cure, there are medications that can ameliorate some of the associated symptoms. Although levodopa has demonstrated efficacy for treating symptoms of Parkinson's disease, long-term use of levodopa is associated with the development of side effects, especially dyskinesias (involuntary movements) (NINDS, 2015). Evidence suggests that the endocannabinoid system plays a meaningful role in certain neurodegenerative processes (Krishnan et al., 2009); thus, it may be useful to determine the efficacy of cannabinoids in treating the symptoms of neurodegenerative diseases.

Are Cannabis or Cannabinoids an Effective Treatment for the Motor System Symptoms Associated with Parkinson's Disease or the Levodopa-Induced Dyskinesia?

Systematic Reviews

The systematic review of cannabis in selected neurologic disorders (Koppel et al., 2014) identified two trials of cannabinoid therapies in patients with levodopa-induced dyskinesias. Nineteen patients with levodopa-induced dyskinesia greater than or equal to 2 as determined by questions 32–34 of the Unified Parkinson's Disease Rating Scale (UPDRS) were randomized in a double-blind, placebo-controlled crossover trial to receive Cannador capsules (containing THC 2.5 mg and CBD 1.25 mg) to a maximum dose of 0.25 mg/kg of THC daily or placebo (Carroll et al., 2004). The primary endpoint was the effect of treatment on the dyskinesia score of the UPDRS. Secondary endpoints included the impact of dyskinesia on function, pathophysiologic indicators of dyskinesia, duration of dyskinesia, quality of life, sleep, pain, and overall severity of Parkinson's disease. The overall treatment effect was +0.52, which indicated a worsening with Cannador, although this worsening was not statistically significant ($p = 0.09$). No effects were seen on the secondary outcomes. Although there were more adverse events on the drug than on the placebo, the investigators felt that the treatment was well tolerated. The study had limited statistical power to detect anything but a large treatment effect due to its small sample size. The second study included in the systematic review was an even smaller low-quality, randomized, double-blind, placebo-controlled crossover trial involving seven patients with

Parkinson's disease who had stable levodopa-induced dyskinesia present for 25–50 percent of the day (Sieradzan et al., 2001). Nabilone dosed at 0.03 mg/kg or a placebo was administered 12 hours and 1 hour before levodopa at a dose of 200 mg. The primary endpoint was total dyskinesia disability as measured using the Rush Dyskinesia Disability Scale.[8] The median total dyskinesia score after treatment with levodopa and nabilone was 17 (range 11–25) compared to 22 (range 16–26) after levodopa and the placebo ($p < 0.05$). The anti-Parkinsonian actions of levodopa were not reduced by nabilone pretreatment. Although the authors stated that "nabilone significantly reduced total levodopa-induced dyskinesia compared with placebo" (Sieradzan et al., 2001, p. 2109), the fact that the results were generated by only seven patients receiving only two doses clearly reduces the ability to draw such an enthusiastic conclusion. Koppel concludes that oral cannabis extract "is probably ineffective for treating levodopa-induced dyskinesias" (Koppel et al., 2014, p. 1560).

Primary Literature

Cannabidiol capsules were evaluated in a randomized, double-blind, placebo-controlled trial conducted in 21 patients with Parkinson's disease (Chagas et al., 2014). The study was an exploratory trial to assess the effect of CBD in Parkinson's disease globally with the UPDRS and the Parkinson's Disease Questionnaire-39 (PDQ-39) used to assess overall functioning and well-being. Possible CBD adverse events were evaluated by a side effect rating scale. Baseline data were collected 1 week before commencing treatment with CBD at 75 mg/day or 300 mg/day or with a placebo, and the same assessments were repeated during the sixth and final week of the trial. No statistically significant differences were seen in the UPDRS between the three study arms. There was a statistically significant difference in the variation between baseline and final assessment in the overall PDQ-39 score between the placebo (6.50 ± 8.48) and CBD 300 mg/day (25.57 ± 16.30) ($p = 0.034$), which suggests that there might be a possible effect of CBD on improving quality of life.

An open-label observational study of 22 patients with Parkinson's disease attending a motor disorder clinic at a tertiary medical center collected data before and 30 minutes after patients smoked 0.5 grams of cannabis (Lotan et al., 2014). The instruments utilized included the UPDRS, the McGill Pain Scale, and a survey of subjective efficacy and adverse effects of cannabis. In addition, the effect of cannabis on motor symptoms was evaluated by two raters. The investigators found that the total

[8] The Dyskinesia Disability Scale is a 0–4 scale (absent to most severe) measuring the severity of dyskinesia (Goetz et al., 1994).

motor symptoms score on the UPDRS improved from 33.1 (± 13.8) to 23.2 (± 10.5) ($p < 0.001$). Subcategories of the UPDRS that showed statistically significant improvement included tremor, rigidity, and bradykinesia. Pain and sleep were also reported to be improved after smoking cannabis. The results from this low-quality observational study prompted the investigators to propose that their findings should be confirmed in a larger, longer, randomized, double-blind, placebo-controlled trial.

Discussion of Findings

Small trials of oral cannabinoid preparations have demonstrated no benefit compared to a placebo in ameliorating the side effects of Parkinson's disease. A seven-patient trial of nabilone suggested that it improved the dyskinesia associated with levodopa therapy, but the sample size limits the interpretation of the data. An observational study of inhaled cannabis demonstrated improved outcomes, but the lack of a control group and the small sample size are limitations.

CONCLUSION 4-11 There is insufficient evidence that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia.

DYSTONIA

Dystonia is a disorder characterized by sustained or repetitive muscle contractions which result in abnormal fixed postures or twisting, repetitive movements (NINDS, 2016b). Idiopathic cervical dystonia is the most common cause of focal dystonia. Oral pharmacological agents are generally ineffective, with repeated injections of botulinum toxin being the most effective current therapy. The pathophysiologic mechanisms of dystonia are poorly understood, but, as in other hyperkinetic movement disorders, underactivity of the output regions of the basal ganglia may be involved. Stimulation of the cannabinoid receptors has been postulated as a way to reduce dystonia (Zadikoff et al., 2011). Anecdotal reports have suggested that cannabis may alleviate symptoms associated with dystonia (Uribe Roca et al., 2005). In a 1986 preliminary open pilot study in which five patients with dystonic movement disorders received cannabidiol, dose-related improvements were observed in all five patients (Consroe et al., 1986).

Are Cannabis or Cannabinoids an Effective Treatment for Dystonia?

Systematic Reviews

The American Academy of Neurology systematic review (Koppel et al., 2014) identified one study that examined the effect of dronabinol on cervical dystonia. The review described the study as being underpowered to detect any differences between dronabinol and the placebo. Overall, nine patients with cervical dystonia were randomized to receive dronabinol 15 mg daily or a placebo in an 8-week crossover trial (Zadikoff et al., 2011). The primary outcome measure was the change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) part A subscore at the beginning and the end of each 3-week treatment phase. There was no statistically significant effect of dronabinol on the dystonia compared with the placebo as measured by the TWSTRS-A ($p = 0.24$).

Primary Literature

Fifteen patients with a clinical diagnosis of primary dystonia received a single dose of nabilone or placebo (0.03 mg/kg to the nearest whole milligram) on the study day (Fox et al., 2002). The primary outcome measure was the dystonia-movement scale portion of the Burke-Fahn-Marsden dystonia scale. Treatment with nabilone produced no significant reduction in the total dystonia movement scale score when compared with placebo ($p > 0.05$).

Discussion of Findings

Two small trials of dronabinol and nabilone failed to demonstrate a significant benefit of the cannabinoids in improving dystonia compared with placebo. Cannabis has not been studied in the treatment of dystonia.

CONCLUSION 4-12 There is insufficient evidence to support or refute the conclusion that nabilone and dronabinol are an effective treatment for dystonia.

DEMENTIA

Dementia is characterized by a decline in cognition that typically affects multiple cognitive domains such as memory, language, executive function, and perceptual motor function (NIH, 2013). Alzheimer's disease, vascular dementia, and Parkinson's disease with dementia are three prominent dementing disorders (NIA, n.d.). Behavioral and psychological symptoms, including agitation, aggression, and food refusal, are common

in the more advanced stages of dementia. These symptoms cause distress to the patient and caregivers and may precipitate the patient being placed in institutional care. Current treatments for dementia (e.g., cholinesterase inhibitors) have only modest effects, and treatments for behavioral disturbances such as antipsychotic medications have both modest benefits and substantial adverse effects (Krishnan et al., 2009).

CB_1 receptors are found throughout the central nervous system, and the endogenous cannabinoid system is thought to be important in the regulation of synaptic transmission (Baker et al., 2003), a process that is disordered in patients with dementia. Accumulating evidence suggests that cannabinoids have the potential for neuroprotective effects (Grundy, 2002; Hampson et al., 1998; Shen and Thayer, 1998). This developing understanding of the endogenous cannabinoid system, along with cannabinoids anxiolytic and appetite-stimulating effects, provides a rationale for its study in patients with dementia.

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms Associated with Dementia?

Systematic Reviews

We identified two good-quality systematic reviews (Krishnan et al., 2009; van den Elsen et al., 2014) that evaluated cannabis for dementia. Both reviews identified the same two RCTs, which were synthesized qualitatively. A small randomized crossover trial (Volicer et al., 1997) evaluated dronabinol in 15 hospitalized patients with probable Alzheimer's disease who had behavior changes and were refusing food. Patients were randomized to dronabinol (2.5 mg twice daily) for 6 weeks and to a placebo for 6 weeks. Data in this trial with a high risk of bias were presented in such a way that they could not be abstracted for analysis by systematic review authors. The primary study authors reported: increased weight during the 12 weeks regardless of order of treatment (dronabinol, 7.0 [SD 1.5] pounds, and placebo, 4.6 [SD 1.3] pounds, during the first 6 weeks); decreased disturbed behavior during dronabinol treatment, an effect that persisted in patients treated first with dronabinol, then the placebo; decreased negative affect scores in both groups during the 12 weeks, more so when taking dronabinol than the placebo; and no serious adverse events attributed to dronabinol, although one patient suffered a seizure following the first dose. One other open-label pilot study (Walther et al., 2006), which evaluated six patients with severe dementia for the effects of dronabinol on nighttime agitation, did not meet eligibility criteria for the review by Krishnan et al. (2009).

Primary Literature

We identified one good-quality RCT that evaluated THC in 50 patients with Alzheimer's disease, vascular or mixed dementia, and neuropsychiatric symptoms (van den Elsen et al., 2015). THC 1.5 mg given three times daily for 3 weeks did not improve overall neuropsychiatric symptoms, agitation, quality of life, or activities of daily living versus a placebo. Although the study recruited less than one-half of the planned sample, the authors estimated that there was only a 5 percent chance that enrolling more participants would have shown a clinically important effect on neuropsychiatric symptoms.

Discussion of Findings

The authors of the good-quality Cochrane systematic review concluded that the "review finds no evidence that cannabinoids are effective in the improvement of disturbed behavior in dementia or treatment of other symptoms of dementia" (Krishnan et al., 2009, p. 8). Subsequently, a larger good-quality RCT found no benefit from low-dose THC. We agree that the evidence is limited due to the small number of patients enrolled, limits in the study design and reporting, and inconsistent effects. The current limited evidence does not support a therapeutic effect of cannabinoids.

CONCLUSION 4-13 There is limited evidence that cannabinoids are ineffective treatments for improving the symptoms associated with dementia.

GLAUCOMA

Glaucoma is one of the leading causes of blindness within the United States (Mayo Clinic, 2015). This disorder is characterized as a group of eye conditions that can produce damage to the optic nerve and result in a loss of vision. This damage is often caused by abnormally high intraocular pressure (NEI, n.d.). Because high intraocular pressure is a known major risk factor that can be controlled (Prum et al., 2016, p. 52), most treatments have been designed to reduce it. Research suggests that cannabinoids may have potential as an effective treatment for reducing pressure in the eye (Tomida et al., 2007).

Are Cannabis or Cannabinoids an Effective Treatment for Glaucoma?

Systematic Reviews

We identified one good-quality systematic review (Whiting et al., 2015) that evaluated medical cannabis for the treatment of glaucoma. This review identified a single randomized crossover trial (six participants) in patients with glaucoma. The trial compared THC (5 mg oromucosal spray), cannabidiol (20 mg oromucosal spray), cannabidiol spray (40 mg oromucosal spray), and a placebo, examining intraocular pressure intermittently up until 12 hours after treatment. Elevated intraocular pressure is one of the diagnostic criteria for glaucoma, and lowering intraocular pressure is a goal of glaucoma treatments (Prum et al., 2016). The trial was evaluated as "unclear" risk of bias. No differences in intraocular pressure were found between placebo and cannabinoids.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the symptoms of glaucoma and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Lower intraocular pressure is a key target for glaucoma treatments. Non-randomized studies in healthy volunteers and glaucoma patients have shown short-term reductions in intraocular pressure with oral, topical eye drops, and intravenous cannabinoids, suggesting the potential for therapeutic benefit (IOM, 1999, pp. 174–175). A good-quality systemic review identified a single small trial that found no effect of two cannabinoids, given as an oromucosal spray, on intraocular pressure (Whiting et al., 2015). The quality of evidence for the finding of no effect is limited. However, to be effective, treatments targeting lower intraocular pressure must provide continual rather than transient reductions in intraocular pressure. To date, those studies showing positive effects have shown only short-term benefit on intraocular pressure (hours), suggesting a limited potential for cannabinoids in the treatment of glaucoma.

CONCLUSION 4-14 There is limited evidence that cannabinoids are an ineffective treatment for improving intraocular pressure associated with glaucoma.

TRAUMATIC BRAIN INJURY/INTRACRANIAL HEMORRHAGE

Traumatic brain injury (TBI) is an acquired brain injury that can result from a sudden or violent hit to the head (NINDS, 2016c). TBI accounts for about 30 percent of all injury deaths in the United States (CDC, 2016). Intracranial hemorrhage (ICH), bleeding that occurs inside the skull, is a common complication of TBI which is associated with a worse prognosis of the injury (Bullock, 2000; CDC, 2015). There is a small body of literature reporting the neuroprotective effects of cannabinoid analogues in preclinical studies of head injuries (Mechoulam et al., 2002) as well as in observational studies in humans (Di Napoli et al., 2016; Nguyen et al., 2014).

Are Cannabis or Cannabinoids an Effective Treatment or Prevention for Traumatic Brain Injury or Intracranial Hemorrhage?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that evaluated the efficacy of cannabinoids as a treatment or prevention for traumatic brain injury or intracranial hemorrhage.

Primary Literature

There were two fair- to high-quality observational studies found in the literature. One study (n = 446) examined the TBI presentation and outcomes among patients with and without a positive THC blood test (Nguyen et al., 2014). Patients who were positive for THC were more likely to survive the TBI than those who were negative for THC (OR, 0.224, 95% CI = 0.051–0.991). The authors used regression analysis to account for confounding variables (e.g., age, alcohol, Abbreviated Injury Score, Injury Severity Score, mechanism of injury, gender, and ethnicity). In the only other observational study that examined the association between cannabis use and brain outcomes, a study of intracranial hemorrhage patients (n = 725) found that individuals with a positive test of cannabis use demonstrated better primary outcome scores on the modified Rankin Scale[9] (adjusted common OR, 0.544, 95% CI = 0.330–0.895) (Di Napoli et al., 2016). In their analysis, the authors adjusted for confounding variables that are known to be associated with worse ICH outcomes, including age, sex, Glasgow Coma Scale as continuous variables, and anticoagulant use.

[9] The modified Rankin Scale is a clinical assessment tool commonly used to measure the degree of disability following a stroke. Outcome scores from the scale range from 0 (no symptoms) to 6 (death) (Di Napoli et al., 2016, p. 249).

Discussion of Findings

The two studies discussed above (Di Napoli et al., 2016; Nguyen et al., 2014) provide very modest evidence that cannabis use may improve outcomes after TBI or ICH. However, more conclusive observational studies or randomized controlled trials will be necessary before any conclusions can be drawn about the neuroprotective effect of cannabinoids in clinical populations.

CONCLUSION 4-15 There is limited evidence of a statistical association between cannabinoids and better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage.

ADDICTION

Drug addiction has been defined as a chronically relapsing disorder that is characterized by the compulsive desire to seek and use drugs with impaired control over substance use despite negative consequences (Prud'homme et al., 2015). The endocannabinoid system has been found to influence the acquisition and maintenance of drug-seeking behaviors, possibly through its role in reward and brain plasticity (Gardner, 2005; Heifets and Castillo, 2009). Furthermore, in laboratory settings orally administered dronabinol has been found to reduce cannabis withdrawal symptoms in cannabis users who were not seeking treatment to reduce cannabis use (Budney et al., 2007; Haney et al., 2004) and therefore may be expected to be useful as a substitute to assist to achieve and maintain abstinence of cannabis.

Are Cannabis or Cannabinoids an Effective Treatment for Achieving Abstinence from Addictive Substances?

Systematic Reviews

We identified two recent published reviews that examined randomized trials evaluating the effects of cannabis or cannabinoids on the use of addictive drugs, including cannabis: one systematic review by Marshall et al. (2014) and one comprehensive review by Prud'homme et al. (2015).[10]

The review by Marshall et al. (2014) is a high-quality systematic

[10] Prud'homme (2015) is often categorized as a systematic review; however, the committee determined that the review lacks certain key elements of a systematic review, including a clearly stated research question, independent and duplicate data abstraction efforts, an assessment of the research quality and risk of bias, and a quantitative summary.

review of randomized and quasi-randomized trials assessing the efficacy of drug therapies specifically for cannabis dependence. They identified two trials examining THC: one published by Levin et al. (2011), examining dronabinol, and one published by Allsop et al. (2014), examining nabiximols.

The trial by Levin et al. (2011) was a randomized, placebo-controlled double-blind trial, which assigned cannabis-dependent adults to receive dronabinol (n = 79) or a placebo (n = 77) for 8 weeks, followed by a 2-week taper. Both groups received weekly individual therapy plus motivational enhancement therapy. Retention in the treatment program at the end of the maintenance phase was 77 percent in the dronabinol group and 61 percent in the placebo group (p-value for difference between groups = 0.02). Withdrawal symptoms declined more quickly in the dronabinol group than in the placebo group (p = 0.02). However, the primary outcome, the proportion of participants who achieved 2 consecutive weeks of abstinence at weeks 7 to 8, was 17.7 percent in the dronabinol group and 15.6 percent in the placebo group, which were not statistically significantly different from one another (p = 0.69).

The trial by Allsop et al. (2014) was randomized, placebo-controlled, and double-blind, and it enrolled adults seeking treatment for cannabis dependence. Subjects were patients who were hospitalized for 9 days and who received a 6-day regimen of nabiximols oromucosal spray (n = 27) or a matching placebo (n = 24) together with standardized psychosocial interventions. The primary outcome was a change in the Cannabis Withdrawal Scale, which is a 19-item scale that measures withdrawal symptom severity on an 11-point Likert scale for the previous 24 hours. Over the 6-day treatment period, subjects in the nabiximols group reported a mean 66 percent reduction from baseline in the cannabis withdrawal scale, while patients in the placebo group reported a mean increase in the cannabis withdrawal scale of 52 percent (p-value for between-group difference = 0.01). The median time between hospital discharge and relapse to cannabis use was 15 days (95% CI = 3.55–26.45) in the nabiximols group and 6 days (95% CI = 0–27.12) in the placebo group. The difference between these times was not statistically significant (p-value for between-group difference = 0.81).

Based on the Levin et al. (2011) and Allsop et al. (2014) trials, Marshall et al. (2014) concluded that there was moderate-quality evidence that users of THC preparations were more likely to complete treatment than those given a placebo (RR, 1.29, 95% CI = 1.08–1.55). However, the systematic review further concluded that, based on these two trials, the studied THC preparations were not associated with an increased likelihood of abstinence or a greater reduction in cannabis use than a placebo.

The review by Prud'homme et al. (2015) is a comprehensive review

that broadly examined evidence on the effects of cannabidiol on addictive behaviors. The only randomized trial assessing the role of cannabis in reducing the use of an addictive substance was published by Morgan et al. (2013). That study was a pilot placebo-controlled trial that randomized cigarette smokers who wished to quit smoking to receive 400 µg inhaled cannabidiol (n = 12) or inhaled placebo (n = 12) for 1 week. Participants were instructed to use the inhaler when they felt the urge to smoke. The reduction in the number of cigarettes smoked per week was higher in the cannabidiol group than in the placebo group, although the difference was not statistically significant (p = 0.054). Rates of abstinence were not reported.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the reduction in use of addictive substances and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Based on the systematic reviews, neither of the two trials evaluating the efficacy of a cannabinoid in achieving or sustaining abstinence from cannabis showed a statistically significant effect. However, given the limited number of studies and their small size, their findings do not definitively rule out the existence of an effect. The only study examining the efficacy of a cannabinoid in cigarette smoking cessation was a pilot study that did not examine rates of abstinence. Thus, its efficacy for smoking cessation has not been thoroughly evaluated.

CONCLUSION 4-16 There is no evidence to support or refute the conclusion that cannabinoids are an effective treatment for achieving abstinence in the use of addictive substances.

ANXIETY

Anxiety disorders share features of excessive fear and anxiety which induce psychological and physical symptoms that can cause significant distress or interfere with social, occupational, and other areas of functioning (APA, 2013). In a given year, an estimated 18 percent of the U.S. adult population will suffer from symptoms associated with an anxiety disorder (NIMH, n.d.). Given the role of the endocannabinoid system in mood

regulation, the committee decided to explore the relationship between anxiety and cannabis.

Are Cannabis or Cannabinoids an Effective Treatment for the Improvement of Anxiety Symptoms?

Systematic Reviews

The review by Whiting et al. (2015) was the most recent good-quality review. This review identified one randomized trial with a high risk of bias that compared a single 600 mg dose of cannabidiol to a placebo in 24 participants with generalized social anxiety disorder. Cannabidiol was associated with a greater improvement on the anxiety factor of a 100-point visual analogue mood scale (mean difference from baseline –16.52, $p = 0.01$) compared with a placebo during a simulated public speaking test. Four other randomized controlled trials (232 participants) enrolled patients with chronic pain and reported on anxiety symptoms. The cannabinoids studied were: dronabinol, 10–20 mg daily; nabilone, maximum dose of 2 mg daily; and nabiximols, maximum dose of 4–48 sprays/day. Outcomes were assessed from 8 hours to 6 weeks after randomization; three of the four trials were judged to have a high risk of bias. These trials suggested greater short-term benefit with cannabinoids than a placebo on self-reported anxiety symptoms.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the improvement of anxiety symptoms and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

There is limited evidence that cannabidiol improves anxiety symptoms, as assessed by a public speaking test, in patients with social anxiety disorder. These positive findings are limited by weaknesses in the study design (e.g., an inadequate description of randomization and allocation concealment), a single dose of CBD, and uncertain applicability to patients with other anxiety disorders. Limited evidence also suggests short-term benefits in patients with chronic pain and associated anxiety symptoms. In contrast, evidence from observational studies found moderate evidence that daily cannabis use is associated with increased anxiety symptoms

and heavy cannabis use is associated with social phobia disorder (see Chapter 12).

CONCLUSION 4-17 There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders.

DEPRESSION

Depression is one of the nation's most common mental health disorders (ADAA, 2016). Across the many depressive disorders that exist (e.g., persistent depressive disorder, major depressive disorder, premenstrual dysphoric disorder) there are common symptomatic features of feelings of sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that affect the individual's capacity to function (APA, 2013, p. 155). The endocannabinoid system is known to play a role in mood regulation (NIDA, 2015, p. 9); therefore, the committee decided to explore the association between cannabis use and depressive disorders or symptoms.

Are Cannabis or Cannabinoids an Effective Treatment to Reduce Depressive Symptoms?

Systematic Reviews

The review by Whiting et al. (2015) was the most recent good-quality review. No RCTs were identified that specifically evaluated cannabis in patients with a depressive disorder. Five RCTs (634 participants) enrolled patients for other conditions (chronic pain or multiple sclerosis with spasticity) and reported on depressive symptoms. Only one study reported depressive symptoms at baseline; symptoms were mild. Nabiximols (n = 3; maximum dose ranged from 4–48 doses/day), dronabinol (10 mg and 20 mg daily), and nabilone capsules (maximum of 8 mg) were compared to placebo; nabilone was also compared to dihydrocodeine. Outcomes were assessed from 8 hours to 9 weeks following randomization. Three of the five trials were judged to have a high risk of bias and the other two as unclear risk. Three studies (nabiximols, dronabinol) showed no effect using validated symptom scales. One study that evaluated three doses of nabiximols found increased depressive symptoms at the highest dose (11–14 sprays/day), but no difference compared to the placebo at lower doses. The comparison of nabilone to dihydrocodone showed no difference in depressive symptoms.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment to reduce depressive symptoms and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Although patients report using cannabinoids for depression, our search for a good-quality systematic review did not identify any RCTs evaluating the effects of medical cannabis in patients with depressive disorders. Trials in patients with chronic pain or multiple sclerosis with uncertain baseline depressive symptoms did not show an effect. There are no trial data addressing the effects of cannabinoids for major depressive disorder.

In Chapter 12 (Mental Health), the committee reviews epidemiological evidence to examine the association between cannabis use and the development of depressive disorders as well as the impact of cannabis use on the disorder's course or symptoms.

CONCLUSION 4-18 There is limited evidence that nabiximols, dronabinol, and nabilone are ineffective treatments for the reduction of depressive symptoms in individuals with chronic pain or multiple sclerosis.

SLEEP DISORDERS

Sleep disorders can be classified into major groups that include insomnia, sleep-related breathing disorders, parasomnias, sleep-related movement disorders, and circadian rhythm sleep–wake disorders (Sateia, 2014). Fifty million to 70 million adults in the United States report having some type of sleep disorder (ASA, 2016). In 2010, insomnia generated 5.5 million office visits in the United States (Ford et al., 2014). There is some evidence to suggest that the endocannabinoid system may have a role in sleep. THC is associated in a dose-dependent manner with changes in slow-wave sleep, which is critical for learning and memory consolidation. Cannabis may also have effects on sleep latency, decreasing time to sleep onset at low doses and increasing time to sleep onset at higher doses (Garcia and Salloum, 2015). Thus, cannabinoids could have a role in treating sleep disorders.

Are Cannabis or Cannabinoids an Effective Treatment for Improving Sleep Outcomes?

Systematic Reviews

The review by Whiting et al. (2015) was the most recent good-quality review. Two RCTs (54 participants) evaluated cannabinoids (nabilone, dronabinol) for the treatment of sleep problems. A trial deemed to have a high risk of bias conducted in 22 patients with obstructive sleep apnea showed a greater benefit of dronabinol (maximum dose of 10 mg daily) than with a placebo on sleep apnea/hypopnea index (mean difference from baseline −19.64, p = 0.02) at 3 weeks follow-up. A crossover trial deemed to have a low risk of bias in 32 patients with fibromyalgia found improvements for nabilone 0.5 mg daily compared with 10 mg amitriptyline in insomnia (mean difference from baseline, −3.25, 95% CI = −5.26 to −1.24) and greater sleep restfulness (mean difference from baseline, 0.48, 95% CI = 0.01–0.95) at 2 weeks follow-up. Although the antidepressant amitriptyline is an established treatment for fibromyalgia, it is not FDA approved for insomnia, and its use is limited by adverse effects.

Nineteen trials (3,231 participants) enrolled patients with other conditions (chronic pain or multiple sclerosis) and reported on sleep outcomes. Nabiximols (13 studies), THC/CBD capsules (2 studies), smoked THC (2 studies), and dronabinol or nabilone were compared to a placebo. Sleep outcomes were assessed at 2–15 weeks after randomization. Eleven of the 19 trials were judged to have a high risk of bias, 6 had an uncertain risk of bias, and the other 2 were judged to have a low risk of bias. The meta-analysis found greater improvements with cannabinoids in sleep quality among 8 trials (weighted mean difference [WMD], −0.58, 95% CI = −0.87 to −0.29) and sleep disturbance among 3 trials (WMD, −0.26, 95% CI = −0.52 to 0.00). These improvements in sleep quality and sleep disturbance were rated on a 10-point scale and would be considered small improvements. The summary estimate showing benefit was based primarily on studies of nabiximols.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment to improve sleep outcomes and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

A high-quality systematic review found moderate evidence suggesting that cannabinoids (primarily nabiximols) improve short-term sleep outcomes in patients with sleep disturbance associated with obstructive sleep apnea, fibromyalgia, chronic pain, or multiple sclerosis. However, the single study using an active comparator used a drug (amitriptyline) that is considered second-line treatment due to the availability of newer, more effective treatments that have fewer adverse effects. The committee did not identify any clinical trials that evaluated the effects of cannabinoids in patients with primary chronic insomnia.

CONCLUSION 4-19 There is moderate evidence that cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis.

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) falls within the broader trauma- and stressor-related disorders categorized by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V). The diagnostic criteria of PTSD include an exposure to a traumatic event (e.g., the threat of death, serious injury, or sexual violence) and exhibiting psychological distress symptoms that occur as a result of that exposure (e.g., intrusion symptoms, such as distressing memories; avoidance of stimuli that are associated with the traumatic event; negative alterations in mood and cognition; alterations in arousal and reactivity associated with the traumatic event; functional impairment) (APA, 2013, pp. 271–272). Given the known psychoactive effects of cannabis, the committee decided to explore the association between PTSD and cannabis use.

Are Cannabis or Cannabinoids an Effective Treatment for PTSD Symptoms?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for PTSD symptoms.

Primary Literature

We identified a fair-quality double-blind, randomized crossover trial (Jetly et al., 2015) conducted with Canadian male military personnel with trauma-related nightmares despite standard treatments for PTSD. Ten participants were randomized to either nabilone 0.5 mg that was titrated to a daily maximum of 3.0 mg or else to a placebo for 7 weeks. Following a 2-week washout period, subjects were then treated with the other study treatment and followed for an additional 7 weeks. Effects on sleep, nightmares, and global clinical state were assessed by the investigators; sleep time and general well-being were self-reported. Nightmares, global clinical state, and general well-being were improved more with nabilone treatment than with the placebo treatment ($p < 0.05$). There was no effect on sleep quality and quantity. Global clinical state was rated as very much improved or much improved for 7 of 10 subjects in the nabilone treatment period and 2 of 10 subjects in the placebo treatment period.

Discussion of Findings

A single, small crossover trial suggests potential benefit from the pharmaceutical cannabinoid nabilone. This limited evidence is most applicable to male veterans and contrasts with non-randomized studies showing limited evidence of a statistical association between cannabis use (*plant derived forms*) and *increased* severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (see Chapter 12). A search of the grey literature identified several recently initiated randomized controlled trials examining the harms and benefits of marijuana for PTSD.[11] One trial examines the effects of four different types of cannabis with varying THC and CBD content on PTSD symptoms in 76 veterans (Bonn-Miller, 2016). Another trial is a Canadian study that evaluates different formulations of THC and CBD in 42 adults with PTSD (Eades, 2016). If these trials are successfully completely, they will add substantially to the knowledge base, expanding the range of cannabinoids evaluated and the opportunity to examine the consistency of effects across studies.

CONCLUSION 4-20 There is limited evidence (a single, small fair-quality trial) that nabilone is effective for improving symptoms of posttraumatic stress disorder.

[11] ClinicalTrials.gov: NCT02102230, NCT02874898, NCT02517424, NCT02759185.

SCHIZOPHRENIA AND OTHER PSYCHOSES

Schizophrenia spectrum disorders and other psychotic disorders are mental health disorders characterized by three different classes of symptoms: positive symptoms (e.g., delusions, hallucinations, or disorganized or abnormal motor behavior), negative symptoms (e.g., diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia), and impaired cognition (e.g., disorganized thinking) (APA, 2013, p. 87; NIMH, 2015). Evidence suggests that the prevalence of cannabis use among people with schizophrenia is generally higher than among the general population (McLoughlin et al., 2014). In most of the studies reviewed below, schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychotic disorders are used as aggregate endpoints.

Are Cannabis or Cannabinoids an Effective Treatment for the Mental Health Outcomes of Patients with Schizophrenia or Other Psychoses?

Systematic Reviews

Two good-quality reviews (McLoughlin et al., 2014; Whiting et al., 2015) evaluated cannabinoids for the treatment of psychosis. We focus on the good-quality review by Whiting et al. (2015) as it is more current. Two RCTs with high risk of bias (71 total participants with schizophrenia or schizophreniform psychosis) compared cannabidiol to the atypical antipsychotic amisulpride or a placebo. One trial reported no difference on mental health between CBD (maximum dose 800 mg/day) and amisulpride (maximum dose 800 mg/day) at 4 weeks (brief psychiatric rating scale mean difference, −0.10, 95% CI = −9.20–8.90) or on mood (positive and negative syndrome scale mean difference, 1.0; 95% CI = −12.6–14.6). A crossover trial showed no difference in effect on mood between CBD (maximum dose 600 mg/day) and placebo (positive and negative symptom scale mean difference, 1, 95% CI = −12.60–14.60; scale range 30–210).

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the mental health outcomes of patients with schizophrenia or other psychoses and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Good-quality systematic reviews identified only two small, unclear- to high-risk-of-bias trials evaluating cannabinoids for the treatment of schizophrenia. These studies provide only limited evidence due to the risk of bias, the short-term follow-up, and the evaluation of a single cannabinoid. Furthermore, the larger trial was designed to detect a moderate benefit of cannabidiol compared to the antipsychotic amisulpride, but it enrolled only 60 percent of the planned sample. Thus, it did not have the statistical power to detect small or moderate differences between CBD and amisulpride. Overall, the evidence is insufficient to determine if cannabidiol is an effective treatment for individuals with schizophrenia or schiophreniform psychosis.

In Chapter 12, the committee reviews epidemiological evidence to examine the association between cannabis use and the development of schizophrenia and other psychoses, as well as the impact of cannabis use on the disorder's course or symptoms.

CONCLUSION 4-21 There is insufficient evidence to support or refute the conclusion that cannabidiol is an effective treatment for the mental health outcomes in individuals with schizophrenia or schizophreniform psychosis.

RESEARCH GAPS

In reviewing the research evidence described above, the committee has identified that research gaps exist concerning the effectiveness of cannabidiol or cannabidiol-enriched cannabis in treating the following:

- cancer in general
- treating chemotherapy-induced nausea and vomiting
- symptoms of irritable bowel syndrome
- epilepsy
- spasticity due to paraplegia from spinal cord injury
- symptoms associated with amyotrophic lateral sclerosis
- motor function and cognitive performance associated with Huntington's Disease
- motor system symptoms associated with Parkinson's disease or levodopa-induced dyskinesia
- achieving abstinence or reduction in the use of addictive substances, including cannabis itself
- sleep outcomes in individuals with primary chronic insomnia
- posttraumatic stress disorder symptoms

- mental health outcomes in individuals with schizophrenia or schizophreniform psychosis
- cannabidiol short-term relief from anxiety symptoms

SUMMARY

This chapter outlines the committee's efforts to review the current evidence base for the potential efficacy of cannabis or cannabinoids on prioritized health conditions. The health conditions reviewed in this chapter include chronic pain, cancer, chemotherapy-induced nausea and vomiting, anorexia and weight loss associated with HIV, irritable bowel syndrome, epilepsy, spasticity, Tourette syndrome, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dystonia, dementia, glaucoma, traumatic brain injury, addiction, anxiety, depression, sleep disorders, posttraumatic stress disorder, and schizophrenia and other psychoses. The committee has formed a number of research conclusions related to these health endpoints; however, it is important that the chapter conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections above. See Box 4-1 for a summary list of the chapter's conclusions.

We found conclusive or substantial evidence (ranging in modest to moderate effect) for benefit from cannabis or cannabinoids for chronic pain, chemotherapy-induced nausea and vomiting, and patient-reported symptoms of spasticity associated with multiple sclerosis. For chemotherapy-induced nausea and vomiting and spasticity associated with multiple sclerosis, the primary route of administration examined was the oral route. For chronic pain, most studies examined oral cannabis extract, although some examined smoked or vaporized cannabis. It is unknown whether and to what degree the results of these studies can be generalized to other products and routes of administration. For many of the other conditions discussed above, there is insufficient or no evidence upon which to base conclusions about therapeutic effects. The potential efficacy of cannabinoids for several of these conditions, such as epilepsy and posttraumatic stress disorder, should be prioritized, given the substantial number of persons using cannabis for those conditions (Cougle et al., 2011; Massot-Tarrús and McLachlan, 2016). As identified in the chapter's Discussion of Findings sections, there are common themes in the type of study limitations found in this evidence base. The most common are limitations in the study design (e.g., a lack of appropriate control groups, a lack of long-term follow-ups), small sample sizes, and research gaps in examining the potential therapeutic benefits of different forms of cannabis (e.g., cannabis plant). These limitations highlight the need for substantial research to provide comprehensive and conclusive evidence on the therapeutic effects of cannabis and cannabinoids.

BOX 4-1
Summary of Chapter Conclusions*

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chron c pa n n adu ts (cannab s) (4-1)
- As ant emet cs n the treatment of chemotherapy- nduced nausea and vom t ng (ora cannab no ds) (4-3)
- For mprov ng pat ent-reported mu t p e sc eros s spast c ty symptoms (ora cannab no ds) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improv ng short-term s eep outcomes n nd v dua s w th s eep d sturbance assoc ated w th obstruct ve s eep apnea syndrome, fibromya g a, chron c pa n, and mu t p e sc eros s (cannab no ds, pr mar y nab x mo s) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increas ng appet te and decreas ng we ght oss assoc ated w th HIV/AIDS (cannab s and ora cannab no ds) (4-4a)
- Improv ng c n c an-measured mu t p e sc eros s spast c ty symptoms (ora cannab no ds) (4-7a)
- Improv ng symptoms of Tourette syndrome (THC capsu es) (4-8)
- Improv ng anx ety symptoms, as assessed by a pub c speak ng test, n nd v dua s w th soc a anx ety d sorders (cannab d o) (4-17)
- Improv ng symptoms of posttraumat c stress d sorder (nab one; a s ng e, sma fa r-qua ty tr a) (4-20)

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (.e., morta ty, d sab ty) after a traumat c bra n njury or ntracran a hemorrhage (4-15)

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ADAA (Anxiety and Depression Association of America). 2016. Depression. https://www.adaa.org/understanding-anxiety/depression (accessed November 17, 2016).

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improv ng symptoms assoc ated w th dement a (cannab no ds) (4-13)
- Improv ng ntraocu ar pressure assoc ated w th g aucoma (cannab no ds) (4-14)
- Reduc ng depress ve symptoms n nd v dua s w th chron c pa n or mu t p e sc eros s (nab x mo s, dronab no , and nab one) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, nc ud ng g oma (cannab no ds) (4-2)
- Cancer-assoc ated anorex a cachex a syndrome and anorex a nervosa (cannab no ds) (4-4b)
- Symptoms of rr tab e bowe syndrome (dronab no) (4-5)
- Ep epsy (cannab no ds) (4-6)
- Spast c ty n pat ents w th para ys s due to sp na cord njury (cannab no ds) (4-7b)
- Symptoms assoc ated w th amyotroph c atera sc eros s (cannab no ds) (4-9)
- Chorea and certa n neuropsych atr c symptoms assoc ated w th Hunt ngton's d sease (ora cannab no ds) (4-10)
- Motor system symptoms assoc ated w th Park nson's d sease or the evodopa- nduced dysk nes a (cannab no ds) (4-11)
- Dyston a (nab one and dronab no) (4-12)
- Ach ev ng abst nence n the use of add ct ve substances (cannab no ds) (4-16)
- Menta hea th outcomes n nd v dua s w th sch zophren a or sch zophren - form psychos s (cannab d o) (4-21)

* Numbers in parentheses correspond to chapter conclusion numbers

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Part III

Other Health Effects

5

Cancer

Chapter Highlights

- The evidence suggests that smoking cannabis does not increase the risk for certain cancers (i.e., lung, head and neck) in adults.
- There is modest evidence that cannabis use is associated with one subtype of testicular cancer.
- There is minimal evidence that parental cannabis use during pregnancy is associated with greater cancer risk in offspring.

Cancer is a major public health problem in the United States. With 1,685,210 new cancer cases and 595,690 cancer-related deaths expected to occur in 2016, it is a leading cause of disease and death among Americans (NCI, 2016). Cannabis use has been associated with cigarette smoking—to which 28.6 percent of all cancer deaths in the United States in 2014 have been attributed—and, like tobacco smoke, cannabis smoke contains carcinogens (Lortet-Tieulent et al., 2016; Tashkin, 2013). These potential risk factors for cancer have prompted epidemiological research examining the association between cannabis use and the risk of developing several types of cancer, including lung, head and neck, testicular, esophageal, and other cancers that occur in adults, as well as cancers that occur in children. The present chapter reviews the findings of three recent, good- to fair-quality systematic reviews, including one pooled analysis, as well as three pri-

mary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in six formal conclusions.

CANCER

Is There an Association Between Cannabis Use and the Incidence of Lung Cancer?

Systematic Reviews

Zhang et al. (2015) pooled data on 2,159 lung cancer cases and 2,985 controls from six case-control studies, four of which were unpublished. The impact of key characteristics of cannabis smoking (e.g., intensity and duration of cannabis smoking, cumulative exposure, age at start of smoking) on lung cancer incidence was evaluated for all study participants and for a subgroup who were not tobacco smokers. Among all study participants there was no statistically significant difference in the risk of lung cancer for habitual cannabis smokers as compared to non-habitual smokers (odds ratio [OR], 0.96, 95% confidence interval [CI] = 0.66–1.38); similarly, among participants who did not smoke tobacco, the risk of lung cancer was not significantly higher or lower for habitual cannabis smokers than for non-habitual cannabis smokers (OR, 1.03, 95% CI = 0.51–2.08).[1] When only adenocarcinoma cases were compared to controls, Zhang et al. (2015, p. 898) observed a "suggestive," but still statistically nonsignificant, association between lung cancer incidence and either smoking more than 1 joint per day (OR, 1.73, 95% CI = 0.75–4.00) or having a cumulative exposure of more than 10 joint-years (OR, 1.74, 95% CI = 0.85–3.56).

Primary Literature

Huang et al. (2015) conducted an epidemiologic review on the association between cannabis use and the incidence of several cancers, including lung cancer. They evaluated six studies on lung cancer, including Zhang et al. (2015) and two studies included in that review. Of the three remaining studies, two were described by Zhang et al. (2015) as having several limitations, including an inability to adequately control for tobacco use and potential reporting bias, and are not discussed here. The third study

[1] Non-habitual cannabis smokers were defined as those with cumulative cannabis consumption of less than 1 joint-year, including never users. Subjects who did not smoke tobacco were those who reported smoking less than 100 cigarettes over their lifetime, or who fit the cutoffs used in the pooled studies.

evaluated lung cancer risk among 49,321 Swedish male military conscripts over a 40-year period and found that, compared with participants who had reported never using cannabis, those who reported using cannabis more than 50 times at baseline had a statistically significant risk of developing lung cancer (hazard ratio [HR], 2.12, 95% CI = 1.08–4.14) after adjusting for tobacco and alcohol use and other confounders (Callaghan et al., 2013).[2]

Discussion of Findings

Zhang et al. (2015) found no statistically significant association between smoking cannabis and lung cancer incidence; this was true for all study participants as well as for the subgroup of study participants who were not tobacco smokers. Although the risk of lung cancer increased as the duration and intensity of cannabis use increased, even participants who smoked most often and for the longest periods of time were not at significantly greater risk than non-habitual smokers. Huang et al. (2015) did not perform a meta-analysis of the lung cancer studies; studies included in that review but not in Zhang et al. (2015) indicate an increased risk for lung cancer associated with smoking cannabis.

Both studies noted several limitations. Zhang et al. (2015) were unable to account for potential effect measure modifiers, including those related to variations in cannabis smoking techniques and in the characteristics of the cannabis smoked. The authors also noted that the small number of participants who were heavy and chronic cannabis users rendered effect estimates for these subgroups imprecise. Finally, the study relied on self-report without biological validation to assess patterns of cannabis, making it impossible to verify the accuracy of cannabis use data. Regarding Callaghan et al. (2013), detailed information on cannabis and tobacco use before and after baseline was lacking; the study did not adjust or account for tobacco or cannabis during the 40-year follow-up period; the authors were unaware whether study participants mixed tobacco and cannabis; and the self-reporting process was not anonymized.

CONCLUSION 5-1 There is moderate evidence of no statistical association between cannabis smoking and the incidence of lung cancer.

[2] There were 49,321 participants at the start of the study, and 44,257 participants involved in the assessment of cannabis risk. Hazard ratio (HR) includes adjustments for tobacco smoking, alcohol consumption, respiratory conditions, and socioeconomic status at time of conscription.

Is There an Association Between Cannabis Use and the Incidence of Head and Neck Cancers?

Systematic Reviews

De Carvalho et al. (2015) conducted a systematic review and meta-analysis of nine case-control studies derived from six articles and totaling 13,931 study participants (5,732 cases and 8,199 controls) in order to evaluate the association between cannabis use and the incidence of head and neck cancers, including upper aerodigestive tract, oral cavity, and nasopharyngeal cancers as well as on head and neck squamous cell carcinoma. After adjusting for tobacco use, age, gender, and race, the meta-analysis found no significant association between cannabis use and head and neck cancers (OR, 1.021, 95% CI = 0.912–1.143). The authors concluded that there was "insufficient epidemiological evidence to support a positive or negative association of marijuana use and the development of [head and neck cancers]" (de Carvalho et al., 2015, p. 1755).

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and head and neck cancers and were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

In their review, de Carvalho et al. (2015) noted several limitations particular to individual studies. First, although a nonsignificant association was observed for head and neck cancers as a group, this finding does not preclude the existence of a significant positive or negative association between cannabis use and the incidence of specific types of head and neck cancer. The systematic review also relied on cohort studies, which may not detect less pronounced risks or risks that emerge over longer periods. Finally, differences in the methods employed in these studies prevented an analysis of how the characteristics of cannabis use (e.g., frequency, duration, method) affect the risk of head and neck cancers.

CONCLUSION 5-2 There is moderate evidence of no statistical association between cannabis use and the incidence of head and neck cancers.

Is There an Association Between Cannabis Use and the Incidence of Testicular Cancer?

Systematic Reviews

Gurney et al. (2015) conducted a systematic review and meta-analysis on the association between cannabis use and testicular germ cell tumors. The authors identified three case-control studies totaling 2,138 study participants (719 cases and 1,419 controls). Compared to participants who never smoked cannabis, participants who reported ever smoking cannabis had a statistically nonsignificant increased risk of developing testicular germ cell tumors (OR, 1.19, 95% CI = 0.72–1.95). By comparison, statistically significant associations between cannabis use and the risk of developing testicular germ cell tumors were seen for the subgroups of participants who were current smokers (OR, 1.62, 95% CI = 1.13–2.31) or who reported smoking cannabis at least once a week (OR, 1.92, 95% CI = 1.35–2.72) or for 10 years or longer (OR, 1.50, 95% CI = 1.08–2.09). Among current users, including the subgroups of those who used cannabis at least once weekly or for at least 10 years, the risk of developing non-seminoma tumors was higher than the risk of developing seminoma tumors. For example, compared to never smokers, participants who smoked at least once per week had a statistically significant risk of developing non-seminoma tumors (OR, 2.59, 95% CI = 1.60–4.19), while the risk for developing seminoma tumors was not statistically significant (OR, 1.27, 95% CI = 0.77–2.11). Gurney et al. (2015) observed that because non-seminoma tumors are frequently diagnosed at a younger age than seminoma tumors the stronger association between cannabis use and non-seminoma tumors suggests "puberty (rather than later in life) as the key point of exposure" (Gurney et al., 2015, p. 8).

Primary Literature

Huang et al. (2015) conducted a review and meta-analysis of the same three studies reviewed by Gurney et al. (2015) and found no association between participants who had ever smoked cannabis and the risk of developing testicular cancer. However, compared to participants who had never smoked cannabis, heavy users who had smoked one or more times per day or week (OR, 1.56, 95% CI = 1.09–2.23) and chronic users who had smoked for 10 years or longer (OR, 1.50, 95% CI = 1.08–2.09) had a statistically significant risk of developing testicular cancer.

Discussion of Findings

Gurney et al. (2015) found a statistically significant association between current, frequent, or chronic cannabis use and the incidence of non-seminoma-type testicular germ cell tumors. By comparison, cannabis use was not associated with a statistically significant risk of developing seminoma-type testicular germ cell tumors. Lacking further evidence, an extrapolation of this association to other types of testicular cancer is unwarranted. Huang et al. (2015) found an association between the incidence of testicular cancer (without further specification) and cannabis use that was frequent or of long duration.

Gurney et al. (2015) highlighted several limitations of their review. First, each of the three case-control studies informing the review relied on self-report without biological validation, and the two studies that utilized interviews to collect this data did not indicate whether the interviewers were blinded to the case-control status of the participants. Self-report data cannot be verified, and unblended interviewers are a potential source of bias. Second, two of the studies reported response rates that were both low and unequal: 67.5 percent to 38.2 percent response rate for cases and 73.3 percent to 43.3 percent response rate for controls. Differences in the prevalence of cannabis use among participants who did and did not respond could bias the odds ratios calculated in these studies. Third, the high and growing prevalence of cannabis use in the general population may render the category "ever-smoker" uninformative, since it will encompass not only frequent and chronic users but also individuals who have only minimal exposure to the drug. A final limitation is that the studies informing the review did not all control for the same, potentially relevant confounders: three studies controlled for age and a history of cryptorchidism, two controlled for alcohol and drug use, and only one controlled for other substance use.

As noted in Gurney et al. (2015), Huang et al. (2015) did not distinguish between seminoma and non-seminoma-type tumors and also failed to assess the quality of the reviewed studies. Additionally, the review included limited information on the methods used to conduct the meta-analysis.

CONCLUSION 5-3 There is limited evidence of a statistical association between current, frequent, or chronic cannabis smoking and non-seminoma-type testicular germ cell tumors.

Is There an Association Between Cannabis Use and the Incidence of Esophageal Cancers?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and esophageal cancer.

Primary Literature

The committee identified one primary research study that addressed a potential association with esophageal cancer. To assess the association between cannabis use and the incidence of lung and upper aerodigestive tract cancers, Hashibe et al. (2006) conducted a large population-based case-control study involving 1,040 controls and 1,212 cases, 108 of which were diagnosed with esophageal cancer. Investigators collected data on the use of cannabis, tobacco, and alcohol as well as relevant medical, environmental, and socioeconomic information. After adjustments were made for demographic factors and alcohol and tobacco use, study participants with cumulative cannabis exposure equal to 1 to 10 joint-years were found to have a statistically nonsignificant decreased risk of developing esophageal cancer compared to participants who never used cannabis (OR, 0.77, 95% CI = 0.36–1.6). The risk was further depressed, but still not statistically significant, for participants whose cumulative cannabis exposure was equal to 30 or more joint-years (OR, 0.53, 95% CI = 0.22–1.3). Among participants who never smoked cigarettes, the risk of esophageal cancer was not statistically different between those who had ever smoked cannabis and those who had never smoked cannabis (OR, 0.79, 95% CI = 0.30–2.1).

Discussion of Findings

In conducting their investigation, Hashibe et al. (2006) addressed several methodological issues of previous studies of the association between cannabis use and cancer incidence. These issues included accounting for tobacco use and other confounders, avoiding measurement errors, and protecting the anonymity of participants. On account of these efforts to preemptively address methodological issues, few limitations were identified that could account for the lower risk of esophageal cancer among cannabis smokers as compared to nonsmokers—an unexpected, though not statistically significant, result. The participation rate among esophageal cases was low at 35 percent, creating a potential source of bias if the prevalence of cannabis use was much higher or lower among nonpartici-

pants with esophageal cancer than among participants with esophageal cancer. The subgroup of participants with esophageal cancer and high levels of cumulative cannabis exposure (i.e., ≥30 joint-years) was relatively small (n = 9), thereby limiting the ability to detect an association between cannabis use and cancer incidence in this group. As with other studies, confounders may not have been entirely controlled for, and measurement errors may have persisted. The authors note these potential limitations, but they also speculate that "it is possible that such inverse associations may reflect a protective effect of marijuana" (Hashibe et al., 2006, p. 1833).

CONCLUSION 5-4 There is insufficient evidence to support or refute a statistical association between cannabis smoking and the incidence of esophageal cancer.

Is There an Association Between Cannabis Use and the Incidence of Other Cancers in Adults?

Systematic Reviews

The committee identified no systematic reviews on the association between cannabis exposures and the incidence of other cancers.

Primary Literature

In an epidemiologic review, Huang et al. (2015) reported on the association between cannabis use and the risk of several types of cancer. A cohort study involving 27,920 men and 36,935 women ages 15 to 49 years found that, compared to participants who did not smoke cannabis, self-reported current or former use of cannabis on more than six occasions was associated with prostrate cancer in men who never smoked cigarettes (relative risk [RR], 3.1, 95% CI = 1.0–9.5) and with cervical cancer in women who never smoked cigarettes (RR, 1.6, 95% CI = 1.2–2.2), after adjusting for age, race, education, and alcohol use (Sidney et al., 1997). However, when compared to participants who did not smoke cannabis or who had smoked cannabis on only one to six occasions, those who were current or former cannabis smokers were not at statistically significant risk of developing prostate or cervical cancer, after adjusting for tobacco and alcohol use and other potential confounders.

Another large cohort study involving 133,881 participants ages 25 years and older found that, compared to nonuse of cannabis, self-reported cannabis use at least once per month was associated with a statistically significant risk of malignant adult-onset glioma compared to nonuse of cannabis, after controlling for potential confounders, including demo-

graphic and socioeconomic factors and alcohol and tobacco use (RR, 2.8, 95% CI = 1.3–6.2) (Efird et al., 2004). Compared to participants who did not use cannabis, there was statistically signficant risk of developing a brain tumor among those participants who reported using cannabis weekly (RR, 3.2, 95% CI = 1.1–9.2) or monthly (RR, 3.6, 95% CI = 1.3–10.2).

Huang et al. (2015) also reviewed two studies on non-Hodgkin lymphoma risk. Holly et al. (1999) conducted a population-based case-control study involving 3,376 women and heterosexual men to determine risk factors for non-Hodgkin lymphoma. Compared to participants who never used cannabis, those who reported using cannabis less than 40 times had a statistically significant decreased risk of developing non-Hodgkin lymphoma, after adjusting for age, sex, and education (OR, 0.68, 95% CI = 0.55–0.84). Among participants who used cannabis on 40 or more occasions, the risk of non-Hodgkin lymphoma was further depressed (OR, 0.57, 95% CI = 0.44–0.74). In another population-based case-control study, 378 HIV-negative men and women diagnosed with non-Hodgkin lymphoma were matched by age, biological sex, race, language of interview, and neighborhood of residence at time of diagnosis to HIV-negative controls (Nelson et al., 1997). There was no statistically significant difference in the risk of developing non-Hodgkin lymphoma among participants who reported using cannabis at any time as compared to those who reported never using cannabis (OR, 0.86, 95% CI = 0.50–1.48). The lack of a statistical difference in non-Hodgkin lymphoma risk between cannabis users and nonusers was true whether participants reported using cannabis only 1 to 5 times (OR, 0.68, 95% CI = 0.34–1.38) or on more than 900 occasions (OR, 1.09, 95% CI = 0.48–2.48).

Other studies reviewed by Huang et al. (2015) examined the association between cannabis use and the risk of Kaposi's sarcoma and penile and anal cancer. Maden et al. (1993) conducted a case-control study involving 110 cases and 355 age-matched controls to identify risk factors for penile cancer. After adjusting for alcohol and cigarette use, age, and number of sexual partners, there was no statistically significant difference in the risk of developing penile cancer among participants who reported ever using cannabis as compared to those who never used cannabis (OR, 1.5, 95 % CI = 0.7–3.2). In a case-control study on risk factors for anal cancer, 148 men and women diagnosed with anal cancer were matched by age, biological sex, year of diagnosis, and area of residence to 166 male and female controls diagnosed with colon cancer (Daling et al., 1987). There was no statistically significant difference in the risk of anal cancer among participants who had ever used cannabis as compared to those who had never used cannabis, after adjusting for age, residence, and cigarette use (RR, 0.8, 95% CI = 0.2–4.0). Chao et al. (2009) conducted a cohort study to determine the association between use of cannabis and other recreational

drugs and the risk of Kaposi's sarcoma in homosexual men coinfected with HIV and human herpes virus 8 (HHV-8). Among 1,335 participants, those who used cannabis in the 6 months preceding data collection were not significantly more likely to develop Kaposi's sarcoma than participants who did not use cannabis during that period (HR, 1.00, 95% CI = 0.79–1.28), after adjusting for potential confounders, including alcohol use, tobacco smoking, and characteristics of sexual activity.

To assess the association between cannabis use and bladder cancer risk, Thomas et al. (2015) reviewed data from 84,170 men ages 45 to 69 years who were participants in the California Men's Health Study. After adjusting for age, race, and body mass index, the risk of developing bladder cancer was significantly reduced for participants who used cannabis but not tobacco, compared to those who used neither cannabis nor tobacco (HR, 0.55, 95% CI = 0.31–1.00). After stratifying cannabis use by levels of cumulative cannabis exposure, the authors found that the depression in bladder cancer risk was statistically significant only for participants who reported smoking cannabis on 3–10 occasions (HR, 0.57, 95% CI = 0.34–0.96). Similarly, stratification by participant age revealed that, among participants who smoked cannabis but not tobacco, the risk of bladder cancer was significantly decreased only for those ages 45 to 54 years (HR, 0.26, 95% CI = 0.07–0.92). In a case-control study involving 52 Veterans Affairs patients younger than 61 years old and age-matched to 104 controls, Chacko et al. (2006) found that a significantly higher proportion of cases as compared to controls reported ever using cannabis (88.5 percent versus 69.2 percent, $p = 0.008$). The mean number of joint-years of cannabis smoked was also signficantly higher among cases than controls (48.0 joint-years versus 28.5 joint-years, $p = 0.022$). After adjusting for potential confounders, including tobacco use, a statistically significant association between increasing joint-years of cannabis and the risk of transitional cell carcinoma remained (p trend = 0.01).

Discussion of Findings

Huang et al. (2015, p. 26) reviewed eight studies that reported on the association between cannabis use and prostate, cervical, anal, bladder, and penile cancer, as well as glioma, non-Hodgkin lymphoma, and Kaposi's sarcoma, and they concluded that "there are still insufficient data to make any conclusions on an association with marijuana." Separately, Thomas et al. (2015) found no statistically significant difference in the risk of developing bladder cancer among participants who used cannabis but not tobacco as compared to those who used neither. These studies have several limitations.

In the study on cervical and prostate cancers, Sidney et al. (1997,

p. 727) relied on self-report to determine patterns of cannabis use and did not assess for changes in those patterns during follow-up. The study cohort included no participants older than 49 years of age at baseline, and participants were followed for a mean of 8.6 years; consequently, the study was unable to ascertain whether there is an association between cannabis use and the incidence of cancer in older populations. The authors stated that they "do not consider any of the findings to be conclusive."

In the study on malignant adult-onset glioma, investigators did not assess for changes in patterns of cannabis use after baseline; only a small number of cases (n = 8) reported using cannabis at least once per month, and more than one in four cases (26 percent) did not provide data on cannabis use (Efird et al., 2004). Holly et al. (1999) note that responses to questions concerning events that occurred many years previously (e.g., lifetime cannabis use) or addressing sensitive topics (e.g., illegal drug use) can be affected by recall and response biases, respectively. Nelson et al. (1997) also list recall bias as a potential limitation. Of these two studies, Huang et al. (2015) note that the association between cannabis use and risk of non-Hodgkin lymphoma may be the result of confounding cause by the observed protective association of sexual behavior and cocaine use. For a discussion on the effectiveness of cannabis and cannabinoids as a treatment for glioma and other cancers, see Chapter 4.

Maden et al. (1993) assert that the low rate of participation among cases (50.2 percent) and controls (70.3 percent) was a major limitation of their study on penile cancer. In the study on anal cancer, Daling et al. (1987) note that all control participants were diagnosed with colon cancer. Other investigators have noted that this control group may not be appropriate for assessing the association between cannabis use and anal cancer incidence, as cannabis smoking is a potential risk factors for colorectal cancer (Hashibe et al., 2005). Limitations of the study on Kaposi's sarcoma include the lack of consistent HHV-8 testing for all participants, the use of noncontinuous categories for describing frequency of cannabis use and the resultant potential for ambiguous reporting, and the use of self-report to collect data on patterns of cannabis use (Chao et al., 2009).

Thomas et al. (2015) note that the observational design of their study creates the potential for participation and response biases. Other limitations of the study include the failure to differentiate the risks for bladder cancer associated with current as opposed to former cannabis use, the lack of an evaluation of other potential risk factors for bladder cancer, and the fact that the study findings apply only to men. Findings from Chacko et al. (2006) are limited by a high proportion of ever tobacco smokers among both cases (94.2 percent) and controls (93.3 percent). According to Huang et al. (2015), the limitations of this study also include its small size, the

use of self-report to collect data on cannabis use, and failing to adjust for tobacco smoking—an acknowledged bladder cancer risk factor.

Further research is needed to better characterize whether and how cannabis use is associated with the risk of developing these cancers. Additionally, since important biological distinctions exist among cancers that occur in a given organ, including histological and molecular subtypes, such research will need to separately investigate and identify the risk factors associated with each.

CONCLUSION 5-5 There is insufficient evidence to support or refute a statistical association between cannabis use and the incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer.

Is There an Association Between Parental Cannabis Use and the Incidence of Cancer in Offspring?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between parental cannabis use and subsequent cancer incidence in offspring.

Primary Literature

Huang et al. (2015) reviewed three studies on the association between parental cannabis use and the risk of leukemia. Robison et al. (1989) conducted a case-control study involving 204 cases diagnosed with acute non-lymphoblastic leukemia (ANLL) by 17 years of age that were matched to controls by age, race, and residential location. Maternal use of cannabis during, and in the year preceding, pregnancy was associated with a statistically significant risk of ANLL (RR, 10, $p = 0.005$). By comparison, the risk of ANLL associated with paternal use of cannabis during the same period was not statistically significant (RR, 1.47, $p = 0.32$). Children whose mothers used cannabis during, or in the year preceding, pregnancy were significantly younger in the age at diagnosis of ANLL than children whose mothers did not use cannabis during this period (37.7 months [mean] versus 96.1 months [mean], $p = 0.007$). There was also a statistically significant difference in the distribution of morphological types of ANLL cases between the cases and the controls ($p = 0.02$). For example, M1/M2 and M4/M5 morphologic types respectively comprised 10 percent and 70 percent of ANLL cases among children whose mothers

used cannabis, while they comprised respectively 58 percent and 31 percent of cases among children whose mothers did not use cannabis. Logistic regression to identify independent risk factors for ANLL found that "maternal marijuana use was the single most predictive factor" identified in the study (Robison et al., 1989, p. 1907).

In contrast to these findings, Trivers et al. (2006) conducted a case-control study involving 517 cases diagnosed with acute myeloid leukemia (AML) by 17 years of age and matched to 610 controls by age, race, and residential location, and they found that children whose mothers used cannabis during, or in the 3 months preceding, pregnancy were at significantly lower risk of developing AML than children whose mothers did not use cannabis during that period, after adjusting for household income and parental age and education (OR, 0.43, 95% CI = 0.23–0.80).[3] Among children whose mothers reported using cannabis in the 3 months before pregnancy, those whose mothers used cannabis at least once weekly had a lower risk of developing AML than those whose mothers used cannabis less than once weekly (OR, 0.19, 95% CI = 0.06–0.59 versus OR, 0.57, 95% CI = 0.26–1.29). Although overall paternal use of cannabis was significantly associated with the risk of AML (OR, 1.37, 95% CI = 1.02–1.83), there was no statistically significant association between paternal use of cannabis during, and in the 3 months preceding, pregnancy and the risk of AML (OR, 1.02, 95% CI = 0.67–1.53). The authors concluded that "[p]arental marijuana use is unlikely as a strong risk factor for childhood AML" (Trivers et al., 2006, p. 117).

Finally, Wen et al. (2000) conducted a case-control study to evaluate the association between exposures related to paternal military service, such as cannabis use, and the incidence of AML or acute lymphoblastic leukemia (ALL) in their children. Among 2,343 cases diagnosed with AML or ALL and matched by age, race, biological sex, and residential location to 2,723 controls, participants whose fathers had ever used cannabis had a statistically significant risk of developing ALL or AML compared to those whose fathers had never used cannabis (OR, 1.5, $p < 0.01$).

Huang et al. (2015) also reviewed studies on the association between parental cannabis use and the incidence of rhabdomyosarcoma, neuroblastoma, and astrocytoma in pediatric populations. A case-control study of 322 children younger than 21 years of age and diagnosed with rhabdomysarcoma matched by age, race, and biological sex to 322 controls found that children whose mothers used cannabis in the 12 months before their child's birth were significantly more likely to develop the disease than children whose mothers had not used cannabis during this

[3] Acute myeloid leukemia and acute non-lymphoblastic leukemia refer to the same type of cancer.

period (OR, 3.0, 95% CI = 1.4–6.5), after adjusting for complications during pregnancy and other potential confounders (Grufferman et al., 1993). Similarly, children whose fathers used cannabis in the year prior to their child's birth were at significantly greater risk of developing rhabdomyosarcoma than children whose fathers did not use cannabis at this time (OR, 2.0, 95% CI = 1.3–3.3). However, use of cannabis and cocaine were highly correlated, as was maternal and paternal use of cannabis, making it impossible to isolate the effects of maternal and paternal cannabis use from each other or from the effects of parental cocaine use.

Kuijten et al. (1990) conducted a case-control study involving 163 cases diagnosed by 14 years of age with astrocytoma or related tumors and matched to controls by age, race, and residential location, and they found a borderline statistically significant association between maternal use of cannabis in the 10 months preceding their child's birth and the risk of astrocytoma (OR, 2.8, 95% CI = 0.9–9.9, p = 0.07).[4] By comparison, maternal use in the 9 months preceding their child's birth was not associated with the risk of astrocytoma (OR, 4.0, p = 0.11).

Bluhm et al. (2006) examined the association between maternal cannabis use and the risk of neuroblastoma in their offspring. Among 538 cases diagnosed with neuroblastoma by 19 years of age—age-matched to 504 controls—maternal use of cannabis during pregnancy, as compared to nonuse of cannabis during any measured time period, was significantly associated with greater risk of neuroblastoma in their offspring, after adjusting for use of other recreational drugs (OR, 2.51, 95% CI = 1.18–5.83). After stratifying maternal use of cannabis by time period, the authors found a statistically significant association between the incidence of neuroblastoma and maternal use of cannabis during the first trimester (OR, 4.75, 95% CI = 1.55–16.48), but not between neuroblastoma incidence and maternal cannabis use in the second or third trimester, in the month preceding conception, or in the period between birth and diagnosis. Age at diagnosis, but not frequency of maternal cannabis use, had large effects on neuroblastoma risk. For example, among children diagnosed with neuroblastoma before 12 months of age, maternal cannabis use was significantly associated with risk of neuroblastoma (OR, 15.61, 95% CI = 3.07–285.89), while the risk was similar for children whose mothers used either less than one or more than one pipeful of cannabis during the first trimester (OR, 4.16, 95% CI = 1.52–14.61 and OR, 4.42, 95% CI = 1.09–29.58).

[4] Cases were diagnosed with astrocytoma, glioblastoma multiforme, mixed glioma with astrocytic elements, or brainstem glioma.

Discussion of Findings

Findings on the association between parental cannabis use and risk of pediatric leukemia were mixed: maternal cannabis use in the months preceding birth was determined to be at once a risk factor for, and protective against, the development of ANLL/AML in children (Robison et al., 1989; Trivers et al., 2006). Differences in the design of questionnaires employed in these studies, including the extent to which questions on recreational drug use were distinguished from other exposure questions, may have affected participant reporting and contributed to these contradictory results. Limitations of Robison et al. (1989) include findings based on small sample sizes (nine cases), wide confidence intervals for risk estimates, and the possibility that, as a consequence of the large number of parameters analyzed in the study, the association between ANLL incidence and maternal cannabis use was a chance finding. Although the reported frequency of maternal cannabis use was considerably lower in Robison et al. (1989) than in other studies, there was no evidence of difference in reporting between cases and controls. In Trivers et al. (2006), reported rates of maternal cannabis use were lower among cases and higher among controls than in other studies, suggesting the potential for differences in reporting by cases and controls.

While Robison et al. (1989) and Trivers et al. (2006) found that paternal cannabis use during and in the months preceding pregnancy was not associated with ANLL/AML incidence in their offspring, Wen et al. (2000) found that any paternal cannabis use was significantly associated with the incidence of AML or ALL in their offspring. Limitations in Wen et al. (2000) included the potential for selection bias due to a lower participation rate among controls than cases and the potential for residual confounding due to the lack of data on the duration and frequency of exposure to cigarette smoking. A similar lack of data on patterns of cannabis use (e.g., duration, frequency, cumulative exposure) prevented investigation of a dose–response relationship between paternal cannabis use and risk of ALL in their offspring.

Grufferman et al. (1993) found that parental cannabis use was significantly associated with the incidence of rhabdomyosarcoma in their offspring, and Bluhm et al. (2006) found that maternal cannabis use during the first trimester was significantly associated with neuroblastoma. In the latter study, very few mothers reported using cannabis more than once per day during any of the measured time periods, suggesting the potential for underreporting the frequency of cannabis use. Additionally, there was insufficient data to assess dose–response relationships; findings on paternal cannabis use were limited due to low response rates; and confidence intervals were wide due to the small number of women reporting cannabis use during and just before pregnancy. In Grufferman et al.

(1993), 25 percent of cannabis users were also cocaine users. As a result of this correlation, any association between parental cannabis use and risk of rhabdomyosarcoma is confounded by polysubstance use. In addition, the authors did not collect data on frequency and duration of cannabis use and therefore were unable to assess for a dose–response relationship.

CONCLUSION 5-6 There is insufficient evidence to support or refute a statistical association between parental cannabis use and a subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring.

RESEARCH GAPS

To address the research gaps relevant to cancer incidence, the committee suggests the following:

- There is need for robust epidemiological studies to investigate the association between cannabis exposure and several types of cancers, including but not limited to lung, head and neck, testicular, and esophageal cancers.
- Further investigation is needed to resolve any contradictory findings on, and to characterize the nature and strength of, any potential associations between parental cannabis use and the risk of cancer in their offspring.
- To promote the development of a body of high-quality evidence on the association between cannabis exposure and cancer incidence, researchers need to prioritize rigorous study designs and implement data collection protocols and methods that allow them to control for key confounders and to precisely measure cannabis exposure.
- Because of changing exposures to cannabis and the fact that many associations are based on single studies, replication of existing studies in targeted areas is needed.

SUMMARY

The committee identified good- or fair-quality systematic reviews on the association between cannabis use and the risk of lung, testicular, and head and neck cancers. Good-quality primary literature on the association between cannabis use and lung, testicular, esophageal, childhood, and several other cancers was also identified. Due to a paucity of research,

mixed findings, and numerous methodological limitations, the committee judged the evidence from the studies on childhood cancers, esophageal cancer, and various other cancers in adults to be insufficient to support or refute a statistically significant association between cannabis use and the incidence of these cancers. More conclusive findings and less extensive methodological limitations in the literature on lung, testicular, and head and neck cancers allowed the committee to conclude that there is moderate evidence that there is no statistically significant association between cannabis use and the incidence of lung or head and neck cancer, and limited evidence that there is a statistically significant association between current, frequent, or chronic cannabis use and the incidence of non-seminoma-type testicular germ cell tumors. Below, Box 5-1 summarizes the chapter conclusions.

BOX 5-1
Summary of Chapter Conclusions*

There is moderate evidence of *no* statistical association between cannabis use and:

- Inc dence of ung cancer (cannab s smok ng) (5-1)
- Inc dence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:

- Non-sem noma-type test cu ar germ ce tumors (current, frequent, or chron c cannab s smok ng) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Inc dence of esophagea cancer (cannab s smok ng) (5-4)
- Inc dence of prostate cancer, cerv ca cancer, ma gnant g omas, non-Hodgk n ymphoma, pen e cancer, ana cancer, Kapos 's sarcoma, or b adder cancer (5-5)
- Subsequent r sk of deve op ng acute mye o d eukem a/acute non- ymphob ast c eukem a, acute ymphob ast c eukem a, rhabdomyosarcoma, astrocytoma, or neurob astoma n offspr ng (parenta cannab s use) (5-6)

* Numbers in parentheses correspond to chapter conclusion numbers

Epidemiological studies that investigate the association between cannabis use and the risk of various cancers face methodological challenges similar to those found in studies of other clinical outcomes. These challenges include, but are not limited to, small sample sizes and low participation rates, the inability to verify cannabis use data based on self-report alone, and difficulties in controlling for potential confounders and accounting for potential effect modifiers. Additionally, some special—if not unique—methodological challenges pertain to cancer studies. For example, cancer is a diverse set of diseases that occur in different organs and organ systems and have different histopathological characteristics and risk factors. Some of these risk factors, such as family cancer history, occupational exposures, and diet, are difficult to measure and were often not accounted for by the studies reviewed in this chapter. Additionally, the long incubation period of many cancers requires a similarly extended observation period, and that makes it difficult to fully characterize the relevant cannabis exposure and to control for other relevant exposures.

Future research will need to address the limited scope and quality of epidemiological studies on the association between cannabis use and cancer incidence. Investigators will need to confirm existing evidence on lung and head and neck cancers and to expand the evidence base on testicular, esophageal, and childhood cancers, as well as other cancers in adults. To address the methodological limitations described above, future studies will also need to be well designed and to employ rigorous methods of data collection and measurement.

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6

Cardiometabolic Risk

Chapter Highlight

- The evidence is unclear as to whether and how cannabis use is associated with heart attack, stroke, and diabetes.

An estimated 85.6 million American adults have at least one cardiovascular disease such as heart disease, stroke, heart failure, or hypertension (Mozaffarian et al., 2016). Each year cardiovascular diseases account for more than 800,000 deaths (i.e., they are the underlying cause listed on the death certificate), or 30 percent of all deaths in the United States (Mozaffarian et al., 2016).

Heart disease is the leading cause of mortality in the United States, accounting for more than 600,000 deaths per year (Kochanek et al., 2016). Within subcategories of heart disease, coronary heart disease (CHD) is by far the largest, with 364,000 deaths annually (Kochanek et al., 2016). CHD is a disease in which a waxy substance called plaque builds up inside the blood vessels supplying the heart (i.e., the coronary arteries). Over the course of years or decades, the plaque can harden or rupture, resulting in an inadequate supply of blood to the heart which may, in some instances, result in death of heart muscle (myocardial infarction).

Both coronary heart disease and stroke are associated with aging, with nearly 93 percent of CHD deaths and 94 percent of stroke deaths occurring in individuals 55 years and older (Kochanek et al., 2016). More

than one-third (about 36 percent) of CHD deaths occur in individuals ages 85 years and older, while 43 percent of stroke deaths occur in this age group (Kochanek et al., 2016).

Current (past-month) cannabis use is fairly low in the older populations most likely to experience cardiovascular diseases—in particular, about 2 percent past-month prevalence in those ages 50 years and older. In younger adults, by contrast, the prevalence of cannabis use has been estimated to be as high as 19.6 percent for past-month use among those ages 18 to 25 years (Azofeifa et al., 2016), but these rates decline dramatically with aging. In contrast, tobacco smoking—a known risk factor for heart disease and stroke—has a much higher prevalence among older adults: 18 percent in those ages 45 to 64 years and 8.5 percent in those ages 65 years and older who smoke (Jamal et al., 2015).

Cardiometabolic disorders result in a substantial economic burden on the United States. From 2011 to 2012 the estimated annual cost of cardiovascular diseases, including heart disease, stroke, hypertensive disease, and other circulatory conditions, was $316.6 billion ($207.3 billion for heart disease, $33.0 billion for stroke). The total estimated cost of diagnosed diabetes in 2012 was $245 billion (Mozaffarian et al., 2016).

The objective of the review of cannabis and cardiometabolic conditions was to assess the independent association of cannabis with these conditions in studies in which the association has been quantified. The justification for examining cannabis use in relation to cardiometabolic conditions is that these conditions are among the leading causes of death; are highly prevalent in the United States; account for high levels of medical care utilization and cost; and are caused, in significant part, by modifiable lifestyle risk factors, including diet, physical activity, and cigarette smoking. The high prevalence of these conditions means that a behavior that is associated with a small degree of increased risk for heart disease, stroke, or diabetes can be associated with a high level of attributable risk, that is, the number of cases of disease that result from that behavior. While the prevalence of cardiometabolic conditions is concentrated in the older-adult age groups which have low rates of cannabis use, it is expected that the expanding legalization of cannabis use will cause the rates of use to increase.

The discussion in this review is limited to acute myocardial infarction, stroke, metabolic dysregulation and metabolic syndrome, and diabetes. Sudden death and arrhythmias such as atrial fibrillation were other topics of interest for which no data were available to quantify the association with cannabis use. The 1999 Institute of Medicine (IOM) report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) reviewed the cardiovascular system; however, no conclusions or recommendations related to cannabis use and cardiometabolic outcomes were included in that report.

The literature search conducted by the current committee did not identify any systematic reviews that were rated as "good" or "fair" for cannabis use and acute myocardial infarction, stroke, dyslipidemia or metabolic syndrome, or diabetes, so all of the available primary literature for these outcomes dating back to 1999 was reviewed and the 12 primary articles rated as "good" or "fair" by the committee have been included in this chapter.

ACUTE MYOCARDIAL INFARCTION

Each year, an estimated approximately 550,000 Americans have an incident (i.e., first-time) heart attack (acute myocardial infarction, or AMI) and about 200,000 have a recurrent attack (Mozaffarian et al., 2016). Of those who have a heart attack each year, about 116,000 die as a result of their coronary event (Mozaffarian et al., 2016). The committee responsible for the IOM report *Marijuana and Medicine: Assessing the Science Base* (1999) did not make any conclusions or recommendations regarding cannabis use and acute myocardial infarctions.

The acute cardiovascular effects of cannabis include increases in heart rate and supine blood pressure and postural hypotension (Beaconsfield et al., 1972; Benowitz and Jones, 1981). Smoking cannabis decreases exercise test duration on maximal exercise tests and increases the heart rate at submaximal levels of exercise (Renaud and Cormier, 1986). These acute effects provide a physiological basis for cardiac ischemia to develop in cannabis users. In fact, the time from exercise to the onset of angina pectoris is decreased by smoking one cannabis cigarette (Aronow and Cassidy, 1974). Tolerance develops to the acute effects of tetrahydrocannabinol (THC) over several days to a few weeks (Gorelick et al., 2013). Reported cardiovascular effects that may increase the risk of AMI include irregular heart rate (Khiabani et al., 2008) and impaired vascular endothelial function (demonstrated in rates from exposure to secondhand cannabis smoke) (Wang et al., 2016). Additionally, carbon dioxide production from smoked cannabis decreases the oxygen-carrying capacity of the blood and may contribute to the development of cardiac ischemia.

There have been numerous case reports suggesting that cannabis use is associated with the occurrence of AMI. The two primary studies that have quantified the risk of AMI associated with cannabis use and that were rated as good or fair are reviewed below.

Is There an Association Between Cannabis Use and Acute Myocardial Infarction?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis and AMI. Three descriptive review articles provided useful background: Sidney (2002), Thomas et al. (2014), and Franz and Frishman (2016).

Primary Studies

A retrospective cohort study (Sidney, 2002; Sidney et al., 1997) assessed the risk of hospitalization for AMI associated with cannabis use in a cohort of 62,012 men and women ages 15 through 49 years who had, from mid-1979 through 1985, completed self-administered research questions on their cannabis, tobacco, and alcohol use. AMI was assessed by linkage to electronically maintained records of all overnight hospitalizations in Kaiser Permanente Northern California. Follow-up was conducted for up to 12 years. Current use of cannabis was reported by 22 percent and former use by 20 percent of the cohort. There were 209 incident AMIs, 173 in men and 36 in women. The relative risk associated with cannabis use was assessed by a Cox proportional hazards model with adjustments for age, race, education, body mass index (BMI), history of hypertension, smoking, and alcohol use. The relative risk for AMI in current users was 1.1 (95% confidence interval [CI] = 0.7–1.7) for men and 1.8 (95% CI = 0.5–6.3) for women; in former users it was 0.9 (95% CI = 0.6–1.5) for men and 1.0 (95% CI = 0.2–4.5) for women. Both current and former cannabis use were unassociated with an increased risk of AMI.

Study limitations included a reliance of self-report of cannabis use which may result in misclassification of this exposure; the lack of availability of longitudinal data on cannabis use; and the relatively young age (mean age 33 years), which meant that the AMIs occurred in a relatively young age range that is not representative of the older age range in which the vast majority of AMIs occur. Cannabis use was assessed at only one point in time.

A case crossover study design was used to examine the role of cannabis use as a possible trigger for myocardial infarction in 3,882 AMI patients in an inception cohort study identified between August 1989 and September 1996 from 64 community and tertiary medical centers in the United States that were part of the Determinants of Myocardial Onset Study (Mittleman et al., 2001). The mean ages of cannabis users and abstainers were 43.7 and 62.0 years, respectively, while 68 percent of cannabis users and 32 percent of abstainers were current tobacco smok-

ers. Nine patients (0.2 percent) interviewed soon after admission for AMI reported cannabis use during the hour preceding the symptoms of AMI. The risk for AMI associated with cannabis use during the hour preceding symptoms of AMI was 4.8 (95% CI = 2.9–9.5) as assessed by a case-crossover analysis. The exclusion of three of the nine patients who reported other triggering behaviors during the hour prior to the AMI (cocaine use and/or sexual intercourse) resulted in a relative risk of 3.2 (95% CI = 1.4–7.3).

The major limitations of this study were its small size and its reliance on self-report for cannabis use status, which meant that any misclassification could have had a significant effect on the results. While the case-crossover design controls for confounding by traditional risk factors for cardiovascular disease, it does not control for interaction of these factors, and one cannot determine whether cannabis acts as a trigger in low-risk individuals or those who are nonsmokers of tobacco.

Discussion of Findings

While there are a number of reports of an association between cannabis use and AMI, only the two studies described above quantify risk, with the Sidney (2002) study demonstrating no association with an increased or decreased risk of AMI and the Mittleman et al. (2001) study finding that cannabis use may act as a trigger for AMI. The limitations of these studies were described. More generally, with the Mittleman study as an exception, most reports of adverse cardiovascular effects of cannabis, including AMI, have been conducted in a relatively young age range, while major cardiovascular events are concentrated in older adults and the findings may not be generalizable to this age group. Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g, smoked, edible, etc.); dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and total lifetime duration/dose of cannabis use. Overall, the articles were judged to be of fair quality for assessing the risk of acute myocardial infarction associated with cannabis use.

The role of cannabis as a trigger of AMI is plausible, given its cardiostimulatory effects, which may cause ischemia in susceptible hearts. Carboxyhemoglobinemia from combustion of cannabis resulting in a decreased oxygen-carrying capacity of blood may also contribute to ischemia. Given the physiologic plausibility for a trigger effect, smoking cannabis may put individuals, particularly those at high risk for cardiovascular disease, at increased risk for AMI.

CONCLUSION 6-1

6-1(a) There is limited evidence of a statistical association between cannabis smoking and the triggering of acute myocardial infarction.

6-1(b) There is no evidence to support or refute a statistical association between chronic effects of cannabis use and the risk of acute myocardial infarction.

STROKE

Stroke is the fifth leading cause of death in the United States, accounting for 133,000 deaths annually (Kochanek et al., 2016). A stroke is the death of a portion of brain tissue due to a disruption of the blood supply. Strokes may be ischemic (inadequate blood/oxygen supply) or hemorrhagic (bleeding into the brain) in origin. Each year, approximately 795,000 people experience a new or recurrent stroke. Approximately 610,000 of these are first stoke occurrences and 185,000 are recurrent stroke events (Mozaffarian et al., 2016). The committee responsible for the IOM report *Marijuana and Medicine: Assessing the Science Base* (1999) did not make any conclusions or recommendations regarding cannabis use and stroke.

Numerous reports have suggested that smoking cannabis increases the risk of stroke, including case series (Phillips et al., 2011) and studies describing cannabis-associated vascular changes that may be associated with stroke (Herning et al., 2001; Wolff et al., 2011, 2015). Several reports have indicated a close temporal relationship between cannabis smoking and stroke (Wolff et al., 2013). The cardiovascular effects of cannabis that have been proposed as a possible mechanism in the etiology of stroke include orthostatic hypotension with secondary impairment of the autoregulation of cerebral blood flow, altered cerebral vasomotor function, supine hypertension and swings in blood pressure, cardioembolism with atrial fibrillation, other arrhythmias, vasculopathy, vasospasm, reversible cerebral vasoconstriction syndrome, and multifocal intracranial stenosis (Wolff et al., 2015).

Is There an Association Between Cannabis Use and Stroke?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and stroke.

Primary Studies

A large reported study on the association of cannabis and stroke by Rumalla et al. (2016a) used the Nationwide Inpatient Sample, which provides admission data from a 20 percent sample of all U.S. hospitalizations, to examine the cross-sectional association between cannabis use and hospitalization for acute ischemic stroke (AIS) among patients ages 15 to 54 years during the time period 2004–2011. The primary *International Classification of Diseases* (ICD)-9-CM discharge code was used to identify AIS, and current cannabis use was identified using the ICD-9-CM code 340.30, which includes both cannabis dependence and non-dependent cannabis abuse. Current cannabis use was identified in 11,320 of 478,649 AIS events (2.4 percent). Tobacco use prevalence was higher in current cannabis users than in nonusers (64.4 percent versus 31.5 percent) as was cocaine use (26.7 percent versus 3.1 percent). The odds ratio (OR) associated with current cannabis use and hospitalization for AIS was 1.17 (95% CI = 1.15–1.20) as calculated with multivariable logistic regression adjusted for age, gender, race, substance use, payer status, Charlson's comorbidity index, and other comorbid risk factors. Analyses stratified on tobacco use status were not available. The limitations of this study include the cross-sectional design; the probable under-ascertainment of current cannabis use (2.4 percent is low for this age range); the absence of data on duration of tobacco use; and the absence of analyses that are stratified by tobacco and by cocaine use to determine the OR in non-tobacco use and non-cocaine users, given the high prevalence of these known risk factors for ischemic stroke.

In a case-control study conducted in a New Zealand hospital (Barber et al., 2013), 160 of 218 (73 percent) of ischemic stroke/transient ischemic attack (TIA) patients, ages 18 to 55 years, had urine drug screens between January 2009 and April 2012 (150 ischemic stroke, 10 TIA). Control urine samples were obtained from 160 patients matched for age, sex, and ethnicity. Twenty-five (15.6 percent) of the stroke/TIA patients and 13 (8.1 percent) of the control patients had positive cannabis drug screens. Eighty-eight percent of cannabis-positive patients were current tobacco smokers versus 28 percent of cannabis-negative patients. The OR associated with current cannabis use was 2.30 (95% CI = 1.08–5.08), but it was no longer statistically significant when an additional adjustment was made for tobacco use (1.59, 95% CI = 0.71–3.70).

In a cross-sectional analysis by Westover et al. (2007) of all ischemic (N = 998) and hemorrhagic strokes (N = 937) identified in 2003 by ICD-9 codes from an administrative database maintained by the state of Texas in young adults ages 18 to 44 years the ORs of cannabis and other illicit drugs being associated with ischemic and hemorrhagic stroke were estimated using a multivariable logistic regression adjusting for alcohol,

tobacco, amphetamines, cocaine, opioids, cardiovascular risk factors, and other medical conditions associated with increased risk of these outcomes. The prevalence of cannabis use, identified by ICD-9 codes, was approximately 1 percent. Cannabis was associated with an increased risk of ischemic stroke (OR, 1.76; 95% CI = 1.15–2.71) but was not associated with a risk of hemorrhagic stroke (OR, 1.36; 95% CI = 0.90–2.06). The prevalence rate of tobacco use was not reported, and analyses stratified by category of tobacco use were not performed.

A retrospective cohort study (Sidney, 2002; Sidney et al., 1997) assessed the risk of hospitalization for stroke associated with cannabis use in a cohort of 62,012 men and women of ages 15 to 49 years who had, from mid-1979 through 1985, completed self-administered research questions on cannabis, tobacco, and alcohol use. Stroke was assessed by linkage to electronically maintained records of all overnight hospitalizations in Kaiser Permanente Northern California. Follow-up was conducted for up to 12 years. Current use of cannabis was reported by 22 percent and former use by 20 percent of the cohort. There were 130 incident strokes, 68 in men and 62 in women. The relative risk associated with cannabis use was assessed by Cox proportional hazards model with adjustments for age, race, education, BMI, history of hypertension, smoking, and alcohol use. The relative risk for stroke in current users was 1.0 (95% CI = 0.5–1.9) for men and 0.7 (95% CI = 0.3–2.2) for women; in former users it was 0.8 (95% CI = 0.4–1.8) for men and 1.5 (95% CI = 0.7–3.5) for women. Both current cannabis use and former cannabis use were not associated with increased risk of stroke.

The study's limitations included its reliance on self-report of cannabis use, which may result in misclassification of this exposure; the lack of availability of longitudinal data on cannabis use; and the relatively young age of subjects (mean age 33 years) so that the strokes occurred in a relatively young age range that is not representative of the older age range in which the vast majority of strokes occur. Cannabis use was assessed at only one point in time.

Rumalla et al. (2016b) used the Nationwide Inpatient Sample, which provides admission data from a 20 percent sample of all U.S. hospitalizations, to examine the cross-sectional association between cannabis use and hospitalization for aneurysmal subarachnoid hemorrhage (SAH) among patients ages 15 to 54 years during the time period 2004–2011. The primary ICD-9-CM discharge code was used to identify SAH, and current cannabis use was identified using the ICD-9-CM code 340.30, which includes both cannabis dependence and nondependent cannabis abuse. Current cannabis use was identified in 2,104 of the 94,052 (2.2 percent) SAH events. Tobacco use prevalence was higher in current cannabis users than in nonusers (59.3 percent versus 25.4 percent). The OR associated

with current cannabis use was 1.18 (95% CI = 1.12–1.24) according to a multivariate logistic regression adjusted for age, gender, race, substance use, primary payer status, Charlson's comorbidity index, and other SAH risk factors. The limitations of this study include its cross-sectional design, the probable under-ascertainment of current cannabis use (2.2 percent is low for this age range), the absence of data on duration of cannabis use, and the absence of analyses that are performed stratified by tobacco to determine the OR in non-tobacco use, given the high prevalence of this known risk factor for ischemic stroke.

Discussion of Findings

The studies by Rumalla et al. (2016a,b) and Westover et al. (2007) were cross-sectional studies using administrative data consisting of ICD-9 codes. Cross-sectional studies do not allow one to assess temporality between exposure and outcome. The miscoding of strokes does occur, although the reliability is probably reasonable for epidemiological studies. The classification of exposure status using ICD-9 is particularly concerning, given the likelihood that the percentage of cannabis users appears to be low compared to population norms in each of these studies, most notably the Westover et al. (2007) study.

With the exception of the Sidney (2002) study, none of the studies have data on the temporal relation between the cannabis or tobacco use and the stroke. A general problem was the analytic treatment of tobacco use. Given the much longer duration and frequency of tobacco smoking than of cannabis smoking for most people and the very common co-use of both substances, it is not appropriate to assume that an adjustment for tobacco use in a multivariable model will provide an accurate assessment of the risk associated with cannabis use. Additional analytic approaches, when feasible, may include testing the interaction between cannabis and tobacco use and performing stratified analyses to test the association of cannabis use with clinical endpoints in nonusers of tobacco. Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g., smoked, edible, etc.); the absence of information on dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and the lack of information on the total lifetime duration/dose of cannabis use.

All the articles were judged to be of fair quality for assessing the risk of stroke associated with cannabis use. With the exception of Sidney (2002) and Barber et al. (2013), all showed an increased risk of stroke associated with cannabis use but had significant limitations. For ischemic stroke, two of the studies indicated an increased risk while one showed a

nonsignificant finding in the direction of increased risk. For subarachnoid hemorrhage, the single study found an increased risk. For the combined hemorrhagic stroke endpoint assessed by Westover et al. (2007), the study showed no association of cannabis use with the risk of this endpoint.

CONCLUSION 6-2 There is limited evidence of a statistical association between cannabis use and ischemic stroke or subarachnoid hemorrhage.

METABOLIC DYSREGULATION, METABOLIC SYNDROME, PREDIABETES, AND DIABETES MELLITUS

Ranked as the seventh-leading cause of death in the United States, diabetes accounts for more than 76,000 deaths annually (Kochanek et al., 2016). An estimated 29 million adults in the United States have diabetes (CDC, 2014a), which is a group of conditions characterized by high blood glucose (sugar) levels due to the inability to metabolize glucose effectively. The number of new (incident) cases of diabetes diagnosed annually is more than 1.4 million (CDC, 2015). Similar to the case with cardiovascular diseases, the prevalence of diabetes increases with age, from 4.4 percent among those ages 20 to 44 years, to 16.2 percent at ages 45 to 64 years, and 25.9 percent at ages 65 years and older (CDC, 2014a). A major risk factor for the development of the most common type of diabetes (type 2) is obesity, which results in resistance to the effect of the glucose regulating hormone, insulin. An epidemic of obesity has resulted in the prevalence of obesity increasing from 22.9 percent in 1988–1994 to 34.9 percent in 2011–2012 (Flegal et al., 2002; Ogden et al., 2014), contributing to a near tripling of the prevalence of diabetes since 1990 to its current level of 9.3 percent (CDC, 2014b). The committee responsible for the IOM report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) did not make any conclusions or recommendations regarding cannabis use and metabolic dysregulation, metabolic syndrome, prediabetes, or diabetes mellitus.

Obesity, most notably central adiposity, is the dominant risk factor for the development of type 2 diabetes (Klil-Drori et al., 2016). Stimulation of the endogenous cannabinoid receptor system (the CB_1 receptor and, to a lesser extent, the CB_2 receptor) by Δ^9-THC, the major psychoactive component of cannabis, and by endogenous cannabinoids increases appetite and promotes adipogenesis, the production of body fat (Di Marzo et al., 2011). This physiological pathway suggests that cannabinoids such as Δ^9-THC may promote weight gain, which would increase the risk of an individual developing diabetes.

As noted earlier, the approximately 30-year epidemic of increasing

obesity rates in the United States has been associated with increasing rates of diabetes. A number of studies have examined the association of cannabis use with BMI and obesity. Counterintuitively, the majority of the reviewed studies showed that cannabis was associated with a lower BMI or a lower prevalence of obesity, or both (Hayatbakhsh et al., 2010; Le Strat and Le Foll, 2011; Smit and Crespo, 2001; Warren et al., 2005), or to have no association with BMI or obesity (Rodondi et al., 2006).

Because of the significance of diabetes as a highly prevalent disease, as a risk factor for cardiovascular diseases, and as a significant economic burden in our society, the question of whether cannabis use is associated with increased risk of diabetes is important. Included in this review are the assessments of three studies of cannabis use and metabolic dysregulation/metabolic syndrome, one study of cannabis use and prediabetes, and three studies of cannabis use and diabetes.

Is There an Association Between Cannabis Use and Metabolic Dysregulation, Metabolic Syndrome, Prediabetes, or Diabetes Mellitus?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis and metabolic dysregulation, metabolic syndrome, prediabetes, or diabetes mellitus. A review by Sidney (2016), published after the cutoff date for literature considered in this report, informed the discussion regarding the studies described in this section.

Primary Studies

Metabolic Dysregulation and Metabolic Syndrome Three cross-sectional studies were conducted using data from the National Health and Nutrition Examination Survey (NHANES) to examine the associations between cannabis use and glucose, insulin, and insulin resistance (Penner et al., 2013); cannabis use and the metabolic syndrome (Vidot et al., 2016); and cannabis use and tobacco cigarette smoking with metabolic syndrome (Yankey et al., 2016).

The study by Penner et al. (2013) included 4,657 NHANES participants from three exams conducted from 2005 to 2010 who were categorized as current, former, or never users of cannabis. The fasting mean glucose levels were not found to be significantly different in current users than in never users according to multivariable analyses that adjusted for age, sex, race/ethnicity, income, marital status, tobacco use, alcohol use,

BMI, and physical activity. Hemoglobin A1c did not vary by cannabis use status, while fasting insulin and homeostasis models of insulin resistance (HOMA-IR) were about 12 percent lower in current cannabis users than in never users. A study by Vidot et al. (2016) of 8,478 NHANES participants from three exams conducted from 2005 to 2010 found that the odds of metabolic syndrome were lower in current users than in never users, with an OR of 0.69 (95% CI = 0.47–1.00) according to a multivariable analysis that adjusted for age, sex, race/ethnicity, poverty-to-income ratio, tobacco smoking, and exam cycle year. Yankey et al. (2016) studied the association between cannabis and cigarette smoking with the prevalence of metabolic syndrome, using data from 3,051 2011–2012 NHANES participants. Compared with findings from respondents who reported never having used cannabis, regular use of cannabis (defined as smoking cannabis or hashish at least once per month for more than 1 year) was associated with reduced odds for metabolic syndrome (OR, 0.23; 95% CI = 0.06–0.90). The multivariable analysis controlled for age, education, family-income-to-poverty ratio, sex, medical insurance, marital status, tobacco smoking, physical activity, other drug use, and rehabilitation.

Prediabetes Bancks et al. (2015) examined the association of self-reported cannabis use with both the prevalence and the incidence of prediabetes in the Coronary Artery Risk Development in Young Adults (CARDIA) study. A cross-sectional analysis for diabetes was conducted in 3,024 participants at the Year 25 exam. Cannabis use was assessed by self-administered questions. Prediabetes was defined according to American Diabetes Association criteria and was present in 45 percent of participants. Relative to never use, the current use of cannabis was associated with an OR for prediabetes of 1.65 (95% CI = 1.15–2.38), and lifetime cannabis use of at least 100 times was associated with an OR of 1.49 (95% CI = 1.06–2.11). The multivariable analysis adjusted for age, sex, race, tobacco smoking, alcohol use, education, field center, systolic blood pressure, C-reactive protein (CRP), physical activity, and the use of other illicit drugs. The CARDIA longitudinal analysis examined the association of self-reported cannabis use at the Year 7 follow-up exam to incident prediabetes (51 percent of participants) at the four subsequent follow-up examinations, with an average of 13.8 years of follow-up. The adjusted hazard ratio (HR) for prediabetes associated with lifetime use of at least 100 times relative to never use of cannabis was 1.39 (95% CI = 1.13–1.71).

Diabetes Bancks et al. (2015) also examined the association of self-reported cannabis use and diabetes in both cross-sectional and longitudinal analyses conducted in the CARDIA study. The study population was the same for the cross-sectional analysis, and the adjustment variables

were the same as described for the prediabetes analysis. Diabetes was present in 11.8 percent of Year 25 exam participants. The ORs for diabetes were 1.18 (95% CI = 0.67–2.10) for current use and 1.42 (95% CI = 0.85–2.38) for lifetime use of at least 100 times relative to never use of cannabis. The longitudinal analysis examined the association between Year 7 exam and self-reported cannabis use to incident diabetes (11.1 percent of participants) at the four subsequent follow-up examinations (years 10, 15, 20, and 25). Relative to never use, the HR associated with diabetes for lifetime use of at least 100 times was 1.10 (95% CI = 0.74–1.64), adjusted for the same variables as the longitudinal analysis of prediabetes.

Two cross-sectional studies were conducted using data from the NHANES to examine the association of cannabis use with diabetes (Alshaarawy and Anthony, 2015; Rajavashisth et al., 2012). The first study (Rajavashisth et al., 2012) used interviewer-administered data regarding cannabis use and diabetes collected from 10,896 adults, ages 20 to 29 years, during NHANES III, conducted from 1988 to 1994. Relative to nonusers, the OR for diabetes associated with current and past cannabis use was 0.36 (95% CI = 0.24–0.55), adjusted for race/ethnicity, physical activity, alcohol use, alcohol × cannabis use interaction, BMI, total cholesterol, triglyceride, CRP, and hypertension.

In the second study, Alshaarawy and Anthony (2015) examined the association of cannabis use with diabetes in eight different replication samples and in a meta-analysis. The samples were obtained from four NHANES surveys (2005–2006, 2007–2008, 2009–2010, 2011–2012) and from a survey performed for the National Survey on Drug Use and Health (NSDUH) during the same time periods. A composite indicator of diabetes from the NHANES data combined interview reports of diabetes, current use of insulin and/or oral hypoglycemic medication, and lab-derived glycohemoglobin. Self-report of cannabis was assessed from the NSDUH surveys. Compared to nonusers, the adjusted odds ratios (aORs) for diabetes associated with current cannabis use ranged from 0.4 to 0.9, with a meta-analytic OR summary of 0.7 (95% CI = 0.6–0.8). Meta-analytic summary analyses performed within cigarette smoking strata found aORs were 0.8 (95% CI = 0.5–1.2) in respondents who reported never having smoked cigarettes and 0.8 (95% CI = 0.6–1.0) in current smokers.

Discussion of Findings

Overall, the articles reviewed by the committee were judged to be of good to fair quality for assessing the risk of metabolic dysregulation, metabolic syndrome, prediabetes, or diabetes mellitus associated with cannabis use. In their review of the evidence, the committee found that cannabis use had either an inverse association or no association with

BMI, an inverse association with metabolic dysregulation and metabolic syndrome, and an inverse association or no association with diabetes mellitus. The only study showing an increased risk was the prediabetes portion of the CARDIA study analysis.

As noted earlier, these are counterintuitive findings because THC tends to stimulate appetite, promote fat deposition, and promote adipogenesis. Potential explanations include the following:

- Cross-sectional studies do not allow one to assess temporality between exposure and outcome. With the exception of the longitudinal findings reported in the CARDIA study, all of the reported findings were from cross-sectional analyses.
- Dose estimates of cannabis exposure were generally imprecise and lacking information on cannabis strength, dose, frequency of use, and duration of use, although this may be because the cumulative dose for most cannabis users is not high enough to affect fat and glucose-insulin metabolism. Statistical confounders may exist in these studies which are not adequately controlled for by standard multivariable modeling. For example, in general, high levels of cannabis use are strongly associated with younger age, which is inversely associated with the incidence and prevalence of diabetes. They are also associated with tobacco cigarette smoking, a known risk factor for diabetes (Willi et al., 2007). Cannabis use was associated with increases in physical activity in the CARDIA study (Bancks et al., 2015) and in one of the NHANES studies (Rajavashisth et al., 2012). Physical activity is protective against obesity and diabetes.
- Reverse causality might result in a chronic illness such as diabetes leading to the cessation of potentially unhealthy habits, including cannabis use. This might help to explain why cannabis use is associated with prediabetes but not with diabetes.

CONCLUSION 6-3

6-3(a) There is limited evidence of a statistical association between cannabis use and decreased risk of metabolic syndrome and diabetes.

6-3(b) There is limited evidence of a statistical association between cannabis use and increased risk of prediabetes.

RESEARCH GAPS

The major gaps and opportunities relate to the paucity of longitudinal data for all of the cardiometabolic disorders and to the lack of data on the impact of cannabis use on risk in the older-adults age groups in which the majority of cardiovascular endpoints (e.g., acute myocardial infarction, stroke) occur. To address research gaps the committee suggests the following:

- Establishing a population cohort(s) in which cannabis use is regularly evaluated with standardized questionnaires accounting for the type of preparation, THC/other cannabinoid strength, the amount smoked or consumed, assessment of frequency and duration of use, and other cardiovascular disease (CVD) risk data, and in which researchers collect medical record and toxicology data or other biological marker data for cannabis use on incident CVD events.
- The cohort(s) need to be large enough that the association of cannabis with CVD events in the presence of potential statistical confounding variables (e.g., tobacco use, physical activity) can be validly assessed.
- Promote the collection of cannabis use data in electronic health records.

An additional suggestion is that basic research needs to be carried out to better understand the mechanisms for the role of cannabis as a possible trigger of AMI.

SUMMARY

This chapter summarizes the good and fair cardiometabolic literature published since 1999. The committee found limited evidence of an association between acute cannabis use—but not chronic cannabis use—and AMI risk. The committee also determined that there is limited evidence of an association between cannabis use and an increased risk of ischemic stroke or subarachnoid hemorrhage and also prediabetes and an association between cannabis and a decreased risk of metabolic dysregulation, metabolic syndrome, and diabetes. The limitations of the reviewed studies include a lack of information on different routes of cannabis administration (e.g, smoked, edible, etc.), a lack of adequate dose information, insufficient information on potential additives or contaminants, and inadequate data on total lifetime duration/dose of cannabis use. The committee has formed a number of research conclusions related to these health endpoints; however, it is important that each of these conclusions be

BOX 6-1
Summary of Chapter Conclusions*

There is limited evidence of a statistical association between cannabis use and:

- The tr gger ng of acute myocard a nfarct on (cannab s smok ng) (6-1a)
- Ischem c stroke or subarachno d hemorrhage (6-2)
- Decreased r sk of metabo c syndrome and d abetes (6-3a)
- Increased r sk of pred abetes (6-3b)

There is no evidence to support or refute a statistical association between *chronic effects* of cannabis use and:

- The ncreased r sk of acute myocard a nfarct on (6-1b)

* Numbers in parentheses correspond to chapter conclusion numbers

interpreted within the context of the limitations discussed in the Discussion of Findings sections. Box 6-1 contains a summary of the conclusions for this chapter.

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7

Respiratory Disease

Chapter Highlights

- Smoking cannabis on a regular basis is associated with chronic cough and phlegm production.
- Quitting cannabis smoking is likely to reduce chronic cough and phlegm production.
- It is unclear whether cannabis use is associated with chronic obstructive pulmonary disorder, asthma, or worsened lung function.

Environmental exposures are the leading causes of respiratory disease worldwide. Exposures to tobacco smoke and household air pollution consistently rank among the top risk factors not only for respiratory disease burden but also for the global burden of disease (Lim et al., 2012). Less is known, however, about the attributable effects of cannabis use on respiratory disease despite shared similarities with that of cigarette use and the fact that cannabis is the most commonly used inhaled drug in the United States after tobacco, with an estimated 22.2 million people ages 12 years and older reporting current use (CBHSQ, 2015). Moreover, it is estimated that more than 40 percent of current users smoke cannabis on a daily or near daily basis (Douglas et al., 2015). Given the known relationships between tobacco smoking and multiple respiratory conditions, one could hypothesize that long-term cannabis smoking leads to similar deleterious

effects on respiratory health, and some investigators argue that cannabis smoking may be even more harmful than that of tobacco smoking. Indeed, data collected from 15 volunteers suggest that smoking one cannabis joint can lead to four times the exposure to carbon monoxide and three to five times more tar deposition than smoking a single cigarette (Wu et al., 1988). This may be, in part, because cannabis smokers generally inhale more deeply and hold their breath for longer than do cigarette smokers (Wu et al., 1988) and because cannabis cigarettes do not commonly have filters as tobacco cigarettes often do. On the other hand, cannabis cigarettes are not as densely packed as tobacco cigarettes (Aldington et al., 2008), and cannabis users usually smoke fewer cannabis cigarettes per day than tobacco users smoke tobacco cigarettes per day.

The committee responsible for the 1999 Institute of Medicine (IOM) report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999, p. 6) concluded that cannabis smoking was an important risk factor in the development of respiratory disease and recommended that "studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent." The literature search conducted by the current committee did not identify any fair- or good-quality systematic reviews for cannabis use and respiratory disease published since 2011 (the cutoff established by the current committee); however, the committee identified—and elected to include—a systematic review by Tetrault et al. (2007) that provides a detailed synthesis of the available literature through 2005. A review by Tashkin (2013) and a position statement by Douglas et al. (2015), which summarized current evidence of the link between cannabis smoking and respiratory disease, were also considered by the committee. Fourteen primary articles published since 1999 that were not included in the systematic review from Tetrault et al. (2007) provided additional evidence on the association between smoking cannabis and respiratory diseases (Aldington et al., 2007; Bechtold et al., 2015; Hancox et al., 2010, 2015; Kempker et al., 2015; Macleod et al., 2015; Papatheodorou et al., 2016; Pletcher et al., 2012; Tan et al., 2009; Tashkin et al., 2012; Van Dam and Earleywine, 2010; Walden and Earleywine, 2008; Weekes et al., 2011; Yadavilli et al., 2014).

PULMONARY FUNCTION

Pulmonary function refers to lung size and function. Common measures of pulmonary function include forced expiratory volumes, lung volumes, airways resistance and conductance, and the diffusion capacity of the lung for carbon monoxide (DLCO). Spirometry values include the measurements of forced expiratory volumes, including forced expiratory

volume at 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC. The latter is a measure of airflow obstruction and, when combined with bronchodilator therapy, is used in the diagnosis of chronic obstructive pulmonary disorder (COPD).

Is There an Association Between Cannabis Use and Pulmonary Function?

Systematic Reviews

Tetrault et al. (2007) systematically reviewed the evidence found in 34 publications, of which 12 reported on the effects of airway response and 14 reported on the effects of pulmonary function. The authors found that short-term exposure to cannabis smoking resulted in bronchodilation. Specifically, acute cannabis smoking was consistently associated with improvements in specific airway conductance, peak flow measurements, and FEV_1, as well as reversed bronchospasm from challenges by either methacholine or exercise. Any short-term benefits, however, were offset by the effects of long-term cannabis smoking. Specifically, regular cannabis smoking was associated with a lower specific airway conductance on average by 16 percent and also with a lower FEV_1. There was also a dose–response effect between average daily quantity of cannabis and a lower specific airway conductance. However, the clinical significance of the association between regular cannabis smoking and a lower specific airways conductance is not known. Other studies that examined the association between long-term cannabis smoke exposure and pulmonary function have inconsistently found lower or no change in FEV_1, FVC, FEV_1/FVC, DLCO, and airway hyperresponsiveness (Tetrault et al., 2007).

Primary Studies

Aldington et al. (2007) examined the cross-sectional relationship between long-term cannabis smoking and pulmonary function in a convenience sample of 339 participants in the Wellington Research Study. The inclusion criteria for cannabis and tobacco smokers were a lifetime exposure of at least 5 joint-years of cannabis (defined as smoking 1 joint per day for 1 year) or at least 1 pack-year of tobacco, respectively. Cannabis smoking was based on self-report. The researchers did not find an association between long-term cannabis smoking and pulmonary function variables. However, when cannabis smoking was analyzed in terms of joint-years, Aldington et al. (2007) found a significantly lower FEV_1/FVC, lower specific airways conductance, and a higher total lung capacity per joint-year smoked in cannabis smokers compared to nonsmokers. Based

on their analyses, the authors estimated that the negative association between each cannabis joint and a lower FEV_1/FVC was similar to that of 2.5 to 5 tobacco cigarettes. The committee identified a couple of problems with the analyses and the presentation of the results in the paper by Aldington et al. (2007). First, the authors reported main effects only from their analysis of covariance. A more conservative analysis would have considered the examination of interaction effects between cannabis smoke (or joint-years) and tobacco smoke (or pack-years) in a regression model to better dissect the contribution of cannabis smoke (or joint-years) versus tobacco smoke (or pack-years). Second, the authors incorrectly labeled the association with continuous measures of pulmonary function with cannabis smoke (or joint-years) as odds ratios (ORs) in tables 3 and 4; however, their methods correctly state that a multivariable analysis of covariance methods was used for continuous data.

Papatheodorou et al. (2016) analyzed cross-sectional data from 10,327 adults who participated in the National Health and Nutrition Examination Survey (NHANES) between 2007 and 2012. Cannabis smoking was based on self-report, but the researchers could not quantify joint-years. Cannabis smokers were categorized as never smokers (n = 4,794), past cannabis smokers (n = 4,084), cannabis smokers in the past 5–30 days (n = 555), and cannabis smokers in the past 0–4 days (n = 891). Current cannabis smokers were heavier tobacco smokers than were past and never smokers of cannabis, as measured by mean pack-years. In multivariable analyses, the investigators found that current smokers had a smaller FEV_1/FVC than never smokers (–0.01 and –0.02, respectively), and they observed moderate to large increases in FEV_1 (49 mL and 89 mL, respectively) and FVC (159 mL and 204 mL, respectively) when comparing current smokers to never smokers. There was also an important decrease in exhaled nitric oxide among current smokers when compared to never smokers (–7 percent versus –14 percent), but it is unclear if this effect was confounded by the high prevalence of tobacco smoking in current cannabis users or if it represented a true decrease in exhaled nitric oxide due to cannabis smoking. The study by Papatheodorou et al. (2016) has some shortcomings. First, the researchers' analyses were based on cross-sectional data. Second, cannabis use was obtained by self-report and there may have been a bias of underreporting. Finally, there was a lack of data on the method of smoke inhalation and the frequency of cannabis smoking, thus not allowing for an analysis of the relationship between the frequency of cannabis use and pulmonary function.

Pletcher et al. (2012) analyzed longitudinal data from 5,115 adults in the Coronary Artery Risk Development in Young Adults (CARDIA) study and concluded that occasional and low cumulative cannabis smoking was not associated with adverse effects on pulmonary function. The

investigators noted that there was a trend toward decreases in FEV_1 over 20 years only in the heaviest cannabis smokers (≥20 joint-years). Similar to the findings of Papatheodorou et al. (2016), CARDIA investigators found a higher-than-expected FVC among all categories of cannabis smoking intensity. Despite the large sample size, the study by Pletcher et al. (2012) had a small number of heavy cannabis smokers. Other limitations include the risk of bias due to the self-reporting of cannabis use, a lack of data on the method of cannabis smoke inhalation, and bias due to unmeasured confounders as cannabis smoking was not the main objective of this study.

The study by Hancox et al. (2010) analyzed data of a cohort of 1,037 adult participants in Dunedin, New Zealand, followed longitudinally since childhood and asked about cannabis and tobacco use at ages 18, 21, 26, and 32 years. Cumulative exposure to cannabis was quantified as joint-years since age 17 years. Spirometry was conducted at 32 years. Cumulative cannabis use was associated with higher FVC, total lung capacity, and functional residual capacity and residual volume, but not with lower FEV_1 or FEV_1/FVC.

A small feasibility study by Van Dam and Earleywine (2010) found that the use of a cannabis vaporizer instead of smoking cannabis in 12 adult participants who did not develop a respiratory illness was associated with improvements in forced expiratory volumes at approximately 1 month after the introduction of the vaporizer; however, this study did not have a control group.

Discussion of Findings

Overall, acute cannabis smoking was associated with bronchodilation, but many of the authors agreed that any benefits may be offset when cannabis is smoked regularly. The current findings are inconclusive on a variety of pulmonary function measurements, and the findings may be affected by the quality of the studies, a failure to adjust for important confounders, including tobacco and other inhaled drugs, and other occupational and environmental exposures. The committee's findings are consistent with those reported in another recent review (Tashkin, 2013) and a position statement (Douglas et al., 2015).

The majority of studies, including those evaluated in the systematic review, relied on self-report for cannabis smoking. Many studies failed to control for tobacco smoking and occupational and other environmental exposures; did not control for the dose or duration of cannabis smoking; and did not use joint-years and instead based heavy cannabis smoking on having exceeded a specific threshold of joints. Even among studies that used joint-years, it is unclear how generalizable their findings are, given the potential high variability in lung-toxic content from joint to joint. Prior

studies have inconsistently documented decreases or no change in FEV_1, FEV_1/FVC, DLCO, and airway hyperresponsiveness. Moreover, neither the mechanism nor the clinical significance of the association between cannabis smoking and pulmonary function deficits is known beyond the possible impact of a high FVC in lowering the FEV_1/FVC ratio. While elevated lung volumes could be indicators of lung pathology, an elevated FVC by itself has not been associated with any lung pathology.

CONCLUSION 7-1

7-1(a) There is moderate evidence of a statistical association between cannabis smoking and improved airway dynamics with acute use, but not with chronic use.

7-1(b) There is moderate evidence of a statistical association between cannabis smoking and higher forced vital capacity (FVC).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a clinical syndrome that consists of lower airway inflammation and damage that impairs airflow. Ranked as the fourth-leading cause of death worldwide by the World Health Organization, COPD has been estimated to cause more than 3 million deaths worldwide annually and has an estimated global prevalence of 10 percent in adults (Buist et al., 2007; Diaz-Guzman and Mannino, 2014). COPD is diagnosed with spirometry and is defined by a post-bronchodilator forced expiratory volume at 1 second divided by forced vital capacity (FEV_1/FVC) <70 percent (fixed cutoff) or as a post-bronchodilator FEV_1/FVC below the 5th percentile of a reference population (lower limit of normal). The committee responsible for *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) suspected, but did not conclude, that chronic cannabis smoking causes COPD.

Is There an Association Between Cannabis Use and COPD?

Systematic Reviews

There is no discussion about the association between cannabis and COPD in the systematic review by Tetrault et al. (2007). In the position statement of the American Thoracic Society (Douglas et al., 2015), workshop members concluded that there was minimal impairment in occasional cannabis smokers when controlling for tobacco use. In con-

trast, there was a trend toward higher prevalence in heavier users based on studies of lung function decline (Pletcher et al., 2012; Tashkin et al., 1987); however, workshop members determined that this association was incompletely quantified.

Primary Studies

The study by Aldington et al. (2007) examined high-resolution computed tomography scans among the subgroups of participants with cannabis smoking only, cannabis and tobacco smoking, tobacco smoking only, and never smokers. They found inconsistent results: a decreased mean lung density, which is suggestive of emphysematous changes (mean percent of area below −950 Hounsfield units in three slices at 2.4 percent [95% confidence interval (CI) = 1.0%–3.8%] for cannabis smokers, but −0.6 percent [−2.0%–0.8%] for tobacco smokers when compared to nonsmokers), but almost no evidence of macroscopic emphysema (1.3% versus 16.5% versus 18.5% versus 0% in cannabis-only smokers versus cannabis and tobacco smokers versus tobacco-only smokers versus non-smokers, respectively).

Tan et al. (2009) analyzed cross-sectional data collected in 878 adults ages 40 years and older from Vancouver, Canada, who participated in the Burden of Obstructive Lung Disease study on COPD prevalence. Current smoking of either tobacco or cannabis was defined as any smoking within the past year. Participants who had smoked at least 50 marijuana cigarettes but had no history of tobacco smoking were not at significantly greater risk of having COPD or more respiratory symptoms. There was inconsistent evidence for whether synergy from combined cannabis and tobacco smoking might affect the odds of having COPD or worse respiratory symptoms.

Specifically, the mean estimates for the tobacco and cannabis smoking versus tobacco-only smoking groups do not appear to be different, and the 95% CI for the tobacco and cannabis smoking group appears to overlap significantly with the tobacco-only smoking groups when evaluating either COPD or respiratory symptoms as the outcome.

Yadavilli et al. (2014) examined data from 709 participants over a 33-month period for hospital readmissions of COPD in illicit drug users and tobacco smokers. These investigators found that cannabis users had similar readmission rates to ex-tobacco or current tobacco users (mean readmissions at 0.22 versus 0.26) and much lower readmission rates than other illicit drug users (mean readmissions at 1.0). The unit for mean readmissions was not specified in either the tables or methods of this paper. The limitations of the study by Yadavilli et al. (2014) include a lack of spirometry data on all patients to confirm diagnosis of COPD, the self-

report of tobacco use, the risk for potential underreporting of illicit drug use, and the lack of outpatient visit frequency.

The study by Macleod et al. (2015) examined data from 500 adult participants, all of whom reported either tobacco smoking of ≥20 cigarettes per day for at least 5 years or cannabis of ≥1 joint per day for at least 1 year. There was no difference in the percent with COPD ($FEV_1/FVC < 0.7$) between tobacco-only users and tobacco and cannabis users (24.3 percent versus 25.2 percent; $p = 0.90$) for all ages or at any age group. Tobacco and cannabis users had more respiratory symptoms than did tobacco-only users (cough, phlegm, wheeze), but the investigators do not seem to report multivariable adjusted differences in the paper. The limitations of the study by Macleod et al. (2015) are that its cross-sectional design does not allow one to assess temporality between exposure and outcome, the lack of a nonsmoking group, the fact that its use of a convenience sample may have oversampled unwell participants, and the use of self-report for tobacco and cannabis.

Kempker et al. (2015) analyzed data from the 2007–2010 NHANES cohorts, similar to the work done by Papatheodorou et al. (2016). Kempker et al. (2015), however, also examined the information on cumulative lifetime use of cannabis available in the 2009–2010 NHANES cohort. Main findings were that 59 percent reported using cannabis at least once during their lifetime, and 12 percent reported use during the last month. When evaluating cumulative lifetime cannabis use, those with >20 joint-years had a two times higher odds (OR, 2.1; 95% CI = 1.1–3.9) of having a pre-bronchodilator $FEV_1/FVC < 70$ percent than those with no cannabis exposure. However, as noted by others, cannabis use was associated with a higher FVC and no association with FEV_1, which would spuriously reduce the ratio FEV_1/FVC. Beyond the limitations noted above for the paper by Papatheodorou et al. (2016), who also used NHANES data, the authors were limited to use pre-bronchodilator spirometry instead of using post-bronchodilator spirometry as commonly done in COPD studies.

Discussion of Findings

It is unclear whether regular cannabis use is associated with the risk of developing COPD or exacerbating COPD. Current studies may be confounded by tobacco smoking and the use of other inhaled drugs as well as by occupational and environmental exposures, and these studies have failed to quantify the effect of daily or near daily cannabis smoking on COPD risk and exacerbation. There is no evidence of physiological or imaging changes consistent with emphysema. The committee's findings are consistent with those of a recent position statement from the American Thoracic Society Marijuana Workgroup which concluded that there

was minimal impairment in light and occasional cannabis smokers when controlled for tobacco use and that the effects in heavy cannabis smokers remain poorly quantified (Douglas et al., 2015). The review by Tashkin (2013) concluded that the lack of evidence between cannabis use and longitudinal lung function decline (Pletcher et al., 2012) argues against the idea that smoking cannabis by itself is a risk factor for the development of COPD. This is further supported by the findings of Kempker et al. (2015), who concluded that smoking cannabis was not associated with lower FEV_1 after adjusting for tobacco smoking. However, smoking cannabis was associated with a higher FVC, which may have led to a spuriously lower FEV_1/FVC. Therefore, their analyses also do not support an association between heavy cannabis use (>20 lifetime joint-years) and obstruction on spirometry. The position statement by Douglas et al. (2015) concluded that the lack of solid epidemiologic association suggests that regular cannabis smoking may be a less significant risk factor for the development of COPD than tobacco smoking.

Cross-sectional studies are inadequate to establish temporality, and cohort studies of regular or daily cannabis users are a better design to help establish COPD risk over time. Better studies are needed to clearly separate the effects of cannabis smoking from those of tobacco smoking on COPD risk and COPD exacerbations, and better evidence is needed for heavy cannabis users.

CONCLUSION 7-2

7-2(a) There is limited evidence of a statistical association between occasional cannabis smoking and an increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use.

7-2(b) There is insufficient evidence to support or refute a statistical association between cannabis smoking and hospital admissions for COPD.

RESPIRATORY SYMPTOMS, INCLUDING CHRONIC BRONCHITIS

Respiratory symptoms include cough, phlegm, and wheeze. Chronic bronchitis is defined as chronic phlegm production or productive cough for 3 consecutive months per year for at least 2 consecutive years (Medical Research Council, 1965). Chronic bronchitis is a clinical diagnosis and does not require confirmation by spirometry or evidence of airflow obstruction. The committee responsible for *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) concluded that acute and chronic bronchitis may occur as a result of chronic cannabis use.

Is There an Association Between Cannabis Use and Respiratory Symptoms, Including Chronic Bronchitis?

Systematic Reviews

The systematic review by Tetrault et al. (2007) summarized information from 14 studies that assessed the association between long-term cannabis smoking and respiratory symptoms. Nine of these studies were cross-sectional, 3 were case series, 1 was a case-control study, and 1 was a longitudinal cohort study. Data were relatively consistent in both cross-sectional and cohort studies in indicating that long-term cannabis smoking worsens respiratory symptoms, including cough (ORs, 1.7–2.0), increased sputum production (ORs, 1.5–1.9), and wheeze (ORs, 2.0–3.0). Other studies have reported effects on more episodes of acute bronchitis and pharyngitis, dyspnea, hoarse voice, worse cystic fibrosis symptoms, and chest tightness.

Primary Studies

Aldington et al. (2007) reported higher prevalence of wheeze (27 percent versus 11 percent), cough (29 percent versus 5 percent), chest tightness (49 percent versus 35 percent), and chronic bronchitis symptoms (19 percent versus 3 percent) among cannabis smokers than among nonsmokers. There were no clear additive effects observed in the combined cannabis and tobacco smoking groups on respiratory symptoms.

Hancox et al. (2015) conducted a study in a cohort of 1,037 adults (52 percent male) in the Dunedin Multidisciplinary Health and Development Study. Cannabis and tobacco smoking histories were obtained at the ages of 18, 21, 26, 32, and 38 years. At each assessment, participants were asked how many times they had used cannabis in the previous year. Frequent cannabis users were defined as those who reported using marijuana ≥52 times over the previous year. Quitters were defined as a frequent cannabis user at the previous assessment but less than frequent at the current assessment. Because it was possible to quit frequent cannabis use more than once during the follow-up from 18 to 38 years of age, only the first recorded episode of quitting was used in analyses. In this study, the investigators found that frequent cannabis use was associated with morning cough (OR = 1.97, $p < 0.001$), sputum production (OR = 2.31, $p < 0.001$), and wheeze (OR = 1.55, $p < 0.001$), but not dyspnea ($p = 0.09$) (see Figure 7-1). Quitters (open triangles) also had fewer respiratory symptoms than those who did not quit (solid squares).

Limitations of the study by Hancox et al. (2015) include its reliance on self-reported data of cannabis use without objective confirmation, the

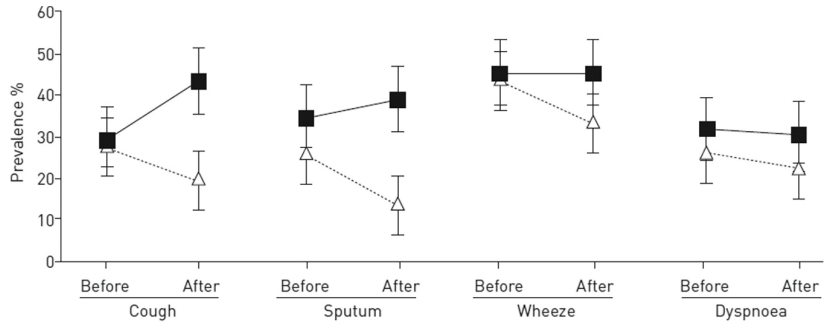

FIGURE 7-1 Prevalence of symptoms before and after quitting regular cannabis use (open triangles) and among those who used cannabis for two consecutive phases (solid squares). Vertical bars show 95% confidence level.
SOURCE: Hancox et al., 2015.

classification of nonusers as those with <52 times of cannabis use, and a lack of data as to whether cannabis use was specifically from smoking.

Walden and Earleywine (2008) conducted a cross-sectional Internet survey of 5,987 adults worldwide who used cannabis at least once per month. They quantified frequency, amount, and degree of usual and maximal intoxication, and they also asked about respiratory symptoms using a composite score produced from the answers to six standard questions about cough, morning phlegm, dyspnea, chest wheezing other than during colds, and nighttime awakenings because of chest tightness. They found that the frequency of use, the amount used (in quarter bags per month), and the degree of usual intoxication were all positively associated with more respiratory symptoms. Limitations for this study include its recruitment of participants from organizations that advocate drug policy reform, its reliance on self-reported data of cannabis or tobacco use without objective confirmation, and the lack of data about cannabis use for medical versus recreational purposes.

Tashkin et al. (2012) followed 299 participants from a longitudinal cohort study for at least two visits over 9.8 years and examined the relationship between symptoms for chronic bronchitis and cannabis use. They found that current cannabis users were more likely to have cough (OR = 1.7), sputum (OR = 2.1), increased bronchitis episodes (OR = 2.3), and wheeze (OR = 3.4) when compared to never users. They also found that current cannabis users were more likely to have cough (OR = 3.3), sputum (OR = 4.2), or wheeze (OR = 2.1) than former users. Similar to

the studies by Hancox et al. (2015) and Walden and Earleywine (2008), these findings demonstrated the benefit of cannabis smoking cessation in resolving preexisting symptoms of chronic bronchitis. The limitations of this study include its reliance on self-reported data of cannabis or tobacco use without objective confirmation and high rates of loss to follow-up or variable follow-up periods.

A small feasibility study by Van Dam and Earleywine (2010) of 12 adult participants who did not develop a respiratory illness during the trial found that the use of a cannabis vaporizer instead of smoking cannabis was correlated with the resolution of cannabis-related respiratory symptoms at approximately 1 month after the introduction of the vaporizer; however, this study did not have a control group.

Discussion of Findings

Regular cannabis use was associated with airway injury, worsening respiratory symptoms, and more frequent chronic bronchitis episodes. There were no clear additive effects on respiratory symptoms observed from smoking both cannabis and tobacco. Cannabis smoking cessation was temporally associated with the resolution of chronic bronchitis symptoms, and a small feasibility study suggests that use of a vaporizer instead of smoking cannabis may lead to the resolution of respiratory symptoms. The committee's findings are consistent with those reported in a recent review (Tashkin, 2013) and position statement (Douglas et al., 2015).

The majority of studies relied on self-report for cannabis smoking. Many studies failed to control for tobacco, occupational, and other environmental exposures; did not control for the dose or duration of the cannabis smoke exposure; and did not use joint-years and instead based heavy cannabis exposure on exceeding a specific threshold of cigarettes. Even among studies that used joint-years, it is unclear how generalizable the findings are, given the potential high variability in tetrahydrocannabinol (THC) content from joint to joint and from year to year.

CONCLUSION 7-3

7-3(a) There is substantial evidence of a statistical association between long-term cannabis smoking and worse respiratory symptoms and more frequent chronic bronchitis episodes.

7-3(b) There is moderate evidence of a statistical association between cessation of cannabis smoking and improvements in respiratory symptoms.

ASTHMA

Asthma is a clinical syndrome that is associated with airways inflammation, airflow limitation, bronchial hyperresponsiveness, and symptoms of episodic wheeze and cough. It is predominantly an allergic disease. Worldwide, asthma is thought to affect 300 million people, and it is responsible for more disability-adjusted life-years lost than diabetes mellitus. Asthma was not specifically addressed in *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999).

Is There an Association Between Cannabis Use and Asthma?

Systematic Reviews

The systematic review by Tetrault et al. (2007) referred to only one study that described the association between cannabis use and asthma exacerbations. Upon retrieving this study, the committee found that this was a letter to the editor which reported findings of a case-control study of 100 participants ages 18–55 years, with and without asthma, admitted to the emergency department. In this study, the authors found no association between THC and asthma (Gaeta et al., 1996).

Primary Studies

Bechtold et al. (2015) reported on a follow-up of a cohort of boys who participated in the Pittsburgh Youth Study. A total of 506 boys were followed longitudinally: 257 scored at or above the 70th percentile of a multi-informant conduct problem score, and 249 scored below the 70th percentile. This study found no link between cannabis use and self-reported asthma symptoms. The limitations of this study include a lack of generalizability to the general population, given the selection criteria for conduct problems, a lack of inclusion of women in their study, and the fact that health outcomes were based on self-report and biased to those who had sought care for health problems.

Weekes et al. (2011) studied a cohort of 110 black urban adolescents with asthma. In this study, the investigators found that 16 percent of the adolescents smoked cannabis, but there was no association between cannabis use and asthma concern or asthma severity or asthma symptoms. The limitations of this study include the reliance on the self-report of cannabis use, which the study authors speculated may be underreported in black adolescents when compared to whites, and a lack of data on asthma medication adherence.

Discussion of Findings

The committee did not find evidence for an association between cannabis use and either asthma risk or asthma exacerbations, and current studies failed to control for other important confounders, including adherence to asthma medications.

The evidence linking cannabis use with asthma risk or exacerbation is limited by the scope and sample size of available studies and by the use of more standardized approaches to measure asthma prevalence or exacerbations of asthma. Few studies have examined the link between cannabis and asthma, and no clear evidence exists of a link between asthma or asthma exacerbation and cannabis use. However, asthma symptoms such as wheeze appear to be common among cannabis users.

CONCLUSION 7-4 There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and asthma development or asthma exacerbation.

RESEARCH GAPS

The effects of cannabis smoke on respiratory health remain poorly quantified. Further research is needed to better elucidate the influence of exposure levels to cannabis smoke on respiratory outcomes, the chronicity of cannabis smoking, the effects of an underlying predisposition to respiratory disease, and possible interaction effects with tobacco smoke to promote airway inflammation, worsen respiratory symptoms, accelerate lung function decline, or increase exacerbation of COPD and asthma. Previous studies have not been able to adequately separate cannabis smoke effects from tobacco smoke effects, and this has meant that some important questions remain unanswered. It is unknown whether or not:

- Long-term cannabis smoking, above and beyond that of tobacco smoking, leads to a more rapid decline in lung function and to the development of chronic bronchitis or COPD.
- Cannabis smoking increases the risk of allergic disease or asthma.
- Alternative inhaled delivery methods of cannabis result in fewer respiratory symptoms.

To address the research gaps relevant to respiratory disease, the committee suggests the following:

- Design better observational studies with both self-reported and quantitative measures of cannabis smoking and systematic approaches to measure the duration and dose to determine if

long-term exposure to cannabis smoke, above and beyond exposure to tobacco smoke, leads to the development of chronic bronchitis or COPD or to a higher rate of COPD exacerbation.

- Design longitudinal studies to determine if long-term cannabis smoking is associated with the development of allergic disease and risk of asthma.
- Conduct clinical trials of alternative inhaled delivery methods versus cannabis smoking to determine if they reduce respiratory symptoms.

SUMMARY

This chapter summarizes all of the respiratory disease literature that has been published since 1999 and deemed to be good or fair by the committee. Overall, the risks of respiratory complications of cannabis smoking appear to be relatively small and to be far lower than those of tobacco smoking. While heavy cannabis users may be at a higher risk for developing chronic bronchitis and COPD or at an increased risk of exacerbating COPD and asthma, current studies do not provide sufficient evidence for a link. Limitations of reviewed studies are that it is difficult to separate the effects of cannabis smoking from those of tobacco smoking from current available data; that exposures have generally been measured by self-report of cannabis smoking; and that there is a lack of cohort studies of regular or daily cannabis users, of adequate controls for environmental factors, and of generalizability of findings. The committee has formed a number of research conclusions related to these health endpoints (see Box 7-1); however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections.

BOX 7-1
Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between cannabis smoking and:

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:

- Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

* Numbers in parentheses correspond to chapter conclusion numbers

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8

Immunity

Chapter Highlights

- There exists a paucity of data on the effects of cannabis or cannabinoid-based therapeutics on the human immune system.
- There is insufficient data to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.
- There is limited evidence to suggest that regular exposure to cannabis smoke may have anti-inflammatory activity.
- There is insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and adverse effects on immune status in individuals with HIV.

The immune system is composed of many different cells that perform a wide variety of functions in order to provide immunity against pathogens and other foreign bodies. Many assays and methods exist to evaluate specific components of the immune system and to assess changes in immune function and status. Toward this end, there is a sizable literature reporting on investigations into the effects of plant-derived, synthetic, and endogenous cannabinoids on various aspects of immune competence in experimental animals and in cell-based assays. The scientific literature is full of studies that used these animal- and cell-based immunological

approaches to show that cannabinoids modulate (either suppressing or enhancing) the functions of most of the types of immune cells that have been evaluated. By contrast, the investigations into the effects of cannabis or cannabinoid-based therapeutics on immunity in human subjects are quite limited.

The majority of studies investigating the association between cannabis or cannabinoid use and effects on human immunity have assessed one or more immunological parameters in patients infected with human immunodeficiency virus (HIV) or viral hepatitis C (HCV). For example, in the case of HIV patients, who are extensively studied within the context of cannabis exposure, these investigations have evaluated only a small number of immunological endpoints, the most common being the number of certain types of T cells (i.e., $CD4^+$ and $CD8^+$ T cells) in circulation and also the viral load. The limited measurements provide little information about the effect of cannabis use on overall immune status among individuals with HIV. Other studies have evaluated the effects of cannabis on immune endpoints in healthy individuals or on their susceptibility to infectious agents. In healthy individuals, these evaluations have focused primarily on the effects of cannabis use on circulating cytokines concentrations, principally inflammatory cytokines. Again, these examples emphasize the very limited and extremely narrow scope of assessments that have been conducted to examine the effects of cannabis on immune competence in humans to date.

This chapter reviews the current evidence on the association between cannabis use and immune competence in healthy populations and in individuals with infectious disease. Because the immune system plays a primary role in fighting and protecting against disease, the chapter will review evidence on the potential association between cannabis use and indicators of immune functioning as well as the potential association between cannabis use and susceptibility to, and progression of, infectious disease and cancer. Due to the paucity of human studies evaluating the effects of cannabis on the immune system, the committee identified no good- or fair-quality systematic reviews reporting on the health endpoints addressed in this chapter. Consequently, this chapter's conclusions are based on a review of 14 primary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in five formal conclusions.

IMMUNE COMPETENCE

In several of the studies reviewed below, the effects of cannabis use on immune competence were assessed via direct measurement of specific

immune effect or functions in healthy individuals. The primary advantage of evaluating specific immune responses is that the immune system is composed of many different cell types, each of which performs several distinct functions. Assessing specific immune responses provides more information on whether, how, and to what extent an agent such as cannabis affects particular cells in the immune system. Although the perturbations in immune competence discussed in this section are not health effects in the sense used throughout this report, they may alter a person's susceptibility to infection or have broad effects on immune competence, and they are reviewed for that reason.

The challenge with this type of information is that it is difficult to ascertain whether a deficit in a specific immune function, unless extreme, necessarily results in greater susceptibility to infection by a pathogen. Conversely, it is difficult to extrapolate results showing enhanced immune responsiveness due to exposure to an agent and to determine whether that exposure may lead to an increased incidence of hypersensitivity or autoimmune disease. Therefore, the evaluation of immune competence requires a comprehensive assessment of a broad range of different cell types and their functions, which to date has not been conducted in cannabis users.

Is There an Association Between Cannabis Use and Immune Competence in Individuals Without an Infectious Disease?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and immune competence in individuals without an infectious disease.

Primary Literature

Keen and Turner (2015) evaluated the serum levels of two inflammatory cytokines, interleukin-1 alpha (IL-1α) and tumor necrosis factor (TNF), in a total of 168 African American study participants of whom 46 were lifetime cannabis users and 77 did not use any illicit drugs. After adjusting for demographic and physiological variables, study participants who did not use illicit drugs were not significantly more likely to have higher background serum IL-1α levels than lifetime cannabis users (odds ratio [OR], 0.77, 95% confidence interval [CI] = 0.34–1.74). By contrast, study participants who did not use illicit drugs were significantly more likely to have higher serum TNF levels than lifetime cannabis users (OR, 2.73, 95% CI = 1.18–6.31).

In another study, several immune parameters were evaluated in adult Egyptians (Abo-Elnazar et al., 2014). The study included 20 cannabis users and 10 controls with no history of drug abuse. $CD4^+$ peripheral blood T cells from cannabis users showed a statistically significant decrease in proliferative response to mitogenic stimulation (phytohemagglutinin [PHA]) in culture as measured by the methyl thiazolyl tetrazolium (MTT) stimulation index when compared to $CD4^+$ T cells from controls (mean = 1.14 ± 0.28 versus mean = 1.47 ± 0.35, p = 0.001). Supernatants from these cultures were quantified for T cell cytokines; interleukin-10 (IL-10), which is an anti-inflammatory cytokine; and interleukin-17 (IL-17), which is a proinflammatory cytokine. When compared to $CD4^+$ T cells from non-drug-using controls, $CD4^+$ T cells from cannabis users showed an approximately 50 percent decrease in proinflammatory IL-17 (129.05 pg/ml ± 44.24 pg/ml versus 206.30 pg/ml ± 51.05 pg/ml, p <0.001) and a two-fold increase in anti-inflammatory IL-10 (mean = 258.10 pg/ml ± 79.91 pg/ml versus mean = 138.70 pg/ml ± 38.11 pg/ml, p = 0.002). A major limitation of Abo-Elnazar et al. (2014) is the very small number of study participants.

Pacifici et al. (2007) conducted a longitudinal study which included an evaluation of total leukocytes as well as the number of $CD4^+$ T cells, $CD8^+$ T cells, B cells, and natural killer (NK) cells at the beginning of the study and 12 months later in 34 healthy controls who had not used illicit drugs in the previous 12 months and in 23 study participants who were occasional or regular users of cannabis. There was a statistically significant difference between controls and cannabis-using study participants with respect to the number of NK cells at the initiation of the study (mean = 205.1 cells/µl ± 83.4 cells/µl versus 126.1 cells/µl ± 80.0 cells/µl) or when evaluated at 12 months (mean = 196.8 cells/µl ± 79.3 cells/µl versus mean = 101.7 cells/µl ± 48.5 cells/µl). By contrast, differences between controls and cannabis-using study participants in the number of $CD4^+$ T cells, $CD8^+$ T cells, and CD19 B cells were not statistically significant at the initiation of the study or 12 months later. In addition, PHA-induced proliferation, supernatant interleukin-2 (IL-2) (a measure of T cell function), and transforming growth factor beta 1 (TGF-β1) (a proinflammatory cytokine) were assessed at the initiation of the study. Statistically significant differences were observed between controls and cannabis users in terms of PHA-induced proliferation (mean = 96.9% ± 15.6% versus mean = 72.3% ± 32.1%) and the activity units per ml of IL-2 (mean = 10.7 U/ml ± 3.8 U/ml versus mean = 6.3 U/ml ± 4.4 U/ml), whereas the difference between controls and cannabis users in the activity units per ml of TGF-β1was not statistically significant.

Jatoi et al. (2002) conducted a study involving 85 study participants with advanced cancer and weight loss to compare the effect of megestrol acetate (800 mg/day) and oral dronabinol tablets (2.5 mg twice daily),

separately and in combination, on levels of serum interleukin-6 (IL-6), a cytokine associated with anorexia and weight loss. There was no statistically significant change in serum IL-6 levels 1 month after study initiation among study participants receiving dronabinol alone (mean difference = −0.62 pg/ml ± 3.5pg/ml) or in combination with megestrol acetate (mean difference = −0.2 pg/ml ± 3.1 pg/ml).

A longitudinal study followed study participants from birth to 38 years of age in order to investigate potential associations between cannabis use occurring between 18 and 38 years of age and physical health problems at 38 years of age, including systemic inflammation as measured by C-reactive protein levels (Meier et al., 2016). Among 947 study participants, there was no statistically significant association between joint-years of cannabis use and systemic inflammation after controlling for biological sex and tobacco use (β 0.00, 95% CI = −0.07–0.08). After controlling for biological sex, systemic inflammation at 26 years of age, and tobacco use, the association between joint-years of cannabis use and changes in systemic inflammation between 26 and 38 years of age was not statistically significant (β 0.05, 95% CI = −0.03–0.13).

Discussion of Findings

One trend that appeared to be supported by several studies was the observation that regular exposure to cannabis smoke decreased several regulatory factors that are secreted by leukocytes and that are well established in mediating inflammation. Consistent with the premise that cannabinoids may possess anti-inflammatory activity, one study showed an enhanced production of an anti-inflammatory mediator, which could be indicative of a decline in immune competence (Abo-Elnazar et al., 2014). By contrast, anti-inflammatory activity of cannabis, under certain conditions, could be beneficial because inflammation is a key event in the processes of many diseases. For example, chronic inflammation is believed to be central in HIV-associated neurocognitive disorders and anti-inflammatory activity of cannabis could potentially be beneficial in decreasing the progression of neurocognitive decline (Gill and Kolson, 2014). The finding that cannabinoids may possess anti-inflammatory activity is consistent with findings in studies conducted in experimental animal and in cell culture experiments (Klein, 2005).

The limitations of the studies conducted to date are numerous, with the most significant being the absence of a comprehensive evaluation of the effects of cannabis smoke on immune competence. In addition, several of the studies used a small number of study participants with very limited information on the study participants' level of exposure to cannabis. Based on the very limited evaluations of only a few immune parameters,

it is not possible to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.

CONCLUSION 8-1

8-1(a) There is limited evidence of a statistical association between cannabis smoking and a decrease in the production of several inflammatory cytokines in healthy individuals.

8-1(b) There is insufficient evidence to support or refute a statistical association between cannabis smoking and other adverse immune cell responses in healthy individuals.

SUSCEPTIBILITY TO AND PROGRESSION OF INFECTIOUS DISEASE

The primary role of the immune system is to protect against infectious agents (e.g., bacteria, viruses, parasites). The immune system confers this protection by its ability to recognize what is foreign, often termed as "non-self," which it then seeks to destroy using a broad repertoire of different cell types and mechanisms. Significant changes in immune competence can result in serious adverse health effects. For example, inappropriate or exaggerated immune responses can result in autoimmunity or allergy. Conversely, the suppression of immune function can lead to an increased susceptibility to infectious agents, an increased duration of infection, or a reduced ability to recognize and destroy cancer cells. A large body of literature using animal models and cell cultures has described the immunosuppressive properties of cannabinoids. Reduced immune competence due to cannabis smoke or cannabinoid treatment would be especially relevant in cases when immunocompromised HIV patients used the cannabis to stimulate their appetite or cancer patients used it to relieve the nausea associated with cancer chemotherapeutic drugs. Very few studies have investigated the effects of cannabis smoke or cannabinoids on the susceptibility to, or clearance of, infectious agents or on progression of cancer in human subjects. This section discusses findings from the few studies that have evaluated the association between cannabis use and immune status in terms of an individual's susceptibility to infection and the health status of individuals with HIV, HCV, and other infectious diseases.

Is There an Association Between Cannabis Use and Immune Status in Individuals with HIV?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and immune status in individuals with HIV.[1]

Primary Literature

Several studies have been conducted with the specific objective of determining whether cannabis smoking or therapeutic dronabinol produces adverse effects on immune competence in HIV patients. In a prospective randomized controlled trial (RCT), 62 study participants ages 18 years and older who were infected with HIV were randomized to receive cannabis (up to three cigarettes daily), dronabinol (2.5 mg oral tablet three times daily), or an oral placebo over a 21-day period (Bredt et al., 2002). The change in absolute lymphocyte concentration among study participants receiving cannabis was statistically significantly greater than among study participants receiving the placebo (median change = 300 cells/µl versus 0.00 cells/µl, $p = 0.1$). As compared to study participants receiving the placebo, those receiving dronabinol experienced significantly greater changes in %CD8+CD38+HLA-DR+ cells (median change −3.50 versus 0.05, $p = 0.001$) and in %CD8+CD69+ cells (median change −0.30 versus 0.05, $p = 0.04$) during the study period. Bredt et al. (2002) state that these statistically significant changes "do not constitute [a] meaningful pattern of changes in immune phenotype of function" (Bredt et al., 2002, p. 87S).

By contrast, study participants in neither of the cannabinoid study arms experienced statistically significantly greater changes in lymphoproliferative responses to various mitogenic stimuli than did study participants in the placebo arm. No cannabis- or dronabinol-related changes were observed. Likewise, changes in cytokine (i.e., IFNγ, IL-2, TNFα) production among study participants in the cannabinoid study arms, and in NK activity among study participants in the dronabinol arm, were not significantly greater than among study participants receiving the placebo. No cannabis- or dronabinol-associated adverse effects were observed over the 21-day exposure period on the percentage of circulating $CD4^+$ or $CD8^+$ cells or on disease progression, as measured by viral load (Abrams

[1] Chapter 4 discusses Lutge et al. (2013), a systematic review that investigates the medical use of cannabis by patients with HIV/AIDS but does not specifically address the association between cannabis use and immune competence in this population.

et al., 2003). Overall, there were no "clear discernible negative changes" (p. 87S) among study participants who received dronabinol or cannabis as compared to those who received the placebo. Significant limitations of this study were the very short time period of cannabinoid exposure and the small number of study participants included in the study.

A longitudinal study evaluated the effects of recreational cannabis use on $CD4^+$ and $CD8^+$ T cell populations and disease progression in men infected with HIV (3,236 participants, of which 59 percent used cannabis) and men not infected with HIV (481 participants, of which 61 percent used cannabis) (Chao et al., 2008). HIV-negative and HIV-positive study participants were followed for a maximum of 18 and 11 years, respectively. After controlling for health risk behaviors and other potential confounders, any cannabis use and monthly or less frequent cannabis use were both associated with a statistically significant 1 percent decrease in $CD4^+$ cell count among men not infected with HIV, while weekly or more frequent cannabis use was associated with a 5 percent decrease in $CD8^+$ cell count among men infected with HIV. However, Chao et al. (2008, p. 5) state that there were no "clinically meaningful associations, adverse or otherwise, between use of marijuana . . . and T cell counts and percentages in either HIV-uninfected or HIV-infected men." A major shortcoming of this study was the absence of information concerning the frequency and level of exposure to cannabis.

Thames et al. (2016) examined the independent and combined effects of HIV and cannabis smoking on neurocognitive function in 55 HIV positive and 34 HIV negative study participants who reported previously using cannabis for 12 months or more. As part of this study, the percentage of $CD4^+$ T cells was monitored. Differences in the frequency of cannabis use were not associated with statistically significant differences in the nadir count of $CD4^+$ T cells. A modest but statistically significant increase in the percentage of circulating $CD4^+$ T cells ($p = 0.04$) and a statistically significant decrease in viral load ($p = 0.03$) were associated with light (i.e., 2–14 times per week) and moderate to heavy (i.e., 18–90 times per week) cannabis use as compared to nonusers. A shortcoming of this study was the small number of study participants.

Discussion of Findings

Collectively, the studies suggest that cannabis smoke and/or cannabinoids do not adversely affect the immune status of HIV patients. However, each of the four studies possessed major shortcomings in experimental design which could have contributed to the absence of adverse effects being observed in HIV patients who used cannabis or cannabinoids; these shortcomings include study durations that where insufficient to

observe adverse effects in the endpoints being measured, small numbers of study participants, and poorly defined and variable levels of cannabinoid exposure.

CONCLUSION 8-2 There is insufficient evidence to support or refute a statistical association between cannabis or dronabinol use and adverse effects on immune status in individuals with HIV.

Is There an Association Between Cannabis Use and the Immune Status of Individuals Infected with Viral Hepatitis C?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the immune status of individuals infected with HCV.

Primary Literature

HCV is a chronic disorder of the liver which can lead to fibrosis and progress to cirrhosis and ultimately to end-stage liver disease or hepatocellular carcinoma. Liver fibrosis is mediated, in part, through a chronic immune-mediated inflammatory response. A study of liver biopsies from 270 untreated patients with chronic hepatitis C was conducted in which patients were categorized as either nonusers, occasional cannabis users, or daily cannabis users (Hezode et al., 2005). A significantly higher proportion of daily cannabis users (68.5 percent)—as compared to occasional cannabis users (42.5 percent) or nonusers (39.7 percent)—had a fibrosis progression rate faster than the median fibrosis progression rate for the cohort as a whole. There was a statistically significant association between daily cannabis use and faster than median fibrosis progression rate when no cannabis use was the referent (OR, 3.4, 95% CI = 1.5–7.4). After controlling for potential confounders, including alcohol and tobacco use, daily cannabis use was also determined to be an independent predictor of severe fibrosis (OR, 2.3, 95% CI = 1.1–4.8). A subsequent prospective study investigated 690 patients infected with both HIV and HCV and who had no significant liver fibrosis or end-stage liver disease at baseline, of whom 40 percent smoked cannabis daily at study baseline (Brunet et al., 2013). This study found no statistically significant association between daily cannabis use and progression to significant liver fibrosis (hazard ratio, 1.02, 95% CI = 0.93–1.12). Finally, Liu et al. (2014) conducted a study to evaluate potential associations between cannabis use and liver disease progression

and outcomes from treatment for HCV. Among 376 participants for whom liver biopsies and cannabis use information was available, cannabis use as compared to nonuse was not significantly associated with fibrosis stage ($p = 0.66$) or with hepatic inflammation grade ($p = 0.75$). Among 348 participants, cannabis use as compared to nonuse was not significantly associated with steatosis as assessed by biopsies ($p = 0.32$). Compared to nonuse of cannabis, there was no statistically significant association between cannabis use and treatment outcomes as measured by rates of sustained viral response among 359 participants receiving interferon-based HCV antiviral treatment ($p = 0.13$).

Discussion of Findings

Although all three studies were of good quality, their results were mixed. Two studies suggested that cannabis use was not significantly associated with progression of liver disease or with fibrosis stage in HCV patients. Since chronic inflammation is a significant contributing factor to the progression of liver fibrosis, these findings appear to be consistent with the anti-inflammatory activity of cannabinoids observed in the immune competence literature reviewed above. However, a third study found that daily cannabis use was significantly associated with the severe fibrosis and faster progression of fibrosis, thereby complicating any conclusions about the association between liver disease progression and cannabis use. Overall, the available evidence that cannabis use is not associated with the progression of liver fibrosis and hepatic disease in individuals with HCV is stronger than the available evidence that cannabis use is associated with the progression of liver fibrosis and hepatic disease in individuals with HCV.

CONCLUSION 8-3 There is limited evidence of no statistical association between daily cannabis use and the progression of liver fibrosis or hepatic disease in individuals with viral hepatitis C (HCV).

Is There an Association Between Cannabis Use and Susceptibility to Oral Human Papilloma Virus (HPV)?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and susceptibility to oral HPV.

Primary Literature

Risk factors associated with oral HPV infection were investigated in a cross-sectional study involving 128 HIV-negative and 161 HIV-positive study participants (Muller et al., 2015). Cannabis use was identified as a statistically significant risk factor for detection of oral HPV in HIV-negative study participants (OR, 4.0, 95% CI = 1.3–12.4), although this risk was statistically nonsignificant after adjusting for other variables, including tobacco, alcohol, and other drug use (OR, 2.1, 95% CI = 0.6–7.5). By comparison, cannabis use was not a statistically significant risk factor for detection of oral HPV in HIV-positive individuals, whether before (OR, 1.6, 95% CI = 0.7–3.4) or after (OR, 1.3, 95% CI = 0.4–3.9) adjusting for potential confounders. The factors responsible for the differential effects between HIV-negative and HIV-positive individuals are unclear. Likewise, Kahn et al. (2015) conducted a cross-sectional study to evaluate the prevalence of oral HPV infection and to investigate associations between vaccination and oral infection in HIV-infected youth. The study included 272 HIV-infected study participants between the ages of 12 and 24 years, with a mean age of 21.5 years. In univariable analyses, no statistically significant association between lifetime cannabis use, as compared to nonuse, and oral HPV infection was identified (OR, 0.68, 95% CI = 0.36–1.30). A significant limitation of both studies was the inability to determine whether regular cannabis use increased risky behavior that would predispose study participants to oral HPV infection. Likewise, there was no follow-up on whether cannabis altered the course of HPV infection or its downstream consequences.

Discussion of Findings

Kahn et al. (2015) reported no statistically significant association between cannabis use and oral HPV. Muller et al. (2015) reported that, prior to adjusting for potential confounders, cannabis use was significantly associated with oral HPV in HIV-negative individuals, but not in HIV-positive individuals. The plausibility of this finding is questionable in light of the fact that HIV-infected patients have decreased T cell–mediated immunity, which is critical in anti-viral immune responses, including against HPV. Therefore, it would be expected that HIV-infected patients would be at least as, if not significantly more, susceptible to HPV infection as would HIV-negative patients. A major limitation of Kahn et al. (2015) is that it is not possible to determine, based on the study design, whether the reported association between regular cannabis use and increased incidence of oral HPV in HIV-negative individuals is attributable to cannabis-mediated immune suppression or to other causes, such as increased high-risk behavior.

CONCLUSION 8-4 There is insufficient evidence to support or refute a statistical association between regular cannabis use and increased incidence of oral human papilloma virus (HPV).

Is There an Association Between Cannabis Use and *Aspergillus* Infection?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and infection with *Aspergillus*.

Primary Literature

Infection with *Aspergillus* species can be life-threatening in immunocompromised patients, including those with prolonged neutropenia, hematopoietic stem cell transplant, solid organ transplant, inherited or acquired immunodeficiencies, diabetes, corticosteroid use, or diabetes (Cescon et al., 2008; Denning et al., 1991). Cannabis has been demonstrated to harbor *Aspergillus* spores, and case reports suggest that cannabis use may be associated with aspergillosis in immunocompromised patients. For example, a letter published in the *Annals of Internal Medicine* in 1975 described a case of *Aspergillus fumigatus* pneumonitis in a 17-year-old male with chronic granulomatous disease. Heavy growth of *Aspergillus fumigatus* was observed in a culture taken from the patient's cannabis and pipe, and the author states that the "infection may have been acquired through inhalation of smoke from marijuana contaminated with fungi" (Chusid et al., 1975, p. 682). More recent case reports and case series have described aspergillosis in current or former cannabis users with acute myelogenous leukemia (Szyper-Kravitz et al., 2001), chronic myelogenous leukemia post bone marrow transplant (Hamadeh et al., 1988), small-cell lung cancer (Sutton et al., 1986), colorectal cancer (Cescon et al., 2008), renal transplant (Marks et al., 1996; Vethanayagam et al., 2000), chronic obstructive pulmonary disease (Sakkour et al., 2008), diabetes (Remington et al., 2015), and HIV/AIDS (Denning et al., 1991; Johnson et al., 1999). Aspergillosis has also been observed in current or former cannabis users with structural lung damage but who were not immunocompromised (Gargani et al., 2011) Many of the case reports involved smoking cannabis, although one involved a diabetic patient who inhaled vaporized cannabis for treatment of neuropathic pain (Remington et al., 2015). Box 8-1 describes a case series and a case-control study on the association between cannabis use and aspergillosis.

BOX 8-1
Cannabis and Aspergillosis

Denn ng et a . (1991) reported on 13 cases of pu monary asperg os s n pat ents w th AIDS or asymptomat c HIV nfect on. Cannab s use was sted as a "poss b e under y ng factor" n 4 of the 13 cases. However, the actua preva ence of cannab s use n th s group may have been h gher, s nce data on cannab s use was not ava ab e for seven pat ents (Denn ng et a ., 1991, p. 656). Between November 1988 and March 1994, *Aspergillus* spec es were detected n nduced sputum or bronchoa veo ar avage spec mens co ected from 19 HIV pos t ve part c pants n the Pu monary Comp cat on of HIV Infect on Study (Wa ace et a ., 1998). A nested case-contro study of these 19 part c pants found that cannab s use at the t me of entry nto the study was not s gn ficant y assoc ated w th *Aspergillus* nfect on (Wa ace et a ., 1998). By contrast, neutropen a (.e., neutroph count <1,000 ce s per cub c m meter), a CD4 count <30 ce s per cub c m meter, cort costero d use, and *Pneumocystis carinii* pneumon t s were among the factors that were s gn ficant y assoc ated w th *Aspergillus* nfect on.

Discussion of Findings

Sporadic case reports published over the last 40 years suggest that *Aspergillus* infection may be associated with cannabis use. The case-control study of *Aspergillus* infection in HIV positive patients did not find cannabis use to be significantly associated with the presence of the fungus in induced sputum or bronchoalveolar lavage specimens, although the number of study participants was small (Wallace et al., 1998). Despite the limited nature of the literature on aspergillosis and cannabis use, consensus guidelines and scientists suggest that immunocompromised patients avoid cannabis use due to its potential for increasing the risk of *Aspergillus* infection (Remington et al., 2015; Sullivan et al., 2001).

RESEARCH GAP

Research is needed to determine whether chronic cannabis smoke or cannabinoid treatment alters immune competence in healthy or immunocompromised individuals as evidenced by an increased incidence of infectious diseases; an extended duration of time to resolution of infectious diseases; and altered progression of cancer through the modulation of immune competence.

SUMMARY

One challenge associated with determining whether an agent alters immune competence is the diversity of the cellular elements that constitute the immune system and the many functions that these different cell types perform. The committee found a very limited number of studies in which the effects of cannabis use on the human immune system were assessed. Almost without exception, these evaluations were very narrow in scope, assessing only one or a few immunological endpoints and thus providing little information concerning the effects of cannabis use on immune status. Some studies were limited to determining the number of circulating leukocyte populations, such as T cells, with no assessments of cell function.

Although based on limited evidence, an interesting finding was the association between cannabis use in healthy individuals and a decrease in

BOX 8-2
Summary of Chapter Conclusions*

There is limited evidence of a statistical association between cannabis smoking and:

- A decrease n the product on of severa nflammatory cytok nes n hea thy nd v dua s (8-1a)

There is limited evidence of no statistical association between cannabis use and:

- The progress on of ver fibros s or hepat c d sease n nd v dua s w th v ra hepat t s C (HCV) (da y cannab s use) (8-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Other adverse mmune ce responses n hea thy nd v dua s (cannab s smok ng) (8-1b)
- Adverse effects on mmune status n nd v dua s w th human mmunodefi- c ency v rus (HIV) (cannab s or dronab no use) (8-2)
- Increased nc dence of ora human pap oma v rus (HPV) (regu ar cannab s use) (8-4)

* Numbers in parentheses correspond to chapter conclusion numbers

the production of certain inflammatory cytokines. Similar findings have been reported in animal- and cell-based experiments. More studies will need to be conducted to verify the anti-inflammatory activity of cannabis in humans. Presently, there is either insufficient or no data to ascertain whether cannabis use alters other immune responses in healthy individuals. In addition, several studies have evaluated the effects of cannabis on either susceptibility to, or progression of, infectious diseases—namely, HIV, HCV, or the papilloma virus. There is insufficient evidence to determine whether there is an association between regular use of cannabis and increased incidence of papilloma virus or between cannabis or cannabinoid (e.g., dronabinol) use and adverse effects on immune status among individuals with HIV. In addition, there is limited evidence to support the conclusion that cannabis use does not enhance the progression of liver disease in HCV patients. Box 8-2 provides a summary of the findings from this chapter.

It is important to emphasize that many of the studies in which the effects of cannabis on the immune system were evaluated possess significant shortcomings in experimental design, such as small numbers of study participants, a study that was insufficient to determine adverse effects, a narrow scope of immunological assessments, and limited information concerning the levels of cannabis exposure. Each of these limitations precludes drawing conclusions concerning the effects of cannabis on immune competence in humans with any reasonable level of certainty.

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9

Injury and Death

Chapter Highlights

- Cannabis use prior to driving increases the risk of being involved in a motor vehicle accident.
- In states where cannabis use is legal, there is increased risk of unintentional cannabis overdose injuries among children.
- It is unclear whether and how cannabis use is associated with all-cause mortality or with occupational injury.

This chapter discusses the association between cannabis use and all-cause mortality, occupational injury, motor vehicle accidents, and overdose injuries and death. These health endpoints are distinguished not only by their status as significant public health issues but also by the extent to which directed public health actions and policy changes hold the potential for lessening their detrimental impacts on population health. Motor vehicle accidents are a leading cause of death and injury in the United States, and occupational injuries, especially those that permanently limit an individual's capacity to perform tasks at home and in the workplace, impose substantial economic burdens on workers, employers, and communities. If research indicates that cannabis use is positively associated with either occupational injury or motor vehicle accidents, evidence-based policies limiting the use of cannabis while driving or in the workplace could potentially reduce the incidence of cannabis-related

accidents and injury. Similarly, research suggesting that cannabis use is linked to mortality could prompt the development of programs to educate health professionals and the general public on the effects of cannabis use and positively influence cannabis-related mortality rates.

In this chapter, the committee reviews and draws conclusions from the findings of six good- to fair-quality systematic reviews and 18 primary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in five formal conclusions.

ALL-CAUSE MORTALITY

The Institute of Medicine (IOM) report *Marijuana and Medicine: Assessing the Science Base* states that "epidemiological data indicate that in the general population marijuana use is not associated with increased mortality" (IOM, 1999, p. 109). More recently, modeling studies have estimated that a substantial disease burden—and the associated decrements in the quality and length of life—can be attributed to cannabis use (Degenhardt et al., 2013; Imtiaz et al., 2016). By contrast, a recent systematic review informed by epidemiological data did not report a statistically significant association between cannabis use and mortality (Calabria et al., 2010). This section reviews the available literature to assess the evidence and develop conclusions about cannabis-related mortality.

Is There an Association Between Cannabis Use and All-Cause Mortality?

Systematic Reviews

Calabria et al. (2010) conducted a systematic review to determine the association between cannabis use and all-cause mortality in the general population, and they identified two prospective epidemiological cohort studies relevant to this health endpoint.[1] A meta-analysis of these studies was not performed; consequently, the results of the individual studies are presented below.

Sidney et al. (1997) assessed the risk of mortality associated with cannabis use in a cohort of 65,171 individuals ages 15 to 49 years who were enrolled in the Kaiser Permanente Medical Care Program and followed

[1] The review also addressed the association between cannabis use and health endpoints that are often or always fatal, such as motor vehicle accidents, cancer, and suicide. These health endpoints are not reviewed in this section, as they are discussed elsewhere in the report.

for a mean length of 10 years. Compared to men who never smoked or who smoked experimentally (i.e., cannabis use on one to six occasions), those who were current smokers were at a significantly increased risk of all-cause mortality after adjusting for several potential confounders, including cigarette smoking, alcohol use, and demographic and socioeconomic factors (relative risk [RR], 1.33, 95% confidence interval [CI] = 1.11–1.59). Notably, among men who currently smoked cannabis, the relative risk of mortality due to AIDS was significantly elevated (RR, 1.90, 95% CI = 1.33–2.73), while the risk of mortality due to known causes other than AIDS was not significantly elevated (RR, 1.12, 95% CI = 0.89–1.39). After accounting for potential confounders, women who currently smoked cannabis were not at a significantly increased risk of all-cause mortality compared to those who had never smoked or who had smoked experimentally (RR, 1.09, 95% CI = 0.80–1.48). Among men who currently smoked cannabis, the frequency of use had only a small effect on the risk of all-cause mortality: those who smoked at least once per week and those who smoked daily were at, respectively, 46 percent (RR, 1.46, 95% CI = 1.19–1.79) and 43 percent (RR, 1.43, 95% CI = 1.08–1.90) greater relative risk of all-cause mortality than nonusers and experimental users. In women, the frequency of use among current smokers had a larger impact on the risk of mortality: those who smoked at least once a week had a less elevated risk of mortality than those who smoked daily as compared to nonusers and experimental users (RR, 1.23, 95% CI = 0.84–1.80 versus RR, 1.44, 95% CI = 0.80–2.56).

Andreasson and Allebeck (1990) reported that among 45,540 Swedish male military conscripts followed for 15 years, the relative risk of mortality was elevated for those who reported having smoked cannabis more than 50 times by the time of conscription compared to nonsmokers (RR, 2.8, 95% CI = 1.9–4.1). After adjusting for multiple confounders, including smoking tobacco, alcohol use, and other drug use, the relative risk of mortality for heavy cannabis smokers was no longer significantly elevated compared with nonsmokers (RR, 1.2, 95% CI = 0.7–1.9). Similarly, participants who reported having smoked cannabis on fewer than 50 occasions by the time of conscription were not at significantly greater risk than nonsmokers after adjustments (RR, 0.7, 95% CI = 0.4–1.2).

Primary Literature

Muhuri and Gfroerer (2011) assessed the risk of all-cause mortality associated with the use of cannabis and other illegal drugs among 20,983 adults over a 15-year follow-up period. After adjusting for confounders, including alcohol use, cigarette smoking, and demographic factors, individuals who reported using cannabis, but not other substances (i.e.,

cocaine, heroin, hallucinogens, inhalants), at baseline were not at increased risk of all-cause mortality compared with individuals who reported not using cannabis or other substances at baseline (hazard ratio [HR], 1.07, 95% CI = 0.85–1.33). Manrique-Garcia et al. (2016) conducted a follow-up study of a cohort of 50,373 Swedish male military conscripts to characterize the potential association between mortality and heavy cannabis use (i.e., using cannabis more than 50 times by 18 years of age). Among the cohort as a whole, heavy cannabis use was associated with a significantly increased risk of mortality compared with nonuse (HR, 1.4, 95% CI = 1.1–1.8). Notably, heavy cannabis use as compared with nonuse did not appreciably affect the risk of mortality among individuals with psychotic disorders—for whom the risk of mortality was particularly elevated (HR, 3.8, 95% CI = 2.6–6.2 versus HR, 3.7, 95% CI = 3.1–4.4).

Discussion of Findings

Sidney et al. (1997) found a statistically significant association between cannabis use and increased risk of all-cause mortality among men diagnosed with AIDS, but not among men without this diagnosis or among women. The authors suggest that the relationship between cannabis use and all-cause mortality among male AIDS patients was not causal; instead, it "most likely represented uncontrolled confounding by male homosexual behavior" (Sidney at al., 1997, p. 589). Limitations in Sidney et al. (1997) include the use of self-report without biological validation to assess patterns of cannabis use; the lack of post-baseline assessments of cannabis use, by which changes over time in the frequency of use could be documented; a lack of data on other substance use, creating the possibility for residual confounding; and, the inability to follow participants into later age, where potential long-term health effects of cannabis use may have emerged.

After accounting for potential confounders, Andreasson and Allebeck (1990) found no statistically significant association between cannabis use and mortality. Furthermore, although a high proportion of deaths among participants who reported smoking cannabis on 50 or more occasions by the time of conscription were due to suicide or uncertain suicide, use of narcotics was also common in these incidents, leading the authors to suggest that a "significant share of the mortality associated with cannabis abuse in this study is attributable to intravenous drug abuse" (Andreasson and Allebeck, 1990, p. 14). Limitations of the study include the use of non-anonymous self-report to collect data on patterns of cannabis use, and the lack of any post-baseline assessments of cannabis use.

Findings from Muhuri and Gfroerer (2011) are based on data from the 1991 National Health Interview Survey's Drug and Alcohol Use supple-

mental questionnaire, and they indicate a lower prevalence of cannabis use than that seen in the 1991 National Household Survey on Drug Abuse (NHSDA) (45.2 percent versus 52.7 percent). If this discrepancy in the prevalence of cannabis use reported by two national surveys conducted in the same year is the result of underreporting by participants who died during the follow-up period, the mortality risk associated with cannabis use could have been underestimated. Other limitations include the use of self-report to collect data on patterns of cannabis use and the lack of post-baseline assessments to detect changes in cannabis use. Strengths of the study include a base population from a national household sample and an analysis that excluded users of other important illicit drug categories—heroin, cocaine, hallucinogens, and inhalants.

Findings from Manrique-Garcia et al. (2016) have several limitations. Risk estimates are based on cannabis use as of the time of conscription rather than lifetime cannabis exposure and therefore do not account for cannabis use during the ~40 year follow-up period. Similarly, data on potential confounders after the time of conscription is unavailable, so the extent to which they affected study participants and potentially impacted all-cause mortality risk is unknown. Finally, since data on cannabis use was collected by non-anonymous self-report without biological validation, cannabis use may have been underreported.

There is an overall dearth of cohort studies empirically assessing general population cannabis use and all-cause mortality. Although the available evidence suggests that cannabis use is not associated with an increased risk of all-cause mortality, the limited nature of that evidence makes it impossible to have confidence in these findings. These conclusions are not informed by the results of existing large-scale modeling studies that synthesized data from a variety of sources to estimate the burden of disease attributable to cannabis use (Degenhardt et al., 2013; Imtiaz et al., 2016). Although these studies were methodologically rigorous, their direct applicability to actual cannabis-related mortality rates in the United States is uncertain. Consequently, the committee chose not to include them in this review. Also excluded from review were studies of mortality among persons with known cannabis addiction or dependence, those who have been under medical treatment for these disorders, or those who were identified through a country's criminal justice system, due to presence in these populations of important and often inadequately controlled confounders such as concurrent mental illness and poly-substance abuse.

CONCLUSION 9-1 There is insufficient evidence to support or refute a statistical association between self-reported cannabis use and all-cause mortality.

OCCUPATIONAL INJURY

The Bureau of Labor Statistics reported that 4,821 fatal occupational injuries occurred in the United States in 2014, or about 3.4 fatal injuries for every 100,000 full-time equivalent workers (BLS, 2016). Private industry and state and local government employers reported another 3,486,400 nonfatal occupational injuries in the same year (BLS, 2015). The economic impact of these injuries is considerable. Leigh (2011) estimated that the average medical costs per nonfatal and fatal injury in 2007 were $5,369 and $55,595, respectively. Nationally, the medical and indirect costs of occupational injuries (fatal and nonfatal) totaled $191.83 billion in 2007 (Leigh, 2011). Marucci-Wellman et al. (2015) estimated that in the United States the direct workers' compensation cost of the most severe, nonfatal occupational injuries was over $51 billion in 2010.[2]

Concurrent with this economic and public health burden is the increasing prevalence of cannabis use among employed U.S. adults ages 18 and older (Azofeifa et al., 2016). In 2015, 14.4 percent of U.S. adults ages 18 and older with full-time employment reported using cannabis during the previous year (CBHSQ, 2016, pp. 246–247). Among those employed part-time, the proportion was higher, at 17.8 percent (CBHSQ, 2016, pp. 246–247).[3]

Determining whether an association exists between cannabis use and occupational injury is the subject of ongoing research. According to the 1994 National Research Council and IOM report *Under the Influence?: Drugs and the American Workforce*, evidence on the relationship between employee drug use and accidents in the workplace is mixed (NRC and IOM, 1994, p. 144). This section updates these findings with a review of the current evidence on cannabis use and occupational injury.

Is There an Association Between Cannabis Use and Occupational Injury?

Systematic Review

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and occupational injury.

[2] Cost estimate is in 2010 dollars.

[3] These percentages correspond to 17,042,000 and 5,770,000 U.S. adults ages 18 or older with full-time and part-time employment, respectively.

Primary Literature

The committee identified six primary literature articles addressing the association between cannabis use and occupational injury. Case series of occupational fatalities, with or without forensic investigation, were not considered if there was no consideration of risk compared to non-cannabis-exposed groups.

To investigate the potential association between cannabis use and work-related and non-work-related injuries and accidents, Wadsworth et al. (2006) sent questionnaires on drug use, history of accidents and injuries, and problems with memory or attention to 30,000 residents of two communities in Wales. Based on data from 7,979 completed questionnaires, there was no statistically significant association between cannabis use in the previous year and the risk of minor occupational injuries (i.e., work-related injuries not requiring medical attention) (odds ratio [OR], 1.17, 95% CI = 0.74–1.86), work-related accidents at work requiring medical attention (OR, 0.91, 95% CI = 0.43–1.89), or work-related traffic accidents (OR, 3.01, 95% CI = 0.89–10.17) as compared to no illicit drug use and after adjusting for potentially confounding risk factors (e.g., mental and physical health problems, history of risk-taking behavior, limited work experience).

Wadsworth et al. (2006) also stratified the study population into groups with low and high levels of potential risk factors for work-related accidents and injuries, and they determined the association between cannabis use and the risk for occupational injury for each. Compared to participants who did not use illicit drugs in the previous year and who had few other risk factors, those who used cannabis in the previous year had a significantly elevated risk of suffering minor occupational injuries in the past year if they also had several other risk factors (OR, 8.49, 95% CI = 5.37–13.42), but not if they had few other risk factors (OR, 1.10, 95% CI = 0.47–2.57). The risk of suffering a work-related accident requiring medical attention in the previous year was also significantly elevated for participants who used cannabis in the previous year and had several other risk factors (OR, 3.85, 95% CI = 1.89–7.82), but not for participants who used cannabis in the previous year and had few other risk factors (OR, 0.92, 95% CI = 0.22–3.92) when compared to those who reported no illicit drug use in the previous year and who had few other risk factors. When individuals who used no illicit drugs in the previous year and who had few other risk factors were the referent, the risk of work-related traffic accidents in the previous year was significantly increased for individuals who used cannabis in the previous year, whether or not they had high levels (OR, 6.06, 95% CI = 1.37–26.77) or low levels (OR, 3.24, 95% CI = 1.19–8.79) of other risk factors.

Hoffmann and Larison (1999) used data on 9,097 full- and part-time employees ages 18 and older who participated in the 1994 NHSDA to

evaluate the potential association between cannabis use and the risk of work-related accidents (i.e., accidents that occur at work and that result in damage to property or equipment, injury to oneself, and/or injury to others). They found no statistically significant association between any category of former cannabis use (i.e., used 3 or more years ago, used 1–3 years ago) or any category of current use (i.e., used 1–2 days in past year, used 3–51 days in the past year, used at least weekly in past year) and the risk of work-related accidents as compared to never using cannabis.[4]

Shipp et al. (2005) conducted a cross-sectional study to assess the association between self-reported nonfatal occupational injuries and the self-reported use of substances among 3,265 students attending high school in Texas who indicated that they currently (or had previously) worked for pay. Compared to currently employed students who did not smoke cannabis, those who reported using cannabis on one to nine occasions in the previous 30 days reported a significantly increased risk of occupational injury (OR, 1.37, 95% CI = 1.06–1.77) after adjusting for potential confounders, including year in high school, biological sex, and ethnicity. Heavier cannabis use was associated with higher risk: students who reported using cannabis more than 40 times in the past 30 days were more than twice as likely to have suffered a nonfatal occupational injury as those who did not use cannabis (OR, 2.47, 95% CI = 1.64–3.71) during this period. Adjusting for intensity of work (hours of work per week) decreased the strength of the association between cannabis use and occupational injury; nevertheless, that association remained statistically significant for students who had used cannabis one or more times over the course of their lifetimes (1 to 9 times: OR, 1.45, 95% CI = 1.10–1.90; 10 to 39 times: OR, 1.46, 95% CI = 1.01–2.12; 40+ times: OR, 1.87, 95% CI = 1.38–5.34) or 40 or more times in the previous 30 days (OR, 2.23, 95% CI = 1.34–3.71) as compared to students who did not used cannabis during these periods.

To investigate the association between cannabis use and occupational injury, urine samples collected from individuals working in the United States who had experienced an occupational injury were tested for the presence of cannabis metabolites and were compared to samples collected from individuals selected for a random employee drug test (Price, 2014). To control for the potential confounding effect of other substances, individuals with samples containing amphetamines, phencyclidine, or cocaine or opiate metabolites were removed from the analysis. Among the

[4] ORs for these variables ranged from 1.51 for "used 1–2 days in past year" to 0.98 for "used 3–51 days in past year," where the referent was never use of cannabis. Hoffmann and Larison (1999) did not provide confidence intervals for these ORs, though they indicated in the text that none achieved statistical significance at the $p < 0.05$ level.

remaining 961 cases and 2,834 controls, individuals whose urine samples contained detectable levels of cannabis metabolites were not significantly more likely to have suffered an occupational injury than those whose samples did not (OR, 0.814, 95% CI = 0.625–1.060).

Macdonald et al. (2010) conducted a literature review to answer several research questions related to workplace drug testing for cannabis, including whether employees who report using cannabis or who test positive for cannabis are at an increased risk for occupational injuries. Findings from the reviewed studies were mixed, with not all studies showing a statistically significant association between cannabis use and occupational injury. The authors also sought to determine whether chronic cannabis users have cognitive deficits that place them at an increased risk for occupational injuries, and they reported that although some studies suggest an association between cannabis use and reduced cognitive functioning, the impact of any such deficits on the risk of occupational injury has not been determined.

Dong et al. (2015) evaluated longitudinal data on 12,686 participants in the National Longitudinal Survey of Youth in order to identify factors associated with work-related incidents resulting in injury or illness. Among participants ages 14 to 22 years at study baseline and who reported working in construction between 1988 and 2000, there was no statistically significant association between either lifetime cannabis use on 1–10 occasions (OR, 1.04, 95% CI = 0.94–1.15) or lifetime cannabis use on 11 or more occasions (OR, 1.10, 95% CI = 0.99–1.21) and the incidence of occupational injury or illness when never use of cannabis was the referent.

In addition to the articles reviewed above, the committee identified several articles that—while relevant—were published prior to 1999 (Kaestner and Grossman, 1995, 1998; Zwerling et al., 1990) or that considered research questions closely related—but not identical—to the one addressed here (Fransen et al., 2006). Although these articles did not directly inform the committee's conclusions, they aided the committee in orienting themselves to the broader literature on risk factors for occupational injury.

Discussion of Findings

Although Wadsworth et al. (2006, p. 11) concluded that their findings "suggest a detrimental impact of cannabis use on safety that is apparent both in and out of the workplace," they also list several limitations of the study and recommend caution in interpreting its results. Data on cannabis use was derived from self-report and did not measure duration or frequency of cannabis use nor the timing of cannabis use in relation to accidents or injuries. Furthermore, the study may not have completely

controlled for the effect of potential confounders, which may work independently of, or interactively with, cannabis use to modify the risk of occupational injuries or accidents. Finally, the risk for occupational injury posed by cannabis use may be attenuated by processes of self-selection in which cannabis users choose on average to work in lower-risk occupations and nonusers choose to work in higher-risk occupations.

Findings from Hoffmann and Larison (1999) also have several limitations. First, the study did not distinguish between work-related accidents resulting in damage to property and those resulting in injury. Second, the study did not determine whether cannabis use took place while at work; consequently, this type of cannabis use could pose a risk for occupational injury, even if current or former cannabis use in general does not. Third, it is not possible to determine from the NHSDA data whether cannabis use occurred proximate to the injury or whether it preceded or followed an occupational accident.

Shipp et al. (2005) note that the scarcity of research on the association between substance abuse and occupational injuries in adolescent populations prevents the comparison of their results with those from other studies. Because the students who were absent from school on the day of the survey may have had a higher or lower risk of injury compared to students who completed the survey, the potential for selection bias exists. Other limitations of the study include the inability to determine whether cannabis use occurred during work hours or at another time, whether cannabis use preceded or followed the injury, or how closely in time the two events occurred.

In Price (2014), urine samples were collected from men and women of different ages living in different states and employed in a variety of industries with unequal levels of safety sensitivity. The analysis did not control for these variables or determine whether they affect the risk of occupational injury. Furthermore, the study results could not be used to distinguish between recent and remote cannabis use or to determine the chronicity of cannabis use or the extent of an individual's tolerance for cannabis.

Results from Dong et al. (2015) were limited to those participants who reported working in construction and do not address the potential association between cannabis use and the risk of occupational injury in other industries. Participants who stated they had experienced an occupational injury during a specific time period were not asked how many such injuries occurred. As a result, the study may have underestimated the true number and risk of occupational injuries. Finally, the reference period for survey questions were long and changed over the course of the study, creating the possibility for recall bias.

In addition to these limitations, the studies were extremely diverse

in terms of the characteristics of study participants and their occupations, the specificity and scope of data on cannabis use and occupational injuries, and the extent to which the authors effectively controlled or accounted for potential confounders or effect modifiers. In light of the diversity among and limitations of these studies, it was not possible to determine whether general, nonmedical cannabis use is associated with a clearly increased risk of occupational accidents and injuries across a broad range of occupational and industrial settings in the absence of other important risk factors.

CONCLUSION 9-2 There is insufficient evidence to support or refute a statistical association between general, nonmedical cannabis use and occupational accidents or injuries.

MOTOR VEHICLE CRASHES

In 2011, motor vehicle crashes (MVCs) were the leading cause of death among U.S. adolescents and adults ages 16 to 25 years (NHTSA, 2015). Among all age groups, MVCs occurring in 2014 resulted in more than 32,000 fatalities and more than 2 million nonfatal injuries in the United States (CDC, 2016a; NHTSA, 2016).[5] Nationally, the combined medical and work loss costs associated with these fatal and nonfatal injuries is substantial at $44 and $51.3 billion, respectively (Bergen et al., 2014; CDC, 2015).[6]

In 2014, 3.2 percent of individuals ages 16 to 25 years reported driving while intoxicated by cannabis (Azofeifa et al., 2015), and the prevalence of THC metabolites detected in the blood or oral fluids of weekend nighttime drivers participating in the National Roadside Survey rose from 8.6 percent in 2007 to 12.6 percent in 2013–2014 (Berning et al., 2015). Given the public health burden of MVC-related morbidity and mortality and the

[5] NHTSA defines a fatal crash as "a police-reported crash involving a motor vehicle in transport on a trafficway in which at least one person dies within 30 days of the crash." Total includes drivers and passengers of motor vehicles, motorcyclists, pedestrians, and cyclists (NHTSA, 2016). Data on nonfatal injuries obtained from the Centers for Disease Control and Prevention's (CDC's) Web-based Injury Statistics Query and Reporting System (WISQARS). Total includes all unintentional injuries that occurred on a public road or highway and were traffic related and that resulted in an emergency department visit (CDC, 2016a).

[6] Total lifetime medical and work loss costs associated with fatal injuries consequent to MVC, based on MVCs occurring in 2013, was $44 billion (CDC, 2015). Total lifetime medical ($18.4 billion) and work loss ($32.9 billion) costs associated with nonfatal injuries consequent to MVC, based on MVCs occurring in 2012, was $51 billion (Bergen et al., 2014). Work loss costs are defined as "estimates of how much a person who died in a motor vehicle crash would have earned over the course of their life, had they not died," and include salary, estimated benefits, and value of household work (CDC, 2015).

presence of cannabis use and intoxication while driving, there is a need for research to understand the effects of cannabis use on the incidence and severity of motor vehicle crashes and the safety and performance of drivers.

Is There an Association Between Cannabis Use and Motor Vehicle Crashes?

Systematic Reviews

The committee identified a total of six systematic reviews of fair or good quality that summarized the association between driving under the influence of cannabis (DUIC) and MVCs (Asbridge et al., 2012; Calabria et al., 2010; Elvik, 2013; Hartman and Huestis, 2013; Li et al., 2012; Rogeberg and Elvik, 2016). Rogeberg and Elvik (2016) was both the most comprehensive and most recently published systematic review. This review pooled studies reviewed in three earlier meta-analyses (Asbridge et al., 2012; Elvik, 2013; Li et al., 2012) and also performed a structured search of online databases. Calabria et al. (2010) evaluated the association between DUIC and fatal MVCs only, but, with the exception of Bedard et al. (2007), all of the studies in this earlier review were also included in Rogeberg and Elvik (2016). Bedard et al. (2007) was excluded by Rogeberg and Elvik (2016) because it was an analysis of cross-sectional data collected by the U.S. Fatal Accident Reporting System registry.

The meta-analysis by Rogeberg and Elvik (2016) summarized evidence from 21 case-control or culpability studies in 13 countries with a combined sample count of 239,739 participants. There were a total of 28 estimates available from these 21 observational studies. The authors of this systematic review limited their analysis to evidence from either case-control studies or culpability studies and did not include evidence from cross-sectional or cohort studies. The primary criterion for inclusion in the review was the quality of information that indicated cannabis use (i.e., laboratory analyses of blood samples, saliva samples, and urine samples; prescriptions; or self-report) and whether cannabis had been used while driving or enough time prior to driving for effects to still persist. The authors included a wide range of recent studies, including non-peer-reviewed data published by Compton and Berning (2015). Rogeberg and Elvik (2016) argued that culpability studies need to be adjusted for baseline culpability rates because the odds of culpable MVCs associated with DUIC are de facto higher than the overall increase in crash risk. Another important strength of this review is the careful adjustment for potential confounders, including alcohol, in the analysis.

Overall, the meta-analysis by Rogeberg and Elvik (2016) found that

DUIC, as indicated by self-reported cannabis use or the presence of THC metabolite in blood, saliva, or urine, was associated with 20 to 30 percent higher odds of an MVC. The authors described the magnitude of this association as low to moderate in range, and the committee agrees with that assessment. Specifically, the estimated ORs were 1.36 (95% CI = 1.15–1.61) for an analysis that used a random-effects approach and 1.22 (95% CI = 1.10–1.36) for a meta-regression analysis using a precision effect estimate with standard errors (PEESE) technique. Subgroup analyses that accounted for alcohol intoxication found that the magnitude of these ORs weakened to 1.11 (95% CI = 1.04–1.18) when using random-effects and to 1.18 (95% CI = 1.07–1.30) when using PEESE; by contrast, an analysis that did not account for alcohol intoxication found that the ORs were 1.79 (95% CI = 1.28–2.51) and 1.69 (95% CI = 1.25–2.28), respectively.

Primary Literature

The committee did not identify any relevant, good-quality primary literature that reported on the association between cannabis use and motor vehicle crashes and were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question. Of the three identified papers with publication dates during or after 2015 that were not included in Rogeberg and Elvik (2016), none contributed new data on the association between DUIC and MVC risk (Allen et al., 2016; Lemos et al., 2015; Meibodi et al., 2015).

Discussion of Findings

Two important methodological limitations of Rogeberg and Elvik (2016) were noted by other researchers (Gjerde and Morland, 2016). First, DUIC may have not just referred to acute intoxication. Indeed, many of the studies considered in this review scored case and control counts as positive using criteria that would also be satisfied by drivers with recent or regular cannabis use but who were neither intoxicated nor impaired while driving (Gjerde and Morland, 2016). Moreover, the association between THC levels in blood and either acute intoxication or driving impairment remains a subject of controversy, and it could represent an important limitation in the interpretation of findings in culpability studies based on blood THC levels (Desrosiers et al., 2014; Khiabani et al., 2006; Logan et al., 2016; Menetrey et al., 2005; Papafotiou et al., 2005). Second, 3 of the 21 studies used different methods to assess cases and controls, which may lead to a non-differential misclassification of exposure. A missing component in this review is a better determination of the dose

at which driving becomes sufficiently unsafe as to increase MVC risk. Finally, Rogeberg and Elvik (2016) did not provide evidence from cohort studies to address DUIC in MVC.

Simulator studies were also not included in Rogeberg and Elvik (2016). Some laboratory and simulator studies that have examined the effects of acute cannabis intoxication on driving performance have found that the psychomotor skills necessary for safe driving become increasingly impaired at higher doses of cannabis (Sewell et al., 2009). While these experiments may have high internal validity regarding dose-related effects on psychomotor performance, they do not necessarily reflect the complex nature of driving ability and MVC risk attributed to DUIC in a real-world scenario. Epidemiological studies of MVC in populations may help to address these limitations and are the only reasonable and ethical alternative to controlled experiments outside the laboratory. However, cannabis smokers have demographic characteristics that are similar to those of other groups with a high crash risk, including youth, males, and those with a high prevalence of drugged and drunk driving (Bergeron and Paquette, 2014; Richer and Bergeron, 2009). In particular, confounding or effect modification with alcohol is an important driver-related factor that needs to be better taken into account. The bulk of the evidence available describing the association between DUIC and MVCs comes from case-control studies that evaluate the odds of a MVC by DUIC status and from culpability studies which evaluate the odds of culpability in drivers involved in collisions by DUIC status.

CONCLUSION 9-3 There is substantial evidence of a statistical association between cannabis use and increased risk of motor vehicle crashes.

OVERDOSE INJURIES AND DEATH

According to the American Association of Poison Control Centers (AAPCC), 2,047 calls to position control centers in the United States made in 2014 were in response to single-substance exposures to cannabis, up from 1,548 such exposures in 2013 (Mowry et al., 2014, 2015). Of these exposures, 37 were classified as having major effects, and death was the outcome in 1 (Mowry et al., 2015).[7] However, these data do not account for overdose injuries or deaths that did not prompt calls to poison con-

[7] Major effects are defined as those that are "life-threatening or [that] resulted in significant residual disability or disfigurement" (Mowry et al., 2015, p. 1125). Exposures classified as resulting in death are those where "the patient died as a result of the exposure or as a direct complication of the exposure" (Mowry et al., 2015, p. 1125).

trol centers. Data from the Wide-ranging Online Data for Epidemiologic Research (WONDER) database of the Centers for Disease Control and Prevention indicate that in 2014 there were 16,822 deaths in the United States due to accidental poisoning by and exposure to narcotics and psychodysleptics—a broad category that includes cannabis as well as cocaine, heroin, codeine, morphine, and several other narcotics (CDC, 2016b; WHO, 2016). Due, in part, to the limitations of current surveillance tools and medical record coding systems, there is a limited amount of more comprehensive and precise data on the association between cannabis use and overdose injury or death.

Meanwhile, the increasing availability, diversity, and potency of cannabis products create the potential for an increased risk of adverse health effects related to cannabis use, including overdose injury and death. Accidental ingestion of cannabis by young children can result in respiratory failure and coma, as noted by several case reports (Amirav et al., 2011; Appelboam and Oades, 2006; Carstairs et al., 2011), and the consumption of cannabis edibles has been identified as a contributing factor in the accidental death of at least one adolescent (Hancock-Allen et al., 2015).

Thus, the emerging cannabis products market creates the potential for an increased risk of cannabis-related overdose injury or death, while limitations in the current clinical and public health surveillance system hinder efforts to detect, characterize, and respond to this population health issue. This section reviews the available evidence on the association between cannabis use and overdose injury and death and discusses possible actions to improve the state of research on this health endpoint.

Is There an Association Between Cannabis Use and Overdose Injuries or Death?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and overdose injuries or death.

Primary Literature

The committee identified a number of studies that directly or indirectly reported on the association between acute cannabis intoxication and overdose death in either adults or children. An analysis of the National Poison Data Systems database involving more than 2 million human exposure cases in 2012 did not list cannabis among the top causes of death related to pharmaceutical products (Dart et al., 2015). According

to AAPCC annual reports, among all calls to U.S. poison centers involving single-substance exposures to cannabis, death was the outcome in two cases in 2012, no cases in 2013, and one case in 2014 (Mowry et al., 2013, 2014, 2015), although the reports do not indicate whether cannabis exposure was a contributing factor in these outcomes. Cannabis was not found to be the main cause of death in any of the fatal intoxications among drug addicts submitted for medico-legal autopsy and toxicological analysis in Denmark, Finland, Iceland, Norway, or Sweden in either 2007 or 2012 (Simonsen et al., 2011, 2015). Nonetheless, tetrahydrocannabinol was commonly identified (21 percent to 38 percent of cases) in the blood samples of these fatal intoxications.

Case reports on cannabis-related deaths are also uncommon. In Colorado, cannabis intoxication was determined to be a chief contributing factor in the death by trauma of a teenager who jumped from a fourth-floor balcony after ingesting a cookie containing 65 mg of THC (Hancock-Allen et al., 2015). Postmortem analyses revealed no evidence of poly-substance abuse and a delta-9 carboxy-THC whole blood concentration of 49 ng/ml—almost nine times the legal limit for driving in Colorado. Colorado law states that a single-serving edible cannabis product should contain no more than 10 mg of THC; however, currently available edible cannabis products such as cookies and brownies, which are otherwise generally understood as single-serving products, may contain as much as 100 mg (or 10 servings) of THC.[8] In a study on unintentional pediatric cannabis exposure, Wang et al. (2016) described a case where hospital staff members were unable to resuscitate an unresponsive 11-month-old child who presented with tachycardia and metabolic acidosis and who tested positive for THC in a urine drug screen. The authors noted that any relationship between cannabis exposure and the patient's symptoms or outcome was unclear. Although presented here for discussion, these case reports did not inform the committee's conclusions on the association between cannabis use and overdose death.

By comparison with the minimal literature on cannabis-related overdose death in adults or children, several studies reported on potentially serious symptoms associated with cannabis exposure in pediatric populations. Le Garrec et al. (2014) reported that, over a 3.5-year period, seven children ages 11 to 33 months were admitted to a pediatric intensive care unit in Paris with accidental cannabis poisoning. All of the children had central nervous system symptoms, including drowsiness and coma, and three were intubated and placed on mechanical ventilation for less than 24 hours. Between 2010 and 2013, an Arizona poison control center received

[8] Colorado Code of Regulations. Department of Revenue. Marijuana Enforcement Division. Retail Marijuana Rules. 1 CCR 212-2 R604 (C5) (2).

49 calls related to unintentional medical marijuana ingestions among children ages 7 years and younger (Lovecchio and Heise, 2015). Among the 39 records with complete information, the most commonly reported symptoms were lethargy (48 percent of cases), an inability to walk (53 percent), coma (10 percent), and vomiting (21 percent). These and other symptoms, including respiratory depression and aspiration pneumonia, underscore the importance of observation in children suspected or known to have unintentionally ingested cannabis. Although presented here for discussion, these case series were published as letters in scientific journals and therefore did not inform the committee's conclusions on the association between cannabis use and overdose injuries.

These findings are supported by retrospective reviews and cohort studies. Wang et al. (2013) retrospectively reviewed cases of unintentional cannabis ingestions among children ages 11 and younger who required medical attention at a children's hospital in Colorado between 2005 and 2011. Out of 1,378 unintentional ingestions, only 14 were cannabis related, of which 13 were observed in the emergency room or admitted to the hospital. Symptoms included lethargy, ataxia, dizziness, and respiratory insufficiency. The proportion of unintentional ingestions that were cannabis related increased from 0 percent in 2005–2009 to 2.4 percent in 2009–2013, a statistically significant increase coinciding with the October 2009 decision by the U.S. Department of Justice to no longer prosecute users and suppliers of cannabis who act in accordance with state laws. In a subsequent study, Wang et al. (2016) reported the prevalence of unintentional pediatric cannabis exposures occurring between 2009 and 2015 at a children's hospital and a poison center in Colorado. The average number of cannabis-related calls per 1,000 calls to the poison center increased significantly from 0.9 in 2012–2013 to 2.3 in 2014–2015, periods corresponding to the 2 years before and after legalization of recreational cannabis in Colorado. Between these same periods, the average number of cannabis-related emergency department visits per 1,000 visits also increased, though nonsignificantly, from 4.3 to 6.4. Symptoms reported in the 163 calls received by the poison center included drowsiness and/or lethargy (49 percent of cases), ataxia and/or dizziness (12 percent), and agitation (8 percent). Out of 81 cases received by the children's hospital, 40 percent were observed in the emergency department, 22 were admitted to an inpatient ward or the intensive care unit, and 2 required respiratory support. Onders et al. (2016) reviewed data from the National Poison Data System and found that between 2000 and 2013, U.S. poison centers received 1,969 calls related to cannabis exposure among children younger than 6 years old. Most exposures were unintentional (92.2 percent) and occurred as a result of ingesting cannabis or a cannabis product (75.0 percent). Drowsiness and/or lethargy accounted for nearly half of reported

clinical symptoms (45.5 percent), while more serious effects, including coma (0.9 percent), cardiovascular symptoms (4.1 percent), and respiratory depression (0.7 percent), occurred less frequently. The annual rate of exposures increased over time, from a national average of 4.21 per million children in 2006 to 10.42 per million children in 2013, corresponding to a statistically significant increase of 147.5 percent. During the same period, the increase in the annual rate of exposures among states that had legalized medical cannabis prior to 2000 was significant, at 609.6 percent.

Collectively, these findings indicate that state-based legalization of cannabis is associated with a subsequent increase in pediatric cannabis exposures in those states. A similar trend emerges when comparing exposure rates among states where cannabis is legal to exposure rates in states where it is not. Wang et al. (2014) reported that between 2005 and 2011 the rate of calls to poison centers for unintentional pediatric cannabis exposures did not increase in states where cannabis remained illegal as of 2012; increased by 11.5 percent (95% CI = −0.4–24.7) in states where legislation to legalize cannabis was passed between 2005 and 2011; and increased by 30.3 percent (95% CI = 22.5–38.5) in states where cannabis was legalized before 2005. Among children unintentionally exposed to cannabis, those living in states where cannabis was legalized before 2005 were more likely to be evaluated in a health care facility (OR, 1.9, 95% CI = 1.5–2.6), to experience major or moderate effects (OR, 2.1, 95% CI = 1.4–3.1), and to be admitted to critical care units (OR, 3.4, 95% CI = 1.8–6.5) as compared to those living in states where cannabis remained illegal as of 2012. Accounting for 78 percent of all incidents, ingestion was the most common route of unintentional pediatric exposure. Onders et al. (2016) reported that between 2000 and 2013 the annual rate of poison center calls related to cannabis exposures among children younger than 6 was 2.82 times higher in states that had legalized medical cannabis prior to 2000 than in states where medical cannabis remained illegal as of 2013. Another study found that the mean number of calls to poison control centers for unintentional pediatric cannabis exposures increased by 34 percent per year between 2009 and 2015—a significant increase that was also significantly greater than the 19 percent annual increase in cannabis-related calls received by poison control centers throughout the rest of the United States during that same period (Wang et al., 2016). Informed, in part, by these and other findings, a special committee of the Colorado Department of Public Health and Environment found moderate evidence that more unintentional pediatric cannabis exposures have occurred in states with increased legal access to cannabis and that the exposures can lead to significant clinical effects requiring medical attention (CDPHE, 2015).

Discussion of Findings

The committee identified few studies that report on the association between cannabis use and overdose death. Cannabis was not identified as a main cause in the intoxication deaths of drug addicts in five Nordic countries or a top cause of U.S. deaths related to pharmaceutical products. However, studies on the risks to Nordic populations posed by cannabis products available in those countries may not reflect the risks to U.S. populations posed by domestically available cannabis products, and cannabis might still be associated with overdose deaths without also being a top cause among pharmaceutical-related exposure deaths. Data from the National Poison Data System indicate that death was the outcome in a small number of single-substance exposures to cannabis; however, lacking further information, it is not possible to determine whether and to what extent cannabis contributed to these deaths. Case reports implicate acute cannabis intoxication in one accidental death and suggest that cannabis use may pose a risk for sudden cardiac death. However, these individual case reports cannot be used to infer a general association between cannabis use and overdose deaths. Overall, the committee identified no study in which cannabis was determined to be the direct cause of overdose death.

Several studies report that unintentional pediatric cannabis exposure is associated with potentially serious symptoms, including respiratory depression or failure, tachycardia and other cardiovascular symptoms, and temporary coma. Similar symptoms were not reported in adults exposed to cannabis. Most study limitations were related to the origin, quality, and completeness of data. For example, Wang et al. (2013) noted that findings based on data from a single children's hospital or regional poison centers may not be generalizable to other health care facilities or poison centers, especially those in areas where laws regarding cannabis use are different than in Colorado. Search strategies employed in retrospective reviews of records from hospitals and poison centers may fail to capture all pertinent records, and some records may be incomplete (Wang et al., 2016). Data from poison centers will capture only the subset of cannabis-related overdose injuries or deaths that resulted in a call to a poison center and may overrepresent serious cases or cases from states where cannabis is legal (Wang et al., 2014). Moreover, Onders et al. (2016) observed that cannabis exposures are not identical to poisonings and overdoses; consequently, data on trends in cannabis exposures do not necessarily allow for an estimation of trends in cannabis overdose or poisoning.

CONCLUSION 9-4

9-4(a) There is insufficient evidence to support or refute a statistical association between cannabis use and death due to cannabis overdose.

9-4(b) There is moderate evidence of a statistical association between cannabis use and increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal.

RESEARCH GAPS

To address the research gaps relevant to injury and death, the committee suggests the following:

- There is a need for long-term, well-designed cohort studies to determine the association between cannabis use and all-cause and cause-specific mortality among large, representative populations. These studies will need to assess the effects of the various characteristics of cannabis use (e.g., frequency, duration, cumulative exposure) on mortality among demographic and clinical subgroups of interest, to use credible measures of cannabis exposure, and to control for known confounders.
- The association between cannabis use and occupational injury needs to be explored across a broad range of regions, populations, workplace settings, workplace practices (e.g., drug use prevention programs, safety standards), worker characteristics (e.g., medical history, history of drug and alcohol use), work patterns, and occupations.
- There is a need for research to evaluate whether and how the form of cannabis (e.g., edibles, flower, concentrates) affects the risk of overdose and to characterize the incidence and prevalence of overdose deaths in children and adults due to accidental or intentional exposure to edible cannabis.
- There is a need for well-designed surveillance studies to determine the prevalence of acute cannabis use and intoxication among U.S. drivers. Research is also needed to explore how patterns of cannabis use, the degree of acute cannabis intoxication, and geographic and demographic variables affect MVC incidence, driver and passenger outcomes, and driver safety and performance. Finally, research is needed to identify the causal channels through

which cannabis use may adversely or therapeutically affect MVC risk.

- There is a need for research on the association between cannabis use and injury and mortality among unstudied and understudied demographic groups, such as minority groups, working adolescents, and employed older populations.

SUMMARY

This chapter discussed the associations between cannabis use and all-cause mortality, occupational injury, motor vehicle crash, and death and injury due to overdose. Box 9-1 provides a summary of the conclusions from this chapter. Notably, the committee found substantial evidence of a statistical association between cannabis use and motor vehicle crashes. These findings suggest the need for research to further specify the strength of this association and to identify any mediating factors, as well as the need for broader surveillance efforts to track patterns of cannabis use, especially where cannabis use may pose risks to personal and public health.

BOX 9-1
Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between cannabis use and:

- Increased r sk of motor veh c e crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

- Increased r sk of overdose njur es, nc ud ng resp ratory d stress, among ped atr c popu at ons n U.S. states where cannab s s ega (9-4b)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- A -cause morta ty (se f-reported cannab s use) (9-1)
- Occupat ona acc dents or njur es (genera , nonmed ca cannab s use) (9-2)
- Death due to cannab s overdose (9-4a)

* Numbers in parentheses correspond to chapter conclusion numbers

Apart from illuminating potential research objectives, these findings also suggest enacting policies such as making DUIC a direct target for both policy and policing. Such efforts could include checkpoints for DUIC in conjunction with those for sobriety, the development of point-of-care kits for DUIC testing, and a consideration of zero tolerance laws. These proposals find parallels in policies that restrict or prohibit the use of alcohol while driving, and there is both domestic and international precedent for policing the use of cannabis while operating motor vehicles. In Colorado and Washington, an individual whose blood contains 5 ng/ml or more of THC while driving is considered to be under the influence and is guilty of DUIC.[9] In Australia, it is illegal to drive with any level of THC in oral fluid or blood samples (Boorman and Owens, 2009).[10] Some research suggests that policies that legalize cannabis for medical use have been associated with a decrease in the incidence of MVC. For example, an ecological study found a net reduction in traffic crashes associated with the introduction of laws for medical cannabis use (Anderson et al., 2013).

The committee also found moderate evidence of a statistical association between cannabis use and an increased risk of overdose injuries among pediatric populations in states in where cannabis is legal. The potential risks associated with the use of highly potent cannabis products suggest a need for public health policies, such as regulations that require packaging for cannabis products to include child-focused safety features, warnings that ingested cannabis can have different effects from smoked cannabis, and guidance on how to respond to potential emergencies. Again, precedents for such policies exist. For example, Colorado regulations require that medical and retail cannabis products be sold in packages that are child-resistant, that list the potency of the product in mg of THC and cannabidiol, and that contain several warning statements, including the direction to keep the product out of the reach of children.[11,12]

The available evidence was insufficient to draw any conclusions regarding the association between cannabis use and occupational injury or all-cause mortality. The high economic and social costs associated with occupational injuries in this country suggest the need for further research to determine whether these injuries are associated with cannabis use. In pursuing this research, it will be important to determine which individual and work-related factors protect against, or expose workers to, the risk of injury. Emerging evidence suggests that access to legal cannabis can

[9] Wash. Rev. Code Ann. § 46.61.502 (1) (b). Colo. Rev. Stat. Ann. § 42-4-1301 (6) (a) (IV).

[10] Road Traffic Act 1974, Part V, Division 2, Section 64AC (1).

[11] Colorado Code of Regulations. Department of Revenue. Marijuana Enforcement Division. Medical Marijuana Rules. 1 CCR 212-1 M1004.5 (B) and M1005 (B).

[12] Colorado Code of Regulations. Department of Revenue. Marijuana Enforcement Division. Retail Marijuana Rules. 1 CCR 212-2 R1006 (A–B).

increase the incidence of accidental cannabis ingestion among pediatric populations and that such ingestion can lead to depressed respiratory function and other symptoms of overdose. If state-level changes in cannabis policy continue to make cannabis more accessible, there will be an increased need for research to assess the prevalence of injuries and death due to cannabis overdose, especially among children and other vulnerable populations.

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10

Prenatal, Perinatal, and Neonatal Exposure to Cannabis

Chapter Highlights

- Smoking cannabis during pregnancy is linked to lower birth weight in the offspring.
- The relationship between smoking cannabis during pregnancy and other pregnancy and childhood outcomes is unclear.

The issue of exposure to cannabis during pregnancy reflects concerns that two different individuals may experience the potential adverse effects of cannabis, which is the illicit drug used most frequently by women of childbearing age. The Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health found that in 2015, 3.4 percent of pregnant women ages 15 to 44 had used marijuana during the previous month (CBHSQ, 2016). This is compared to 0.8 percent of pregnant women who used pain relievers, the next most used illicit drug among pregnant women (CBHSQ, 2016). In part because cannabis is an illicit drug, there is very little information on the physiological effects of cannabis in pregnancy on the mother. Moreover, most of the data reflect cannabis administered by smoking and not cannabis exposure through other routes of administration.

Concern about the fetus and newborn stems from the fact that tetrahydrocannabinol (THC) crosses the placenta (Bailey et al., 1987). A rapidly

growing body of evidence indicates that endocannabinoids play roles in a broad array of critical neurodevelopmental processes, from early neural stem cell survival and proliferation to the migration and differentiation of both glial and neuronal lineages as well as neuronal connectivity and synaptic function (Lubman et al., 2014). Another potentially important issue is that THC is secreted in breast milk and can accumulate to high concentrations (Garry et al., 2009).

This chapter focuses on exposure to cannabis from the beginning of pregnancy through the infant's first month of life. Thus, the review covers complications of pregnancy, fetal effects, exposure through breast milk, and later effects of fetal exposure. Although the general principle of the overall report is to restrict the literature reviewed to that which has emerged since the publication of *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999), the last Institute of Medicine report on marijuana, the committee chose to include information concerning longer-term outcomes from two older cohorts released in the 1980s, with the rationale that the identification of late adolescent and young adult outcomes would require that length of follow-up. The committee hand-searched additional literature to examine other prioritized long-term health outcomes not covered in these cohort studies.

The committee identified only one recent good- to fair-quality systematic review (Gunn et al., 2016). This review sought information on a comprehensive set of complications of pregnancy and on fetal and neonatal outcomes up to 6 weeks postpartum. Several lower-quality systematic reviews (Fryers and Brugha, 2013; Irner, 2012; Savitz and Murnane, 2010; Williams and Ross, 2007), narrative reviews (Andrade, 2016; Forray et al., 2015; Hashibe et al., 2005; Huang et al., 2015; Huizink, 2014; Metz and Stickrath, 2015; Schempf, 2007; Viteri et al., 2015), and articles from the grey literature (CDPHE, 2015) were used to identify outcomes not reviewed in Gunn et al. (2016), as was a bibliographic search of materials published from 1999 onward. A literature search was also conducted for outcomes in Gunn et al. (2016), from 2014 to August 2016, to identify any more recent articles. The committee identified 30 primary literature articles that best address the committee's research questions of interest.

PREGNANCY COMPLICATIONS FOR THE MOTHER

Is There an Association Between Cannabis Use and Pregnancy Complications for the Mother?

Stillbirth and Spontaneous Abortion

Systematic Reviews The committee did not identify a good- to fair-quality systematic review that reported on the association between cannabis exposure and stillbirth or spontaneous abortion.

Primary Literature Varner et al. (2014) used results from a population-based case-control study conducted by the Stillbirth Collaborative Research Network to compare illicit drug use in pregnancies that did and did not result in stillbirth.[1] Among 663 stillbirth deliveries, women who had a stillbirth were twice as likely as those with a live birth to report having been addicted to an illicit drug. Tetrahydrocannabinolic acid (THCA), the most common individual drug reported by the population, was found in 2.9 percent of women with a stillbirth and 1.7 percent of the controls (odds ratio [OR] for stillbirth, 2.34; 95% confidence interval [CI] = 1.13–4.81). However, the authors indicate that the result may have been partially confounded by exposure to cigarette smoking and that they may not have had the statistical power to disentangle this effect.

Warshak et al.'s 2015 study on the association between marijuana exposure and adverse neonatal outcomes included stillbirth in the outcomes they examined and found no association (1.1 percent among 361 cannabis users versus 1.5 percent among 6,107 cannabis nonusers; $p = 0.54$).

Fetal Distress

Systematic Reviews Gunn et al. (2016) found no association between marijuana use and fetal distress based on two studies (Berenson et al., 1996; Witter and Niebyl, 1990).

Primary Literature The committee did not identify any good-quality primary literature that reported on the association between cannabis use and fetal distress and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

[1] Fetal death was defined in the study as 20 weeks of gestation or less (Varner et al., 2014).

Other Complications

Systematic Reviews The assessment of the literature on pregnancy complications for the mother relied primarily on Gunn et al. (2016). Of the possible complications, only the increased risk of anemia had a significant association with exposure to cannabis (pooled odds ratio [pOR], 1.36; 95% CI = 1.10–1.69). Mixed findings about an association with cannabis use occurred in studies of precipitate labor and the manual removal of the placenta. No associations were found between in utero exposure to cannabis and the following health outcomes: maternal diabetes, rupture of membranes, premature onset of labor, use of prenatal care, duration of labor, placental abruption, secondary arrest of labor, elevated blood pressure, hyperemesis gravidarum, maternal bleeding after 20 weeks, antepartum or postpartum hemorrhage, maternal weight gain, maternal postnatal issues, duration of maternal hospital stay, or hormone concentrations (Gunn et al., 2016).

Primary Literature Three further studies were identified: Budde et al. (2007), Leemaqz et al. (2016), and Warshak et al. (2015). These studies examined the association between cannabis exposure and the following outcomes: anemia, precipitate labor, manual removal of the placenta, maternal diabetes, rupture of membranes, premature onset of labor, use of prenatal care, duration of labor, secondary arrest of labor, elevated blood pressure, hyperemesis gravidarum, maternal bleeding after 20 weeks, antepartum or postpartum hemorrhage, placental abruption, maternal weight gain, maternal postnatal problems, and duration of maternal hospital stay.

Findings in Leemaqz et al. (2016) from 313 women who used cannabis during pregnancy and Warshak et al. (2015) from 4,892 women who used cannabis during pregnancy were consistent with there being no significant association between cannabis exposure and gestational diabetes (adjusted odds ratio [aOR], 1.11; 95% CI = 0.52–2.38; p = 0.949 and aOR, 0.87; 95% CI = 0.66–1.04; p = 0.04, respectively) or gestational hypertension/preeclampsia (aOR, 0.443; 95% CI = 0.13–3.54; p = 0.671 and aOR, 0.84; 95% CI = 0.68–1.04; p = 0.12, respectively). Warshak et al. (2015) did not find a statistically significant association between cannabis use and placental abruption (aOR, 1.17; 95% CI = 0.81–1.70; p = 0.25). Budde et al. (2007) reported an increased risk of placental abruption that did not achieve standard statistical significance (OR, 2.83; 95% CI = 0.86–10.78; p = 0.055).

Discussion of Findings

Despite identifying one good- to fair-quality systematic review addressing pregnancy complications for the mother, the findings of the review must be interpreted with caution. The review relied on a primary literature that is limited in the number, quality, and rigor of the studies that have been carried out to date. By and large, the existing studies have been retrospective cohort studies, many of which looked at a large number of outcomes without biological plausibility or a biological mechanism guiding the test of the hypothesis. For example, the association identified between anemia and cannabis use in pregnancy arises in the absence of a clear mechanism by which these factors would be related. In addition, many studies were underpowered to detect relatively rare pregnancy complications. Therefore, though Gunn's review reports "no association" for the vast majority of conditions selected, it remains unclear whether this represents a type II error. Ethical challenges obviously preclude the ability to conduct randomized controlled trials of cannabis use in pregnancy, thereby precluding the ability to establish causal relationships. Logistical and financial constraints make even prospective cohort studies of adequate size and duration challenging to fund and implement. Even with rigorous study designs, comorbid tobacco and polysubstance use often confound the interpretation of the data. Such considerations markedly diminish the confidence with which the committee can draw conclusions regarding how much risk can be attributed to cannabis in the area of adverse maternal events.

CONCLUSION 10-1 There is limited evidence of a statistical association between maternal cannabis smoking and pregnancy complications for the mother.

FETAL GROWTH AND DEVELOPMENT

Is There an Association Between Cannabis Use and Fetal Growth and Development?

Birthweight

Systematic Reviews Studies reviewed in Gunn et al. (2016) that examined the effect of cannabis exposure on birth weight reported both mean birth weights and the percentage of infants at low birth weight (LBW; defined as 2.2kg or 5.5 lbs). Gunn et al. (2016) found that in utero exposure to cannabis is associated with a decrease in birth weight among cannabis-exposed infants (pOR, 1.77; 95% CI = 1.04–3.01; pooled mean difference

[pMD], −109.42 grams; 95% CI = −38.72 to −180.12) compared to those without cannabis exposure.

Primary Literature Similar to the findings reported by Gunn et al. (2016), Gray et al. (2010) and Fergusson et al. (2002) also reported lower mean birth weights for infants prenatally exposed to cannabis. Among 9,521 mothers, Fergusson et al. (2002) showed a −84.20 gram difference (95% CI = −174.7 to −6.4; p = 0.005) in birth weight for the children of mothers who had used cannabis at least once per week before and throughout pregnancy versus nonusers. Out of 86 total infants of cannabis-using mothers (independent from tobacco use), Gray et al. (2010) reported a mean birth weight of 3,161 grams (standard deviation [SD], 689; p = 0.051) among 41 infants who had been exposed to cannabis and 3,417 grams (SD, 504; p = 0.051) among 45 infants who had not been exposed to cannabis. In contrast, Schempf and Strobino (2008) found that, when adjusted for other drug use (i.e., cocaine and opiates), there was no significant association between cannabis use and LBW (defined as less than 2,500 grams) (aOR, 0.93; 95% CI = 0.55–1.57).

Birth Length

Systematic Reviews In their systematic review, Gunn et al. (2016) found that for the nine studies that reported neonatal length at birth (measured in centimeters), there was no statistically significant association between neonatal length and prenatal exposure to cannabis (pMD, −0.10; 95% CI = −0.65–0.45).

Primary Literature Birth length was also examined by Fergusson et al. (2002), who found that children who had been exposed to cannabis in utero had a lower birth length than children who had not been prenatally exposed to cannabis. However, after adjusting for various confounding factors (e.g., cigarette smoking during pregnancy, alcohol consumption during pregnancy), the association was no longer significant (p = 0.225). Similarly, Gray et al. (2010) found nonsignificant differences in birth length between 41 infants of cannabis-using mothers (independent from tobacco use) (49.8 cm; SD, 3.8; p = 0.156) and 45 infants of non-using mothers (50.8 cm; SD, 2.2; p = 0.156).

Head Circumference

Systematic Reviews Gunn et al. (2016) found that among the 10 studies they reviewed that measured head circumference at birth, no statistical

association was found between cannabis exposure in utero and neonatal head circumference (cm) (pMD, −0.31; 95% CI = −0.74–0.13).

Primary Literature The committee did not identify any good-quality primary literature that reported on the association between cannabis use and head circumference and that was published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Intrauterine Growth Restriction/Small for Gestational Age

There are two ways to describe slower-than-expected growth for a particular duration of gestation. The first is intrauterine growth restriction (IUGR), an obstetric diagnosis based on serial ultrasounds during pregnancy. The second is small for gestational age (SGA), which applies to infants with a birth weight that is less than the 10th or 5th percentile on normative growth curves. The limitation of the latter is that it does not distinguish between those infants with true slow growth and those with normal growth in the lower percentiles.

Systematic Reviews Gunn et al. (2016) addressed two studies that looked at the relationship between in utero cannabis exposure and SGA and concluded that no association can be reported on the association between exposure to cannabis during pregnancy and IUGR/SGA. A pOR was not reported.

Primary Literature Leemaqz et al. (2016) similarly did not find an association between cannabis exposure and SGA (defined as a birth weight less than the 10th percentile) when adjusted for any smoking (aOR, 1.13; 95% CI = 0.80–1.60). In a path analysis of urban black women who reported cannabis use at 50 percent of prenatal visits, Janisse et al. (2014) found a reduction in birth weight for heavy marijuana use alone (−55.2 grams), with a path coefficient of 0.05.[2] Their analysis suggests that LBW resulting from cannabis exposure reflects fetal growth restriction rather than premature delivery.

Congenital Malformation

In this category the committee considered infants who had malformations or anomalies diagnosed prenatally or after birth. Congenital malformations reflect abnormalities of fetal development in one or more

[2] The authors used a z-score of birth weight for duration of gestation residualized.

organ systems and can occur throughout pregnancy. They may be identified before or after birth.

Systematic Reviews Gunn et al. (2016) reported no association between cannabis exposure and chromosomal anomalies. No estimate of effect was provided.

Primary Literature Warshak et al. (2015) analyzed data from among 4,892 cannabis users and 153 marijuana cannabis nonusers and reported no association between cannabis exposure and fetal anomalies (aOR, 1.29; 95% CI = 0.87–1.92). In contrast, Forrester and Merz (2006) found higher rates of cannabis use to be associated with the presence of 19 defects out of a total of 54 selected conditions.[3] However, this study only performed bivariate comparisons for exposure/no exposure without considering other substances, confounders, or multiple comparisons.

Two case-control studies of the association of cannabis exposure to specific malformations were found. Using data from the National Birth Defects Prevention Study (1997–2005), van Gelder et al. (2014) examined the association between maternal cannabis use from 1 month before pregnancy through the end of the third month of pregnancy and 20 selected anomalies (n = 13,859 case infants; n = 6,556 control infants). The authors reported an increased risk of the following anomalies: anencephaly (aOR, 2.2; 95% CI = 1.3–3.7), esophageal atresia (aOR, 1.4; 95% CI = 0.8–2.4), diaphragmatic hernia (aOR, 1.4; 95% CI = 0.9–2.2), and gastroschisis (aOR, 1.2; 95% CI = 0.9–1.7). Williams et al. (2004) obtained an (aOR, 1.90; 95% CI = 1.29–2.81) for the risk of isolated ventricular septal defect (VSD) among 122 isolated VSD cases and 3,029 control infants.

Discussion of Findings

The findings for birth weight are consistent with the effects of noncannabinoid substances in smoked cannabis and cigarette smoking. It has been shown in several studies that the increases in carbon monoxide, with elevated carboxyhemoglobin blood levels, may be up to fivefold higher after marijuana than cigarettes (Wu et al., 1988). In other studies of marijuana exposure during pregnancy, the cause of the fetal growth

[3] The authors found higher rates of association between cannabis use and the following birth defects: encephalocele, hydrocephaly, microcephaly, anotia/microtia, tetralogy of Fallot, ventricular septal defect, atrial septal defect, pulmonary valve atresia/stenosis, hypoplastic left heart syndrome, cleft palate alone, cleft lip with/without cleft palate, pyloric stenosis, anal/rectal/large-intestinal atresia/stenosis, obstructive genitourinary defect, polydactyly, syndactyly, reduction deformity of upper limbs, gastroschisis, and trisomy 21 (Forrester and Merz, 2006).

restriction noted was proposed to be fetal hypoxia due to the shift in the oxyhemoglobin curve caused by carbon monoxide (Frank et al., 1990).

CONCLUSION 10-2 There is substantial evidence of a statistical association between maternal cannabis smoking and lower birth weight of the offspring.

NEONATAL CONDITIONS

Is There an Association Between Maternal Cannabis Use and Neonatal Conditions in the Infant?

Prematurity/Gestational Age

Systematic Reviews Gunn et al. (2016) documented a decrease in gestational age (measured in weeks) associated with cannabis use (pMD, –0.20; 95% CI = –0.62 to –0.22) and increased odds of the risk of preterm delivery (<37 completed weeks) (pOR, 1.29; 95% CI = 0.80–2.08).

Primary Literature Two other studies, Gray et al. (2010) and van Gelder et al. (2014), found no association between cannabis use and shortened gestation. For a total of 86 infants, Gray et al. (2010) reported a median estimated gestational age at delivery of 39 weeks (p = 0.685) both for infants who were exposed to cannabis and for infants who were not exposed to cannabis. van Gelder et al. (2014) found no association between cannabis use and gestational age after adjusting for gestational weight gain (aOR, 0.6; 95% CI = 0.1–2.4; n = 3 exposed; n = 335 nonexposed). The study was likely not to have the power to detect a difference.

Two studies, Dekker et al. (2012) and Leemaqz et al. (2016), reported an increased risk of spontaneous preterm birth associated with cannabis use (aOR, 2.34; 95% CI = 1.22–4.52 and aOR, 2.28; 95% CI = 1.49–3.60; p <0.001, respectively).

Neonatal Intensive Care Unit Admission

Systematic Reviews Gunn et al. (2016) reported increased risk of neonatal intensive care unit (NICU) admission for infants exposed to prenatal cannabis (pOR, 2.02; 95% CI = 1.27–3.21).

Primary Literature Warshak et al. (2015) also found an increased risk of NICU admission among infants born to 4,892 cannabis users and 153 nonusers (aOR, 1.54; 95% CI = 1.14–2.07).

Other Neonatal Conditions

Systematic Reviews Gunn et al. (2016) considered other neonatal conditions and found no association between maternal cannabis use and infant Apgar scores at 1 and 5 minutes. They did not find any differences for jaundice, resuscitation, respiratory distress syndrome, intubation following delivery, hypoglycemia, and sepsis. Studies were mixed as to whether infants exhibited abnormal behavior on neonatal behavioral assessments, in part because different assessment instruments were used in each study.

Primary Literature Warshak et al. (2015) did not find a statistically significant difference in the length of infant hospital stays (aOR, 1.12; 95% CI = 0.95–1.31). Gray et al. (2010) examined Apgar scores at 1 and 5 minutes and found no association between the scores and infant cannabis exposure ($p = 0.709$ and $p = 0.496$, respectively).

Discussion of Findings

The literature with regard to prematurity is mixed and needs further study. No neonatal outcomes appeared to be associated with cannabis exposure, but the studies are limited. Findings related to health care use, such as the increase in NICU admissions, need to be treated with caution. This pattern may reflect protocols requiring admission of all infants whose mothers have a history of substance use in pregnancy or failed toxicological screens during labor, rather than the health of the infant per se, particularly as there appears to be no increase in length of neonatal stay.

CONCLUSION 10-3 There is limited evidence of a statistical association between maternal cannabis smoking and admission of the infant to the neonatal intensive care unit (NICU).

LATER OUTCOMES

Is There an Association Between Maternal Cannabis Use and Later Outcomes for the Offspring?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later outcomes for the child.

Primary Literature

As noted above in the introduction of this chapter, examination of later outcomes relied heavily on three cohorts, with some limited results from other hand-searched studies reported below.

The first of these cohorts was the Ottawa Prenatal Prospective Study (OPPS) by Fried and colleagues (Fried et al., 1998). The sample of 698 pregnant women was a convenience sample obtained through advertising in doctors' offices and in the media. It could be characterized as including low-risk middle-class women of European descent. No gestational criterion was used, but most of the women were in their second trimester of pregnancy. Data collection was by interview about drug use while pregnant, including the use of cigarettes, alcohol, and cannabis, the last of which was characterized in terms of the number of joints per week. Of the original 698 study participants, 140 women reported at least some use of cannabis or drinking at least 0.85 oz. of absolute alcohol per day or smoking at least 16 mg of nicotine per day (Fried et al., 1998). A smaller group of women (n = 50) who did not use any substances during pregnancy were randomly selected as a reference group. Among these women, prenatal maternal cannabis use was categorized into three groups, with levels averaged across pregnancy: (1) no use, (2) mild/moderate use up to six joints per week, and (3) heavy use of at least six joints per week. Offspring were followed until the ages 18 to 22 years, with some attrition as would be expected (Fried et al., 1998).

The second study, started in 1982, was the Maternal Health Practices and Child Development (MHPCD) Study (Day and Richardson, 1991). The sample was recruited from a single inner-city outpatient prenatal clinic in Pittsburgh and thus was of mixed race/ethnicity and lower socioeconomic status. The participants had to be at least 18 years of age and in their fourth month of pregnancy. Of the 1,360 participants who met these criteria and were screened by an interview, pregnant women who used two or more joints per month were then selected for the study, with a random sample of an equal number of women chosen from the remaining non-using subjects, for a total sample of 564 (Huizink, 2014). Prenatal cannabis use was expressed as average daily joints for each trimester of pregnancy separately, although there was some overlap. Follow-up data on offspring have been reported up to the age of 14.

The most recent study was the Generation R study started in 2001, a multiethnic (Dutch, Moroccan, Surinamese, and Turkish) population-based prospective cohort study from fetal life until adulthood in the city of Rotterdam, the Netherlands (Jaddoe et al., 2012). The sample consists of 9,778 mothers with a delivery date between April 2002 and January 2006, and the members of the sample tended to be of higher socioeconomic status (Huizink, 2014). All participating women in Generation R

filled out questionnaires on their substance use at three points in pregnancy corresponding to the three trimesters. In this sample, 220 women reported using cannabis in pregnancy, generally in the first trimester (Huizink, 2014). The study discriminated between cannabis exposure, tobacco smoking, and the use of neither. Data on the resulting children up to age 6 were used in this report.

Sudden Infant Death Syndrome

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and sudden infant death syndrome (SIDS).

Primary Literature Only one study was identified that examined the association between cannabis use and SIDS. In a case-control study of 428 infants who died of SIDS in southern California between 1989 and 1992, Klonoff-Cohen and Lam-Kruglic (2001) found no association between SIDS and cannabis exposure at conception (aOR, 1.1; 95% CI = 0.6–2.0; p = 0.82), during pregnancy (aOR, 0.6; 95% CI = 0.3–1.6; p = 0.33), or postnatally (aOR, 0.6; 95% CI = 0.2–1.8; p = 0.42). An interesting finding is increased risk of SIDS with paternal cannabis use at conception (aOR, 2.2; 95% CI = 1.2–4.2; p = 0.01), during pregnancy (aOR, 2.0; 95% CI = 1.0–4.1; p = 0.05), and postnatally (aOR, 2.8; 95% CI = 1.1–7.3; p = 0.04).

Breastfeeding

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and breastfeeding.

Primary Literature One narrative review (Garry et al., 2009) identified two early studies on the effects of cannabinoids in breast milk on subsequent motor function but found no consistency in the results. The authors noted the difficulty in studying this issue since prenatal exposure is also likely among other confounders of cannabis use. The committee's search identified one study of physical growth (Fried et al., 2001) which makes mention of no difference being found in choice and duration of breastfeeding relative to marijuana use.

Physical Growth

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and physical growth in the child.

Primary Literature Postnatal growth results were obtained from the OPPS (Fried et al., 2001). Growth was measured for 152 participants at 1 year, 2–4 years, 6 years, 12 years, and 13–16 years. There was a dose–response relationship between head circumference and cannabis exposure (measured as heavy or six or more joints per week, moderate or between zero and six joints per week, and none), with children of heavy cannabis users having the smallest head circumferences (Z-score, 0.84; SD = 1.3; p = 0.08), a finding that persisted through age 12 but was not seen at ages 13–16 (Fried et al., 2001). In addition, infants of heavy cannabis users were the lightest at birth (Z-score, 0.32; SD = 0.9), but they experienced substantial weight gain such that they were the heaviest at 1 year. Furthermore, at ages 13–16 no differences were seen in height, weight, ponderal index, or onset of puberty.

Cognition/Academic Achievement

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and cognition and academic achievement of the child.

Primary Literature The committee reviewed this literature in terms of preschool cognitive development and later cognitive development. Among the studies that examined cognitive development up to 3 years of age, no difference was found. In addition, two studies (OPPS and MHPCD) looked at cognitive development at 36–60 months. Both studies reported a weak effect on short-term memory.

Six studies out of two cohorts were identified that addressed the association between cannabis and cognitive function between ages 5 and 16 years using a variety of assessment instruments (Bluhm et al., 2006; El Marroun et al., 2010; Fried and Watkinson, 1988, 1990; Goldschmidt et al., 2012; Richardson et al., 1995). No differences in overall cognitive scores were found, but differences with exposure to different levels of prenatal cannabis were seen for some subscale scores, although they were not replicated across studies. In their assessment of school achievement, Goldschmidt et al. (2012) found worse reading scores at age 14 as measured by the Wechsler Individual Achievement Test (WIAT Screener). The

authors found a WIAT Screener basic reading score of 93.8 among non-exposed children, 93.1 among children exposed to less than one joint per day, and 87.8 among children exposed to one or more joints per day ($p = 0.001$).[4] No differences with cannabis exposure were seen for cognitive or motor development in Fried and Watkinson (1988), Richardson et al. (1995), or El Marroun et al. (2010).

Behavior

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later child behavior.

Primary Literature The committee sought studies linking prenatal marijuana exposure to later child behavior. Of the three cohorts assessed above, only one report dealt with child behavior problems (Bluhm et al., 2006). The remaining reports assessed behavior in testing situations: for example, variability in reaction times and errors on continuous performance tests. Because the committee felt the latter do not really capture the construct of interest, this section reports only on child behavior problems at age 18 months and 3 years. At 18 months, higher aggression scores were seen in girls but not in boys; this effect did not persist at 3 years (El Marroun et al., 2010).

Substance Use and Delinquency

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later substance use and delinquency of the child.

Primary Literature The committee identified five reports from two cohorts (OPPS and MHPCD) that addressed the association between prenatal cannabis exposure and substance use and delinquency among offspring between 14 and 22 years of age. In the study addressing delinquency at age 14 years, prenatal cannabis exposure was found to be correlated with an increased risk of delinquent behavior (OR, 1.84; 95% CI = 1.05–2.96) (Day et al., 2015). However, this effect was mediated by depression and attention difficulties at age 10. Three studies addressed prenatal exposure to cannabis on the use of both cigarettes and cannabis in offspring ages 14 to 22 years. In Porath and Fried (2005), prenatal marijuana exposure more

[4] This can be accounted for by attention and depression at age 10.

than doubled the risk of the initiation of cigarette smoking (OR, 2.58; 95% CI = 1.11–6.00) and daily cigarette smoking (OR, 2.36; 95% CI = 1.00–5.57). The authors also found that prenatal cannabis exposure also increased the risk of initiation of cannabis use in youth (OR, 2.76; 95% CI = 1.11–6.86) and increased the risk of using marijuana regularly (OR, 0.79; 95% CI = 0.33–1.90). Sonon et al. (2015) found that prenatal cannabis exposure was a predictor of offspring marijuana use (OR, 1.22; 95% CI = 1.02–1.44) at age 22 (Sonon et al., 2015).

Mental Health and Psychosis

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later mental health and psychosis in the child.

Primary Literature At age 10, children in the MHPCD study with prenatal cannabis exposure in the first and third trimesters had worse scores on a measure of depressive symptoms. Using the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study Zammit et al. (2009) found no difference in definite psychotic-like symptoms (PLIKS) as measured by a PLIKS semi-structured interview at 12 years of age between those exposed prenatally and those not exposed (aOR for linear trend, 0.91; 95% CI = 0.49–1.71; p = 0.776). Day et al. (2015), working with the MHPCD cohort at age 22, found that prenatal marijuana exposure was associated with an increased risk of psychotic symptoms as measured by the Diagnostic Interview Schedule (incidence density ratio [IDR] 1.31; p <0.05). In a mediation model, considering the effect of early initiation use of cannabis, the youth risk was essentially the same (IDR, 1.27; p = 0.06).

Discussion of Findings

The literature reviewed above does not support an effect of cannabis exposure on overall cognitive function, although some variation in subscale scores has been seen. Only one study has examined overall child behavior, and it found that the results did not persist. More consistency is seen for adolescent outcomes, with increased delinquency, greater cigarette and cannabis use, and some suggestion of increased mental health symptoms. For the later outcomes, attributing the outcomes to prenatal exposures is particularly difficult. While the studies attempted to control for the child's environment using standard measures of socioeconomic status as well as a direct assessment of the home environment, these

approaches may be insufficient to detect potentially subtle differences in the family and neighborhood environments of women who smoke cannabis during pregnancy and those who do not. For example, the association of prenatal cannabis exposure and adolescent substance use may reflect family/neighborhood influences and may not be a direct effect of the prenatal exposure. Likewise, maternal distress/depression during pregnancy, which is likely to continue postpartum, may influence both the use of cannabis and child developmental outcomes. In addition, these studies did not address heritable or epigenetic vulnerability.

CONCLUSION 10-4 There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use).

RESEARCH GAPS

To address the research gaps relevant to prenatal, perinatal, and neonatal outcomes, the committee suggests the following:

- There is a need for systematic inquiry using standardized questions about dose and duration at specific intervals in pregnancy to ascertain the level of prenatal cannabis exposure.
- Capitalizing, where possible, on the increase in toxicological screening at delivery to validate self-report measures.
- With the increased availability of recreational cannabis, observational studies need to be carried out—where ethical—on cannabis use and potential physiologic changes (e.g., blood pressure, etc.).
- Pooling, if possible, to obtain cohorts of women exposed only to THC and not to other drugs.
- A systematic follow-up of children exposed to cannabis prenatally with agreed-upon protocols and tests, with an ascertainment of the home and neighborhood environment regarding concurrent substance use.
- Developing strategies for assessing the effect of cannabis on pregnant women and fetuses through registries or systematic use of administrative data.

SUMMARY

This chapter summarizes the literature on prenatal, perinatal, and neonatal exposure to cannabis that has been published since 1999 and deemed to be of good or fair quality by the committee. Overall, there is substantial evidence of a statistical association between cannabis smoke and lower birth weight, but there is only limited, insufficient, or no evidence in support of any other health endpoint related to prenatal, perinatal, or neonatal outcomes. This may be due to a number of limitations faced by many of the research studies reviewed in this chapter, including an almost exclusive reliance on self-reporting to ascertain cannabis exposure, as is true in many areas of this report. While many studies used standardized questions regarding frequency and duration of cannabis use, others relied on data extracted from the medical record. Also, as with other portions of this report, the potency of cannabis varied across time. The lack of biological validation of self-reporting suggests caution is warranted. Moreover, dosage and timing of exposure in pregnancy is particularly important, as exposures early in pregnancy may affect organogenesis leading to birth defects, whereas later exposures are more likely to affect the growth of the fetus.

Second, even within substantial cohorts, the number of women who used cannabis exclusively was small. These sample sizes may have limited statistical power to detect many outcomes.

Third, cannabis exposure was almost exclusively through smoking and was often confounded by the use of other substances—namely, tobacco and alcohol. Although many authors relied on a variety of statistical techniques to isolate the effects of cannabis exposure, attribution of outcomes to cannabis alone was difficult. Even when cannabis is the sole exposure, it is not straightforward to attribute outcomes to THC alone versus the mode of exposure.

Finally, caution needs to be used in interpreting the numerous findings of "no association" in this chapter. Absent a pooled estimate of effect and confidence intervals, such conclusions may be based on a small number of studies, some of which may even conflict.

The committee has formed a number of research conclusions related to these health endpoints (see Box 10-1); however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections.

BOX 10-1
Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower b rth we ght of the offspr ng (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy comp cat ons for the mother (10-1)
- Adm ss on of the nfant to the neonata ntens ve care un t (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

- Later outcomes n the offspr ng (e.g., sudden nfant death syndrome, cogn t on/academ c ach evement, and ater substance use) (10-4)

* Numbers in parentheses correspond to chapter conclusion numbers

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11

Psychosocial

Chapter Highlights

- Recent cannabis use impairs the performance in cognitive domains of learning, memory, and attention. Recent use may be defined as cannabis use within 24 hours of evaluation.
- A limited number of studies suggest that there are impairments in cognitive domains of learning, memory, and attention in individuals who have stopped smoking cannabis.
- Cannabis use during adolescence is related to impairments in subsequent academic achievement and education, employment and income, and social relationships and social roles.

Adolescence and emerging adulthood are the periods where most youths begin to experiment with substances of abuse, including cannabis (Johnston et al., 2015). Exploration for many substances of abuse have maintained historical consistency for the past few decades, with approximately 24.9 percent of youths having used cannabis at least one time by eighth grade to 51.4 percent having tried cannabis by the time they graduate from high school (Johnston et al., 2015). Yet, recent changes in recreational cannabis use laws have been linked to adolescents' changing perception around accessibility and availability of cannabis and decreased risk of harm from cannabis use, two factors that have been historically connected with rising rates of substance use (Feldstein Ewing et al., 2017;

Schmidt et al., 2016). The result is that we are at the forefront of a changing cannabis landscape for adolescents and young adults.

This is relevant because it is during this precise period of adolescence and young adulthood that the neural substrates that underlie the development of cognition are most active. Indeed, adolescence marks one of the most impressive stretches of neural and behavioral change (Giedd, 2015), with substantial and protracted development in terms of both brain structure and function throughout the teenage years and into the late 20s and early 30s (e.g., Conrod and Nikolaou, 2016). As a result, cannabis and other substance use during this period may incur relatively greater interference in neural, social, and academic functioning as compared to later developmental periods (e.g., adulthood) (Brumback et al., 2016; Jacobus et al., 2015).

However, with the paucity of data on the impact of changes of cannabis policy, coupled with existing limitations in the field of addiction neurodevelopment (e.g., predominance of cross-sectional studies) (Feldstein Ewing et al., 2014), we are still very much at the forefront of beginning to understand how cannabis impacts adolescent through adult cognitive health and broader psychosocial functioning.

COGNITION

Despite what appears, on first glance, to be a very broad existing literature, a surprisingly small number of empirical studies have examined how cannabis impacts the psychosocial domains targeted here. The questions addressed in this section revolve around how cannabis affects three aspects of cognition—memory, learning, and attention—areas that have continued to be prevalent across the self-report, neuropsychological, and magnetic resonance imaging (MRI)/functional magnetic resonance imaging (fMRI) literature since the mid-1970s. Furthermore, these are aspects of cognition that are often explored in other studies. In other words, evaluation of these aspects of cognition increases the potential to compare these findings to other studies, including the 10-year prospective examination of 10,000 youths across 21 sites (the ABCD study; Adolescent Brain Cognitive Development Study, 2016). In terms of the relevance of these aspects of cognition, the domains of learning, memory, and attention are central, as they undergird an individual's success—or failure—across such areas as academic, employment, and social/relationship functioning. This subsequently renders these three domains of cognition strong proxies for examining interference in functioning, one of the key metrics of cannabis use disorder symptomology according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V).

These domains are defined broadly in order to be as inclusive as pos-

sible of how they were measured within the included systematic analyses and component primary manuscripts, and to allow maximal potential for generalization to the broader literature. Thus, within this review, "memory" is defined as the wide array of function that involves the abilities to remember, temporarily store, more extensively store, process, manipulate, recall, and reproduce data (e.g., verbal, auditory, written). In this review, "learning" is defined as the wide array of function that involves the ability to observe, comprehend, absorb, and appropriate new information into an individual's cognitive repertoire (e.g., verbal, auditory, visual). Finally, in this review, "attention" is defined as an individual's ability to stay focused on the task at hand without being distracted but also to be cognitively flexible enough to transfer to a different task or set of information when the time requires (e.g., including brain regions relevant to visual, auditory, and verbal processing as well as executive control).

To investigate how cannabis affects these three domains of human cognition (memory, learning, attention), a search was conducted to identify systematic reviews of the existing published literature since the publication of *Marijuana and Medicine: Assessing the Science Base*, the last Institute of Medicine (IOM) report on marijuana (1999). There were a total of 94 systematic reviews identified that responded to the topic of cannabis and cognition during the period of 2000–2016. Of these, 5 systematic reviews were considered of good quality (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Martin-Santos et al., 2010; Schreiner and Dunn, 2012). No primary manuscripts were utilized in this section because all study questions were addressed by the systematic reviews.

In contrast to other sections of this report, given the diversity of the metrics and constructs in learning, memory, and attention, and the different coverage of these domains within the 5 different systematic reviews, we present summaries from each of the systematic reviews in these domains rather than only presenting one representative systematic review for the topic area of cognition. Furthermore, reflective of the field of cognition at this time, the presented systematic reviews reflect data from the fields of neuropsychology, computer-administered cognitive tests, as well as brain structure and function (e.g., MRI/fMRI). The latter represent some of our most contemporary, sensitive, and specific metrics of cognitive function at this time.

It should be noted that Chapter 12 (Mental Health) highlights the multidirectional and complex relationship between cannabis use and cannabis use disorder and cognitive performance among individuals with psychotic disorders. For further information on this topic, please refer to Chapter 12.

The collection of systematic reviews used in this chapter represents a large body of work. The Broyd et al. (2016) systematic review is the most

recent, evaluating 3,021 total manuscripts, yielding a final number of 105 manuscripts in their review. Within their systematic review, they evaluated cannabis's interference with cognition across a number of assessment methodologies. Furthermore, they evaluated the impact of these cognitive domains across developmental periods, including adolescence, emerging adulthood, and adulthood (for additional information about developmental implications among adolescents, see Box 11-1). Batalla and colleagues began with 142 studies, which they narrowed to 43 manuscripts. As with the Broyd et al. (2016) team, Batalla et al. (2013) included studies

BOX 11-1
Developmental Implications Among Adolescents

Wh e ado escents were c ustered n many of these systemat c rev ews (e.g., Broyd et a ., 2016), t s mportant to note that they were the m nor ty, often ess than 20 percent of the fu samp e, and rare y exam ned ndependent y (e.g., Bata a et a ., 2013) to uncover potent a deve opmenta d fferences n cogn t ve funct on and/or ts nterference between the age groups. Much work needs to be done spec fica y exam n ng the mpact of cannab s on these cogn t ve contexts n ado escents and emerg ng adu ts spec fica y (.e., ages 14–25). Th s s h gh y mportant for three reasons. F rst, data n the c ted systemat c rev ews and e sewhere (e.g., Bata a et a ., 2013, and F bey et a ., 2015) cont nue to nd cate that an ear y age of n t at on tends to be connected to b gger d fferences n bra n funct on dur ng adu thood. Second, the bra n does not comp ete deve opment unt approx mate y age 25 (e.g., G edd, 2015), and data from the fie d of a coho use reflect that substance use exposure dur ng th s per od when the bra n undergoes rap d transformat on cou d have a more ast ng mpact on cogn t ve performance (e.g., L sdah et a ., 2013). Th s nterference n cogn t ve funct on dur ng the ado escent and emerg- ng adu t years, wh ch over ap w th the cr t ca per od n wh ch many youths' and young adu ts' pr mary respons b ty s to be rece v ng the r educat on, cou d very we nterfere w th these nd v dua s' ab ty to opt ma y perform n schoo and other educat ona sett ngs.

Wh e the ev dence for an assoc at on between cannab s use and effects on cogn t ve deve opment dur ng ado escence s m ted at th s t me, the comm ttee recogn zes the mportant n t at ve recent y begun by the Nat ona Inst tutes of Hea th (NIH) for the andmark study on bra n deve opment and ch d hea th, Ado- escent Bra n Cogn t ve Deve opment (ABCD) Study (Ado escent Bra n Cogn t ve Deve opment Study, 2016). The ABCD study s the argest ong-term study on cog- n t ve deve opment, track ng the b o og ca and behav ora deve opment of at east 10,000 ch dren beg nn ng at ages 9 to 10 for 10 years through ado escence nto adu thood us ng neuropsycho og ca eva uat ons and advanced bra n mag ng to observe bra n growth w th prec s on. Th s study, wh ch began n 2015, w exam ne how b o ogy and env ronment nteract and re ate to deve opmenta outcomes such as phys ca hea th, menta hea th, and fe ach evements.

across the age span, including adolescents and adults. One of the older systematic reviews, Grant et al. (2003), commenced their review with 1,830 manuscripts, which were reduced to a group of 117 papers in their final evaluation. Martin-Santos et al. (2010) began their examination with 66 manuscripts, which resulted in a final set of 41 studies of cannabis's effect on cognition. Schreiner and Dunn (2012) started with more than 800 studies, which they narrowed to a final set of 13 studies.

In these systematic reviews, "acute" generally reflects cognitive domains assessed within a short window (often within several hours) immediately after cannabis use. The individual may or may not still be intoxicated during this examination. In contrast, "sustained" generally reflects cognitive domains assessed after a period of abstinence from cannabis. Within the reviewed studies, that ranges from several hours to months after discontinuing cannabis use.

Is There an Association Between Cannabis Use and Learning?

Systematic Reviews

Of our final set of five systematic reviews, three addressed cannabis use on the cognitive domain of learning (Broyd et al., 2016; Grant et al., 2003; Schreiner and Dunn, 2012).

In terms of acute impact of cannabis use on learning, primarily relying on word list learning, data from 11 manuscripts within the Broyd et al. (2016) systematic review contributed to "strong" support of acute cannabis use on interference in learning. However, in terms of sustained effects, Broyd et al. (2016) only showed "mixed" support. Grant et al. (2003) assessed sustained impact of cannabis use on learning via neuropsychological tests (e.g., California Verbal Learning Test–Learning Trials; Rey Auditory Verbal Learning Test–Learning Trial). Across nine component studies, Grant et al. (2003) found a small negative effect size (ES) of −0.21 (99% confidence interval [CI] = −0.39 to −0.022) for the sustained impact of cannabis on learning. Schreiner and Dunn (2012) also examined sustained impact on learning, with component studies also relying on neuropsychological metrics (e.g., California Verbal Learning Test–Learning Trials; Rey Auditory Verbal Learning Test–Learning Trials; VIG–Visual Learning). Using the criteria of cannabis abstinence for at least 1 month (measured as ≥25 days) within their 13 examined studies, they found a very small ES of −0.16 (95% CI = −0.33–0.02).

One example study of the component studies within this section includes a study by Hanson et al. (2010). In this study, 19 adolescent marijuana users (mean age = 18 years) with limited other alcohol and/or other substance use were compared with 21 demographically similar

non-using controls (mean age = 17.4 years). Participants completed neuropsychological batteries assessing learning and other cognitive domains at several points post-cessation (e.g., 3 days; 2 weeks; 3 weeks). Abstinence was verified via decreasing tetrahydrocannabinol metabolite values assessed via serial urine drug screens. Marijuana users showed initial poorer performance on learning as compared with non-using controls in acute assessments (at 3 days; $p < 0.01$). However, they showed significant improvements with cessation, with no differences observed on learning between the cannabis-using and non-cannabis-using groups at either of the sustained time points (e.g., 2 weeks; 3 weeks).

Primary Literature

In this review of cannabis, the primary literature was searched when the systematic review content did not fully cover or address study questions. Given the breadth and scope of the existing systematic reviews in this domain, additional primary literature was not searched for the domain of learning.

Is There an Association Between Cannabis Use and Memory?

Systematic Reviews

Of the final set of five systematic reviews, three addressed cannabis use on the cognitive domain of memory (Batalla et al., 2013; Broyd et al., 2016; Martin-Santos et al., 2010).

In terms of acute impact of cannabis use on memory, the Broyd et al. (2016) systematic review was the only one to address this question. In this review, 22 studies assessed memory, including working memory and other memory function using various neuropsychological tests such as the Sternberg task, Trails B, *n*-back, and Wechsler tests, including spatial working memory, digit span, and digit recall. These studies showed moderate to strong evidence for acute interference of cannabis on memory. In terms of a long-term sustained relationship between cannabis use and learning following abstinence, the 11 studies examined by Broyd et al. (2016) showed mixed to no evidence for interference in memory functioning after cessation from cannabis use. Similarly, Batalla et al. (2013) examined memory using seven MRI/fMRI studies. The range in mean days of abstinence in these studies extended from 7 days to 201 days post-cannabis cessation. Batalla et al. (2013) found that although there was no difference in task performance between cannabis users and cannabis nonusers, cannabis users engaged slightly different parts of their brains as compared to nonusers to accomplish the task, often described in

the neuroimaging literature as the utilization of "compensatory" efforts. Similar to Batalla et al. (2013), Martin-Santos et al. (2010) examined five empirical MRI/fMRI studies. Individuals in these studies had abstained from using cannabis for an average of 24 hours to 26 days. As with Batalla et al. (2013), cannabis users showed equivalent performance across the neuroimaging tasks to the nonusers, but they could have engaged in compensatory efforts to achieve these outcomes.

One example study in the memory systematic analyses includes a recent study by Roten and colleagues (2015). This is a pharmacotherapy trial of 78 youth ages 15 to 21 years seeking treatment for cannabis dependence. These youths were evaluated to ensure their abstinence from cannabis use via urine cannabinoid testing. They received a computer-administered battery of tests, including verbal memory, visual memory, and composite memory. Youths who were recently abstinent and continuously abstinent for 4 weeks showed significantly better memory performance as compared to youths who were still using cannabis at the 4 week measurement (difference [d] = 7.2 ± 2.1, $p < 0.001$ and d = 7.5 ± 2.4, $p = 0.002$, respectively).

Primary Literature

In this review of cannabis, the primary literature was searched when the systematic review content did not fully cover or address study questions. Given the breadth and scope of the existing systematic reviews in this domain, additional primary literature was not searched for the domain of memory.

Is There an Association Between Cannabis Use and Attention?

Systematic Reviews

Of our final set of five systematic reviews, four addressed cannabis use on the cognitive domain of attention (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Schreiner and Dunn, 2012).

To determine the acute impact of cannabis use on attention, Broyd et al. (2016) reviewed 17 studies that assessed attention using several approaches, including using neuropsychological metrics of continuous task performance, divided attention tasks, reaction time, and attention control tasks. The synthesized findings from studies showed strong evidence for acute interference of cannabis on attention, as reported by the authors.

In terms of the long-term sustained relationship between cannabis use and attention following abstinence, 10 studies examined by Broyd et

al. (2016) showed mixed evidence for impairment in attention functioning after cessation from cannabis use. Likewise, using a series of MRI and fMRI measures (e.g., attention network task, functional connectivity via Multi-Source Interference Task) with three studies, Batalla et al. (2013) showed limited evidence of differences in task performance, but as with the other domains, they found evidence that cannabis users may be engaging a different neural network to achieve similar outcomes during the task (e.g., compensatory efforts). In a review of 11 studies, Grant et al. (2003) also examined the long-term sustained relationship between cannabis use and attention following abstinence. In their study, Grant et al. (2003) examined attention primarily using neuropsychological measures, finding a small ES for the influence of cannabis use on attention (ES, −0.083; 99% CI = −0.32–0.15). Finally, Schreiner and Dunn (2012) primarily examined neuropsychological test performance to determine any sustained impact of cannabis on attention performance, including the Continuous Performance Task and the Iowa Gambling Task (IGT). With the 13 component studies, the authors found a small ES for the sustained impact of cannabis on attention (ES, –0.20; 95% CI = −0.49–0.09).

An example of a component study from this section includes Crane et al. (2013). This study included 69 cannabis using 18- to 24-year-olds (mean age = 21 years). Attention was measured with four neuropsychological measures, including the IGT, the Balloon Analogue Risk Task, the Monetary Choice Questionnaire, and the GoStop Task. Interestingly, cannabis use was only associated with a significant difference on one measure (IGT and past year cannabis use, $p < 0.03$; IGT and past-month cannabis use, $p < 0.003$). There were no significant sustained associations between cannabis use on the other three measures of inhibition (for past year cannabis use and past-month cannabis use for the Balloon Analogue Risk Task, the Monetary Choice Questionnaire, and the GoStop Task).

Primary Literature

In this review of cannabis, the primary literature was searched when the systematic review content did not fully cover or address study questions. Given the breadth and scope of the existing systematic reviews in this domain, additional primary literature was not searched for the domain of attention.

Discussion of Findings

In sum, within the domain of learning, the Broyd et al. (2016) systematic review and the component study highlighted within that review showed strong data for the acute (immediate) impact of cannabis use on

learning. However, results from three systematic reviews (Batalla et al., 2013; Broyd et al., 2016; Martin-Santos et al., 2010) reflected limited to no support for the association between the sustained effects of cannabis use after cessation and the cognitive domain of learning. Similarly, for the domain of memory, the Broyd et al. (2016) systematic review and the component study within it showed moderate to strong evidence for the acute (immediate) impact of cannabis use on memory. However, as with learning, there were limited to no data to support the association between the sustained effects of cannabis use after cessation and the cognitive domain of memory in the three systematic reviews that addressed this question (Batalla et al., 2013; Broyd et al., 2016; Martin-Santos et al., 2010). Of interest, the neuroimaging studies reflected that while there was no difference in terms of performance on memory tasks, cannabis users may recruit different parts of their brain to achieve equivalent performance to control subjects on these tasks, suggesting the need to examine how cannabis may impact the neural regions that drive the processing of memory in future research. Finally, for the domain of attention, the Broyd et al. (2016) systematic review showed strong evidence for the acute (immediate) impact of cannabis on attention. However, as with the other domains, the evidence from other systematic reviews (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Martin-Santos et al., 2010; Schreiner and Dunn, 2012) suggest that there were limited to no data to support the association between the sustained effects of cannabis use after cessation and the cognitive domain of attention.

CONCLUSION 11-1

11-1(a) There is moderate evidence of a statistical association between acute cannabis use and impairment in the cognitive domains of learning, memory, and attention.

11-1(b) There is limited evidence of a statistical association between sustained abstinence from cannabis use and impairments in the cognitive domains of learning, memory, and attention.

ACADEMIC ACHIEVEMENT

Is There an Association Between Cannabis Use and Academic Achievement and Education?

For the psychosocial areas that go beyond cognition, there was one systematic review (Macleod et al., 2004) that examined the effects of can-

nabis on a number of psychosocial outcomes as reported in longitudinal studies of general population samples. Specifically, this review contributed to our evaluation of the research literature related to the effects of cannabis on academic achievement as well as social relationships and other social roles. There was no systematic review of the research literature on the effects of cannabis on employment and income.

Because only one systematic review was available, we also focused on the primary literature to address questions related to the effect of cannabis on (1) academic achievement; (2) employment and income; and (3) social relationships and other social roles. The primary literature to be reviewed and summarized is based on studies published subsequent to 1999. In selecting that literature, we focused on studies that met criteria derived from the Newcastle–Ottawa quality assessment scale. In particular, (1) prospective studies in which cannabis use occurred prior to the outcomes of interest; (2) multiple assessments of the variables of interest over time; (3) samples that are representative, either of the nation or a major subgroup; (4) multiple measures of cannabis use, involving frequency and/or quantity of use; (5) a relatively large sample size; and (6) consideration of relevant sociodemographic control variables such as sex/gender, age, family income, ethnicity/race, and/or history related to the outcome of interest.

Systematic Reviews

In their systematic review, Macleod et al. (2004) identified 16 high-quality longitudinal studies of the general population in which the effects of cannabis use on psychosocial outcomes, including educational attainment, were examined. The authors reported that cannabis use was consistently related to negative educational outcomes (measured primarily by drop-out rates), but they also noted that the strength of the association varied across the studies reviewed. In addition, including the appropriate control variables in the analyses typically resulted in a substantial decrease in the strength of the association. There was no evidence of a causal relationship between cannabis use and lower educational attainment.

Primary Literature

The primary literature published subsequent to Macleod et al.'s 2004 review continues to show that it is difficult to document a direct link between cannabis use and negative educational outcomes because other variables play a role. At best, indirect relationships have been reported. For example, Arria et al. (2013) used longitudinal growth curve modeling to analyze cannabis use and grade point average (GPA) data across 4

years of university education. They found no direct links from cannabis to GPA, but they did report an indirect path in which increased cannabis use led to increased skipping of classes, which resulted in lower GPA. Using data from the Coronary Artery Risk Development in Young Adults study, Braun et al. (2000) initially found an inverse relationship between past-month cannabis use and becoming a college graduate. When analyses were adjusted for variables such as age and parental education, this relationship disappeared, so that cannabis use was unrelated to college graduation.

There is some evidence to suggest that a higher frequency and persistence of cannabis use are associated with some negative educational outcomes. Using data from the Victoria Adolescent Health Cohort (1992–2003), Degenhardt et al. (2010) examined a cohort of a representative sample of Australian students (n = 1,943) from an average age of 14.9 years through an average of 24.1 years. Individuals who were persistent or weekly users of cannabis in adolescence and young adulthood had poorer post-school outcomes at age 24 years (adjusted odds ratio [aOR], 0.84; 95% CI = 0.55–1.3; n = 190)[1] compared with individuals who never used cannabis. Adjustment for background factors and cigarette smoking reduced this association.

The age at which cannabis use is initiated may be important in determining negative educational outcomes. Using data from three Australian cohort studies involving more than 6,000 participants, Horwood et al. (2010) reported that individuals who began to use cannabis before age 15 years experienced significantly greater negative educational outcomes, even after reductions in odds ratios (ORs) based on an adjustment for confounding variables. Pooled odds ratios (pOR) estimates indicated that the educational achievement of those who never used cannabis by age 18 years were 1.9 to 2.9 times greater than for those who used cannabis before the age of 15 years. The researchers found that individuals who had not used cannabis by age 18 were more likely to complete high school (pOR, 2.9; 95% CI = 1.8–4.6; $p < 0.001$), enroll in university (pOR, 1.9; 95% CI = 1.5–2.4; $p < 0.001$), and earn a university degree (pOR, 2.5; 95% CI = 1.8–3.5; $p < 0.001$) compared to individuals who had used cannabis before age 18. In related findings, Brook et al. (2002) reported that minority youths ages 10 to 19 years who used cannabis had higher rates of being suspended or expelled from school (aOR, 2.68; 95% CI = 1.73–4.14; $p < 0.001$).

Educational outcomes related to cannabis use tend to be confounded with the use of other substances, particularly tobacco/smoking cigarettes. Mokrysz et al. (2016) analyzed data from the Avon Longitudinal Study of

[1] Adjusted for non-Australian birth, symptoms of depression and anxiety in adolescence, high-risk alcohol use, and maximum level of cigarette smoking in adolescence.

Parents and Children, a propective study of 2,235 adolescents, 24 percent of whom reported using cannabis by the age of 15 years. When analyses included appropriate confounding variables (particularly tobacco use) even heavy (≥50 times) cannabis users (mean educational performance,[2] 69.2 percent; 95% CI = 65.0–73.3) did not significantly differ from never users in their educational performance at age 16 (mean educational performance, 80.8 percent; 95% CI = 80.2–81.4).

Similarly, McCaffrey et al. (2010) followed 4,500 adolescents for 4 years through high school and reported a positive association between cannabis use and dropout rates (OR, 5.6; risk ratio [RR] = 3.8). However, the remaining association (OR, 2.4; RR = 1.7) became statistically insignificant when the data were adjusted for cigarette use. Degenhendt et al.'s 2010 study found that occasional cannabis use was linked to lower educational outcomes (i.e., dropping out of school), but that the initial relationship was attenuated by tobacco use, which was relatively high in their sample. Green and Ensminger (2006) found that heavy use of cannabis during adolescence was associated with dropping out of school.

Discussion of Findings

Researchers have hypothesized and some studies have reported that cannabis use is linked to negative educational outcomes. However, the relationships among these variables are complex as are the ways in which the specific variables of interest are measured. In addition, all such research requires the careful consideration of a wide range of control variables that include sociodemographic confounders (e.g., gender/sex, family socioeconomic status [SES]) and educational confounds (e.g., parental education, intelligence quotient [IQ], student's cognitive ability) (Fergusson and Boden, 2008; Horwood et al., 2010). This complexity requires that researchers use sophisticated data-analytic techniques (e.g., propensity scoring to reduce confounding by measured factors) (McCaffrey et al., 2010). Use of less sophisticated approaches (e.g., correlations, logistic regression) can lead to an overestimation of the association between cannabis use and negative educational outcomes (McCaffrey et al., 2010). Typically, the primary literature cannot elucidate the mechanisms through which cannabis use may produce negative educational outcomes, although some have speculated that these outcomes may be related to cannabis's effects on the brain, including cognitive impairment.

In all of the primary research literature reviewed on the effects of cannabis on academic achievement, employment and income, as well as social relationships and other social roles, there were a number of

[2] Measured in percentage of General Certificate of Secondary Education points.

limitations. Below, we summarize aspects of various studies that make it difficult to draw definitive conclusions regarding the causal relationships among cannabis use and the different psychosocial outcomes that we examined. They include the following:

1. Sample heterogeneity (e.g., differences related to sample's SES, age, gender, ethnicity).
2. Inconsistent measures of cannabis use (yes/no; cross-sectional reports of frequency and/or quantity/amount; categories based on history of use).
3. Inconsistent/varying measures of the duration of cannabis use and outcome variables.
4. Even in longitudinal studies, the measures of interest often are cross-sectional snapshots.
5. The history and persistence of cannabis use is not always considered. In adolescence through adulthood, patterns of cannabis use can vary (groupings include consistent never users, occasional users, persistent heavy users, and so on).
6. In almost every study, the measure of cannabis use is based only on self-report, which cannot be validated.
7. Failure to consider individual characteristics (e.g., attitudes related to the outcomes of interest).
8. Multiple substances being used; it is difficult to separate out effects of cannabis relative to use of other drugs, including alcohol and smoking tobacco. Often cannabis effects are less strongly related to outcomes of interest.
9. The complexity of the relationships means that confounds must be considered and statistical analyses must be sophisticated. Many studies meet criteria for design and samples, but report outcomes based on less sophisticated analyses (e.g., correlations, logistic regressions).

CONCLUSION 11-2 There is limited evidence of a statistical association between cannabis use and impaired academic achievement and education outcomes.

EMPLOYMENT AND INCOME

Is There an Association Between Cannabis Use and Employment and Income?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and employment and income.

Primary Literature

The primary literature to be reviewed and summarized is based on studies published subsequent to 1999. In selecting that literature, the committee focused on studies that met criteria derived from the Newcastle–Ottawa criteria (Wells et al., 2014), as described in the previous section.

Popovici and French (2014) analyzed two waves of panel data from the nationally representative National Epidemiologic Survey on Alcohol and Related Conditions. Initial analyses suggested a significant association between cannabis and employment status (implying poorer labor market outcomes; also see Fergusson and Boden, 2008). However, more sophisticated (fixed-effect) data analyses that considered individual sources of heterogeneity resulted in smaller and less significant relationships between cannabis and unemployment for men and women (OR, 0.813; 95% CI = 0.237–2.791 and OR, 0.777, 95% CI = 0.269–2.239, respectively). The researchers concluded that cannabis use is less detrimental to labor market participation than was suggested in previous research. A similar conclusion was reached by Lee et al. (2015a), who found that cannabis use was not related to unemployment (OR, 0.96; 95% CI = 0.91–1.01), but rather that it is confounded with the use of other substances such as drinking alcohol and tobacco use, which are associated with unemployment.

There are some studies that suggest that the persistent use of cannabis over longer periods of time is associated with unemployment. Zhang et al. (2016) reported that chronic cannabis users (who started in adolescence) were more likely to be unemployed at age 43 (across three decades) than non/experimental users (aOR, 3.51; 95% CI = 1.13–10.91). Braun et al. (2000) also found cannabis users to be less likely to be employed than nonusers. Those who were employed tended to have lower prestige occupations (measured by the Occupational Prestige Score [OPS]; across 10 years) compared to nonusers. Some of this may be related to lessened commitment to work among those who use cannabis over time. Hyggen (2012) found low work commitment (as measured by the Work Involve-

ment Scale) among cannabis users compared to abstainers, starting from young adulthood (ages 17 to 20 years) through to middle age (early to mid-40s).

Some of the negative effects of cannabis use on unemployment may be exacerbated among those from low SES backgrounds (Lee et al., 2015a). Other studies of low SES and minority samples also report that chronic cannabis use is related to increased unemployment (Green and Ensminger, 2006; Lee et al., 2015b). Disentangling the effects of cannabis use from other variables related to having a low SES and/or a disadvantaged background may be fruitful areas for future research.

Discussion of Findings

All of the committee's conclusions are based on primary literature. In some cases, especially with more sophisticated data analyses, cannabis use has not been linked to outcomes such as labor market participation and unemployment. In other cases, a longer duration of cannabis use has been associated with unemployment. A lower SES may exacerbate these negative outcomes. Along with the limitations described on page 280, our examination of the literature on the relationship between cannabis use and employment was limited by the difficulty in determining causality. Because employment status is not static, it is possible that the relationships may be cyclical (e.g., depending on context, unemployment could contribute to the use of cannabis and other substances [Lee et al., 2015a] and cannabis/substance use could contribute to unemployment).

CONCLUSION 11-3 There is limited evidence of a statistical association between cannabis use and increased rates of unemployment and/or low income.

SOCIAL RELATIONSHIPS AND OTHER SOCIAL ROLES

Is There an Association Between Cannabis Use and Social Functioning and Social Roles?

Systematic Reviews

There was one systematic review that examined the effects of cannabis on social functioning as one of a number of outcomes in longitudinal studies of general population samples. In their systematic review, Macleod et al. (2004) identified 16 high-quality longitudinal studies of the general population in which the effects of cannabis use on psychosocial outcomes, including social functioning, were examined. The authors found that can-

nabis use was inconsistently related to social functioning as manifested by antisocial behaviors such as conduct disorder or delinquency, offending, and contact with police. Associations related to an individual's gender and ethnicity also produced inconsistent findings. Using data from the Christchurch Health and Development Study (n = 1,265), Fergusson et al. (1996) reported that cannabis use at younger ages (<15 years) was consistently associated with antisocial behavior (aOR, 1.0; 95% CI = 0.5–2.1). Interestingly, the use of tobacco and alcohol showed similar associations.

Primary Literature

The primary literature has shown that there is a statistical association between cannabis use and social functioning as manifested by negative relationships with others, but there are too few good-quality studies to provide conclusive evidence of causation. Palamar et al. (2014) examined various psychosocial outcomes in a nationally representative sample of high school seniors (n = 7,437) from the Monitoring the Future study. They found that participants who had used cannabis 40 or more times had compromised relationships with teachers, supervisors, and parents. Cannabis users reported less interest in activities and more trouble with police. Interestingly, the adverse psychosocial outcomes for cannabis were less than those for alcohol. In a sample of African American and Puerto Rican young adults, cannabis use was associated with rebelliousness and engagement with fewer productive activities (Brook et al., 2002).

Chassin et al. (2010) reported that in a sample of juvenile offenders, cannabis use in adolescence was inversely related to "psychosocial maturity" (i.e., a measure of responsibility, temperance, and perspective taking) in young adulthood (χ^2 (5) = 13.49, p = 0.02; comparative fit index [CFI] = 0.991, RMSEA = 0.038). Such maturity is integral to being able to successfully engage in social relationships and to transition into adult social roles. Interestingly, in some cases the temporal sequencing of cannabis use and maturity fluctuated over time, suggesting that these relationships were not static; increases in cannabis use were associated with reduced maturity, and reductions in cannabis use were associated with increases in maturity.

There is some evidence to suggest that a higher frequency and persistence of cannabis use or, in particular, cannabis use during adolescence is associated with some negative social outcomes. Among a low-income sample of 274 African Americans, Green and Ensminger (2006) found that "heavy" (>20 times) cannabis use during adolescence (i.e., before age 17 years) was associated with poorer functioning in some social roles at ages 32 to 33 years. Compared to never using or experimenting with cannabis, heavy cannabis use was associated with unemployment (ES, –0.159; 95%

CI = −0.303 to −0.155; p = 0.030) and to parenting outside of marriage (ES, 0.109; 95% CI = −0.042–0.261).

Discussion of Findings

In the systematic review and primary literature, the findings indicate inconsistent relationships between cannabis use and social functioning. The primary literature included studies in which there was a relationship between cannabis use and adverse outcomes such as compromised relationships with authority figures and poorer functioning in social roles such as employment and parenting. Various limitations faced by the primary literature are described on page 282.

Researchers have hypothesized—and some studies have reported—that cannabis use is linked to negative social functioning and the ability to appropriately handle social roles. The relationships among these variables are complex, as are the ways in which the specific variables of interest are measured. In addition, all such research requires the careful consideration of a wide range of control variables that include sociodemographic confounds (e.g., gender/sex, family SES), the use of other substances (alcohol, other illicit drugs), and psychological problems such as depression or a personality disorder (Macleod et al., 2004). This complexity requires that researchers use sophisticated data-analytic techniques (e.g., propensity scoring to reduce selection bias; see Chassin et al., 2010). The use of less sophisticated approaches (e.g., correlations, logistic regression) can lead to an overestimation of the association between cannabis use and negative social outcomes (Macleod et al., 2004).

CONCLUSION 11-4 There is limited evidence of a statistical association between cannabis use and impaired social functioning or engagement in developmentally appropriate social roles.

RESEARCH GAPS

To address the research gaps relevant to cognitive health and psychosocial functioning, the committee suggests the following:

- The systematic reviews that were reviewed by the committee did not necessarily parallel those in other fields of research that are covered in this report. As such, more studies that report quantitative data on the psychosocial effects of cannabis use are required to allow for a greater degree of comparison with the effects of cannabis use on the other health endpoints discussed in this report.

BOX 11-2
Special Consideration for Psychosocial Systematic Reviews

The qua ty assessment of the systemat c rev ews n th s chapter fo owed the methods used n th s report. Most of the systemat c rev ews focused on the terature on cogn t on (.e., earn ng, memory, attent on) as re ated to behav ora , neuropsycho og ca , and neuro mag ng find ngs (Bata a et a ., 2013; Broyd et a ., 2016; Grant et a ., 2003; Mart n-Santos et a ., 2010; Schre ner and Dunn, 2012). There was on y one systemat c rev ew (Mac eod et a ., 2004) that nc uded outcomes re ated to academ c ach evement/educat on and soc a funct on ng/soc a ro es. In the systemat c rev ews on cogn t on, t s mportant to note that the broad report ng standards for the fie d of behav ora , neuropsycho og ca , and neuro mag ng find ngs nc uded m tat ons re ated to the fa ure to cons stent y descr be the methods for scor ng the ev dence for each endpo nt. For examp e, w th n th s exam nat on of the terature, many systemat c rev ews fo owed the standards typ ca y used to eva uate find ngs from the pr mary terature. That s, the rev ews nc ude scores of the strength and cons stency of the ev dence for each outcome, but they prov ded ess nformat on about ssues such as study des gn and stat st ca ana yses. As a resu t, the rev ews d d not nc ude the convent ons genera y found w th n quant tat ve y based systemat c exam nat ons of a top c, or such as wou d be found n meta-ana yt c rev ews (e.g., emp r ca demarcat ons of synergy or d ssonance, as reported v a effect s zes and confidence nterva s). Reasons for th s may nc ude var at ons n study methodo og es, nstrumentat on, popu at ons, and research des gns, wh ch may be re at ve y more preva ent w th n psychosoc a research. Other reasons may reflect the re at ve y sma body of terature that meets the qua ty cr ter a for nc us on n the systemat c rev ew. For examp e, Broyd et a . (2016) eva uated 3,021 manuscr pts that y e ded a fina samp e of on y 105 manuscr pts that addressed the cogn t ve outcomes of nterest. The state-of-the-sc ence n such research often nc udes confounds that make t d fficu t to dent fy effects that unequ voca y can be nked to cannab s. Thus, research des gned to exam ne the mpact of cannab s on the deve op ng bra n often has to contend w th confounds re ated to po ysubstance use (wh ch s character st c of ado escent cannab s use), wh ch obscures the ab ty to answer quest ons about the effects of "cannab s on y" on the deve op ng bra n and cogn t ve funct on ng. In some cases, samp es nc uded d fferent popu at ons (ado escents versus adu ts), cannab s use h story (.e., chron c versus acute), and patterns of use (.e., frequency, dose, quant ty), a of wh ch prov de m xed or ncons stent ev dence as to the effects of cannab s on a spec fic outcome. In the r systemat c rev ew, Mac eod et a . (2004) noted that when ana yses were appropr ate y adjusted to address such confounds, there was a substant a decrease n the strength of assoc at ons between cannab s use and negat ve educat ona outcomes. S m ar conc us ons can be reached when exam n ng the terature n a broad range of top cs. A of these ssues prov de the bas s for recommendat ons regard ng future research on psychosoc a outcomes. The find ngs from such research w beg n to prov de the ev dence base for future systemat c rev ews and meta-ana yses that can better art cu ate the effects of cannab s on behav or and funct on ng.

- It will be necessary to conduct further research on the developmental implications of cannabis use across age groups, particularly among adolescents, children, and the older populations. While the National Institute on Drug Abuse's Adolescent Brain Cognitive Development study is in progress (see Box 11-2), at the time that this report was released, the findings of that study had not been published.

SUMMARY

This chapter summarizes the good- and fair-quality psychosocial literature published since 1999. The committee found that there is moderate evidence of an association between cannabis use and the impairment of the cognitive domains of verbal learning and attention but insufficient evidence for an association between cannabis use and the impairment of working memory. There is mixed evidence for the persistence of impairments or the recovery of function following an abstinence period of 24 hours or several weeks (25–32 days) without cannabis use in the domains of working memory, attention, and verbal learning (Broyd et al., 2016).

The committee found that it is difficult to document a direct link between cannabis use and negative educational outcomes because other variables play a role. There is some evidence to suggest that a higher frequency and persistence of cannabis use is associated with some negative educational outcomes. The age at which cannabis use is initiated may be important in determining negative educational outcomes. Educational outcomes related to cannabis use tend to be confounded with the use of other substances, particularly tobacco/smoking cigarettes. The primary literature has shown that there is an association between cannabis use and social functioning as manifested by negative relationships with others, but there are too few good-quality studies to provide conclusive evidence. There is some evidence to suggest that a higher frequency and persistence of cannabis use or cannabis use during adolescence is associated with some negative social outcomes. The literature provides limited evidence to support the hypothesis that cannabis use contributes to negative social functioning (e.g., conduct disorder, immature behavior) or to a failure to engage in developmentally appropriate social roles (e.g., marriage, parenting). The committee has formed a number of research conclusions related to these health endpoints (see Box 11-3); however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections.

BOX 11-3
Summary of Chapter Conclusions*

There is moderate evidence of a statistical association between cannabis use and:

- The mpa rment n the cogn t ve doma ns of earn ng, memory, and atten- t on (acute cannab s use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impa red academ c ach evement and educat on outcomes (11-2)
- Increased rates of unemp oyment and/or ow ncome (11-3)
- Impa red soc a funct on ng or engagement n deve opmenta y appropr ate soc a ro es (11-4)

There is limited evidence of a statistical association between *sustained abstinence from* cannabis use and:

- Impa rments n the cogn t ve doma ns of earn ng, memory, and attent on (11-1b)

* Numbers in parenthesis correspond to chapter conclusion numbers

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12

Mental Health

Chapter Highlights

- Cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use, the greater the risk.
- In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks.
- Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder.
- For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than for nonusers.
- Heavy cannabis users are more likely to report thoughts of suicide than are nonusers.
- Regular cannabis use is likely to increase the risk for developing social anxiety disorder.

The relationship between substance use and mental health has been a long-standing and complex public health issue. In 2014, a national survey from the Substance Abuse and Mental Health Services Administration found that 20.2 million adults had a substance use disorder, and of these

individuals, 7.9 million had both a mental health disorder and a substance use disorder (SAMSHA, 2015). These statistics emphasize the importance of conducting cross-disciplinary research in order to appropriately inform public health decisions and ultimately improve population health. In this chapter, the committee reviews the current evidence on the association between cannabis use and prioritized mental health outcomes.

The mental health outcomes selected for review in this report were derived from the committee's statement of task and the sponsors' expressed interest and based on committee consensus. Specifically, mental health outcomes with high prevalence (e.g., depression and anxiety disorders) were included, as were outcomes with significant public health implications such as suicide. Studies on the association between cannabis use and schizophrenia and psychosis were included based on the large volume of literature on the subject, and in an effort to evaluate cannabis effects across the mental health diagnostic spectrum, studies on the association between cannabis use and bipolar disorder were reviewed as well.

Concerning each disorder, the committee focused on two key questions: What is the effect of cannabis use on the risk of developing the disorder? And in patients with the disorder, what are the effects of cannabis use on the symptoms or course of the disorder? An initial search of the primary literature (see Appendix B) produced a substantial number of primary articles (e.g., cross-sectional studies, case-control studies, cohort studies, randomized controlled trials [RCTs], or nonsystematic literature reviews) for the committee to review. Due to the time constraints of the study, additional search constraints were added to zero in on the types of studies that would likely produce the clearest research conclusions. For example, for the health endpoints discussed below, literature searches were limited to articles that included the following search terms: longitudinal, prospective, and case-control.[1] The committee's review of the literature focused on identifying studies relevant to answering these specific questions. In this chapter the committee will discuss the findings from 14 of the most recent, good- to fair-quality systematic reviews and from 31 primary literature articles that best address the committee's research questions of interest.

It is important to note that the present review does not include findings from controlled laboratory studies. These studies have been used to assess the effect of cannabis on behavior, to understand how cannabis interacts with alcohol and other drugs to influence behavior, and to characterize the dose-dependent effects of cannabis as they relate to its

[1] The initial search of the primary literature produced a relatively small literature base for the posttraumatic stress disorder section, and as such, the additional search restrictions were not applied.

potential for addiction. Evidence from this body of research—though illuminating at the mechanistic level—does not provide information on the mental health effects of cannabis use in real-world conditions, and was excluded for this reason.

SCHIZOPHRENIA AND OTHER PSYCHOSES

Schizophrenia spectrum disorders and other psychotic disorders are mental health disorders characterized by three different classes of symptoms: positive symptoms (e.g., delusions, hallucinations, or disorganized or abnormal motor behavior), negative symptoms (e.g., diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia), and impaired cognition (APA, 2013, p. 87; NIMH, 2015). Evidence suggests that the prevalence of cannabis use among people with schizophrenia is generally higher than among the general population (McLoughlin et al., 2014). In most of the studies reviewed below, schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychotic disorders are used as aggregate endpoints. Therefore, conclusions regarding the association between cannabis use and psychosis are in general not diagnosis specific.

Is There an Association Between Cannabis Use and the Development of Schizophrenia or Other Psychoses?

Systematic Reviews

Five systematic reviews of fair or higher quality were identified that addressed the committee's research question (Large et al., 2011, Marconi et al., 2016, Moore et al., 2007, Myles et al., 2012, van der Meer et al., 2012). While the systematic review by Marconi et al. was the most recent, it excluded studies that did not consider at least three levels of cannabis exposure because the researchers' main purpose was to address dose–response relationships. In addition to reporting on the systematic review by Marconi et al., the systematic review conducted by Moore et al. is also discussed.This study addressed the broad question of cannabis use and psychotic outcome and included meta-analysis results. The remaining systematic reviews, which are not reported on here, focused on the time to onset of psychosis (or the age of onset of psychosis), the role of concomitant tobacco use, and psychotic symptomatology in patients at high risk of psychosis.

The systematic review by Marconi et al. (2016) included a search of the literature through December 31, 2013, and selected 10 studies for inclusion in the meta-analysis. A key feature of the researchers' inclusion criteria

was the requirement that studies assess cannabis use with a dose criterion and classify cannabis use into at least three exposure groups. Thus, high-quality studies with cannabis assessed as a dichotomous variable were excluded from the analysis. Studies that reported psychotic symptoms on a continuous, rather than categorical, scale were also excluded from the analysis. The 10 studies reviewed were conducted in Australia, Europe, New Zealand, and the United States and reported results for 66,816 individuals. The age and sex of the subjects were not reported. Cannabis use was classified based on lifetime frequency, the frequency of use at baseline, the duration/frequency of current use, and frequency within the last year. The authors did not assess the quality of the papers included in the meta-analysis, but they did conduct analyses to assess publication bias and heterogeneity. They considered the publication bias to be low and acknowledged the existence of heterogeneity within their sample of studies. Marconi et al., (2016) found an association between cannabis use and psychosis (odds ratio [OR], 3.9; 95% confidence interval [CI] = 2.84–5.34) among the most severe cannabis users, as compared to the nonusers. The investigators also report a dose–response relationship with an OR of 1.97 (95% CI = 1.68–2.31) for those at the median of any cannabis use and an OR of 3.40 (95% CI = 2.55–4.54) for those in the top 20 percent of cannabis use. In addition, they reported associations of cannabis use with the presence of psychotic symptoms (pooled odds ratio [pOR], 3.59: 95% CI = 2.42–5.32), as well as with a diagnosis of schizophrenia or psychotic disorder (pOR, 5.07; 95% CI = 3.62–7.09). Subgroup analysis stratified by study design revealed a pOR of 3.99 (95% CI = 2.50–6.37) for cross-sectional studies and 3.83 (95% CI = 2.34–6.29) for cohort studies.

Moore et al. (2007) searched multiple databases from their inception through September 2006 and included only studies that were longitudinal, population-based, or case-control studies nested within longitudinal designs. They assessed study quality by recording information on sampling strategy, response rates, missing data, attrition, attempts to address reverse causation, intoxication effects, and other potential confounders. Their search identified 32 studies, with 11 studies reporting the incidence of psychosis from 7 cohort studies, 5 of which were adult population–based cohorts and 2 of which were birth cohorts. They found no evidence of the presence of publication bias using Egger's test ($p = 0.48$). The authors noted that some individual studies adjusted for psychotic symptoms at previous assessments or baseline and excluded people with psychotic symptoms or diagnosis at baseline to help clarify the temporal order of events. The authors also noted that individual studies excluded psychotic symptoms that arose solely from drug use by using scales to measure drug intoxication. In addition, this group of studies collectively adjusted for approximately 60 different potential confounders, including

other substance use, personality traits, sociodemographic markers, intellectual ability, and other mental health problems. In a pooled analysis, the authors found that in individuals who have ever used cannabis, there was an associated increased risk of a psychotic outcome (adjusted odds ratio [aOR], 1.41; 95% CI = 1.20–1.65). When the analysis was restricted to studies examining the effects of frequent cannabis use, the investigators found a stronger association (aOR, 2.09; 95% CI = 1.54–2.84), suggesting a dose–response relationship between cannabis use and the risk of a psychotic outcome.

Primary Literature

Auther et al. (2015) used the North American Prodrome Longitudinal Study[2] phase 1 sample to examine the impact of the level of cannabis use on conversion to psychosis.[3] From the subjects who contributed to the data, 370 were determined to be at a high risk for developing a psychotic disorder. After excluding subjects who were missing necessary outcome data—or who met criteria for attenuated positive symptom syndrome, brief intermittent psychotic syndrome, genetic high risk, and deterioration syndrome—a total of 283 subjects (mean age = 18.3 years) were included in the study's analysis. Using the subjects' reported level of lifetime use, subjects were divided into three subgroups: no use, use without impairment, and abuse and dependence. The primary outcome, conversion to psychosis, was determined by meeting the full criteria for Presence of Psychotic Syndrome on the Structured Interview for Prodromal Syndrome. In a follow-up assessment (approximately 17 months after the initial baseline assessment), the researchers found that cannabis abuse/dependence was associated with a greater risk of conversion to psychosis within the chronic high-risk population; however, when alcohol use was incorporated into the Cox regression model, cannabis abuse/dependence was no longer significantly related to conversion (hazard ratio [HR], 1.875; 95% CI = 0.963–3.651). Similar research conclusions were reached in a longitudinal study by Valmaggia et al. (2014), where they examined the association between lifetime cannabis use and the development of psychosis. Valmaggia et al. (2014) followed 182 individuals at ultra-high risk for psychosis disorder for 2 years and found that varying degrees of cannabis use (i.e., frequent use, early-onset use, and continued use

[2] The North American Prodrome Longitudinal Study is a collaborative database formed in 2007. The database contains data on various clinical, cognitive, and functioning variables collected from eight independent research centers.

[3] Auther et al. (2015) defined this outcome as having a psychotic level positive symptom that is either seriously disorganizing or dangerous, or that occurs for at least 1 hour per day for an average of 4 days in the past month.

after presentation) among lifetime cannabis users is associated with an increased transition to psychosis. It is of note, however, that within this specific ultra-high risk population, cannabis users were no more likely to develop psychosis than were those who had never tried cannabis.

Using a case-control design of 410 patients with first episode psychosis and 370 population controls, Di Forti et al. (2015) showed that first-episode psychosis patients were more likely to have lifetime cannabis use, more likely to use cannabis every day, and to mostly use high- potency cannabis as compared to the controls. The cases were also more likely to have used cannabis before the age of 15. Duration of use did not differ between patients and controls, nor did other drug use. After adjusting for a variety of confounders, including use of other drugs and alcohol, the researchers found an increased risk of developing psychosis in subjects who used cannabis daily (OR, 3.04; 95% CI = 1.91–7.76) and in subjects who used high-potency cannabis (OR, 2.91; 95% CI = 1.52–3.60). In a cross-sectional study of subjects with first-episode psychosis, Colizzi et al. (2015) examined the association between cannabis use, the risk of psychosis, and the dopamine receptor type 2 (DRD2) polymorphism rs1076560. Researchers found, after adjusting for confounders (e.g., gender, age, ethnicity, polysubstance use), a significant interaction between lifetime frequency of cannabis use and DRD2 polymorphism rs1076560 on psychosis risk. Moreover, a lifetime history of cannabis use was associated with an increased risk of having psychotic disorder in T-carrying subjects, relative to GG carrying subjects (OR, 3.07; 95% CI = 1.22–7.63).[4]

Discussion of Findings

The association between cannabis use and the development of a psychotic disorder is supported by data synthesized in several good-quality systematic reviews. The magnitude of this association is moderate to large and appears to be dose-dependent, and it may be moderated by genetic factors. Factors contributing to the strength of the evidence derived from the cited systematic reviews include large sample sizes, the relative homogeneity of the findings, the presence of relationships between the dose/exposure and the risk, the studies having been controlled for confounders, and the systematic reviews having assessed for publication bias. The primary literature reviewed by the committee confirms the conclusions of the systematic reviews, including the association between cannabis use

[4] T-carrying subjects have at least one allele with the polymorphism. G-carrying subjects do not express the polymorphism. Genotype results of the subjects included homozygote G/G, heterozygote G/T, and homozygote T/T genotype classes. Due to the low number of TT subjects, GT and T/TT subjects were combined and compared to GG carriers.

and psychotic outcome and the dose-dependency of the effects, further bolstering the overall strength of evidence for our conclusions.

The limitations of the summarized studies include their reliance of self-report for cannabis use, issues with study designs (e.g., a lack of randomization), a lack of information on the frequency of use, patterns of long-term use, and possible confounding polysubstance effects. In addition, for the primary studies cited, some are also limited in terms of their sample sizes and controlling for confounders. Overall, the accumulated evidence is suggestive that cannabis use is associated with an increase in psychosis-related outcomes, as made evident in the discussion of Auther et al. (2015) and Valmaggia et al. (2014) above.

As noted in Box 12-1, the relationship between cannabis use and cannabis use disorder, and psychoses may be multidirectional and complex. The committee found this to be consistent with their review of the summarized data demonstrating a strong and consistent association between cannabis use and the subsequent development of psychosis and psychotic disorders. In addition, it is noteworthy to state that in certain societies, the incidence of schizophrenia has remained stable over the past 50 years despite the introduction of cannabis into those settings (Kirkbride et al., 2012); however, the committee did not examine ecologic data (studies of concomitant time trends) to evaluate trends in cannabis consumption and diagnosis of psychosis over time. Multiple factors (including measurement of dose and frequency of cannabis consumption over decades, and patterns of diagnosis of psychosis) limit our ability to draw conclusions from such findings. Of note, future analysis of rates of psychosis in states with increased access to cannabis could be tracked to provide valuable information regarding potential causal relationships between cannabis use and psychosis.

CONCLUSION 12-1 There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.

BOX 12-1
Comorbidity in Substance Abuse and Mental Illness

Nat ona survey stud es suggest that t s not uncommon for nd v dua s w th menta hea th d sorders to use substances of abuse and, kew se, that t s not uncommon for nd v dua s who abuse or are dependent on drug substances to a so meet d agnost c cr ter a for a menta hea th d sorder. In fact, n a 2014 na- t ona survey, a most 8 m on adu ts n the Un ted States reported co-occurr ng substance abuse and menta hea th d sorders. Th s co-occurrence s a so termed *comorbidity*.

There are a number of proposed exp anat ons for why the comorb d ty of sub- stance abuse and menta hea th d sorders ex sts. Three of the most common y exp ored hypotheses are:

1. *Substance use may be a potential risk factor for developing mental health disorders.* G ven the over ap n assoc ated neurochem ca substrates (e.g., dopam ne, seroton n), spec fic neurob o og ca a terat ons due to drug use may have resu t ng effects on the neura processes regu at ng menta hea th.
2. *Mental illness may be a potential risk factor for developing a substance abuse disorder.* Research suggests that nd v dua s who are at r sk for a menta hea th d sorder, or those who exper ence subc n ca symptoms, may be more ke y than others to use drugs as a form of se f-med cat on.
3. *An overlap in predisposing risk factors (e.g., genetic vulnerability, environment) may contribute to the development of both substance abuse and a mental health disorder.* Stud es suggest that the deve opment of menta hea th d sorders and substance abuse d sorders may be a symptomat c outcome of preex st ng neurob o og ca abnorma t es (e.g., receptor abnor- ma t es, ep genet c mod fcat ons).

A though the prec se exp anat on s st unc ear, t s reasonab e to assume that comorb d ty between substance abuse and menta hea th d sorders may oc- cur due to a m xture of proposed scenar os. W th th s context n m nd, however, t s mportant to note that the ssue of comorb d ty d rect y affects the ab ty to determ ne causa ty and/or d rect ona ty n assoc at ons between substance use and menta hea th outcomes. Th s s a comp ex ssue, one that certa n y warrants further nvest gat on.

SOURCES: CBHSQ, 2015; EMCDDA, 2016; NIDA, 2011.

Is There an Association Between Cannabis Use and the Course or Symptoms of Schizophrenia or Other Psychoses?

Systematic Reviews

Positive Symptoms One systematic review was identified that assessed the effects of cannabis use on positive symptoms[5] in patients with psychotic disorders, but the researchers did not conduct a quantitative synthesis of the findings (Zammit et al., 2008). An additional systematic review (Szoke et al., 2014) addressed the effects of cannabis on schizotypal symptom dimensions; however, the committee will report only on the conclusions reported by Zammit et al. (2008) because they provide information about patients with psychotic disorders rather than schizotypy.

After their assessment of the literature, Zammit et al. (2008) found mixed evidence for the effects of cannabis use on positive symptoms in patients with psychotic disorders, with studies reporting statistically significant but small associations between cannabis use and the severity of positive symptoms. The authors searched multiple databases through November 2006, screened 15,303 references, and identified 13 cohort studies (n = 1,413) for their review. Studies were included if they were longitudinal or were case-control studies nested in longitudinal designs to assure that cannabis use was measured before outcome ascertainment. The authors excluded cohorts of individuals with dual diagnoses (psychosis and cannabis misuse or dependence) because of the limitations on comparisons to control groups. The authors assessed the quality of the studies by comparing the response rate at baseline, loss to follow-up, masking of outcome assessment, adjustment for baseline severity, adjustment for alcohol and other substances, and adjustment for confounders. Their quality assessment is reported in a summary table, and the authors noted that the most likely source of confounding would be the lack of adjustment for baseline severity and a lack of adjustment for alcohol and other substances in several of the studies. The authors did not report sample sizes, the age or sex of the study participants, or the definitions of cannabis use. The authors noted that several of the reviewed studies varied in their consideration of confounders, such as the use of other substances and baseline symptom severity, and that the lack of an association may be explained by a random misclassification of exposure data, particularly self-reports of cannabis use.

[5] Positive symptoms of schizophrenia may include delusions, hallucinations, or abnormal motor behavior.

Negative Symptoms In the systematic review described above, Zammit et al. (2008) identified 4 studies (from the 13 cohort studies identified in the larger systematic review) that assessed the effects of cannabis use on negative symptoms[6] in patients with psychotic disorders. Zammit et al. (2008) did not conduct a quantitative analysis of findings; in their review however, they found that cannabis use was not associated with negative symptom scores in three studies, but it was associated with reduced negative symptom scores in a fourth study. It should be noted that the fourth study did not control for confounders or baseline differences in symptoms.

Cognition Three systematic reviews were identified that assessed the relationship between cannabis abuse and dependence and cognition effects (e.g., disorganized thinking) in patients with psychotic disorders (Donoghue and Doody, 2012; Rabin et al., 2011; Yucel et al., 2012). A distinctive feature of this group of studies is the varying approaches to separating cannabis use from other substances. While the systematic review by Donoghue and Doody (2012) reported on all types of illegal substance abuse, it identified a subgroup of three studies focusing on cannabis use. This is in contrast to the work of Yucel and colleagues (2012) who included studies with patient groups who abused substances other than cannabis, and by Rabin et al. (2011), who considered cannabis use without other substance use but relied on cross-sectional studies only.

Donoghue and Doody (2012) conducted a search for relevant studies published between 1980 and October 2010, and from an initial pool of 7,075 studies, the authors selected 19 studies for further review. Three of the 19 studies focused on cannabis use. The three studies (n = 551) used the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria to define cannabis abuse or dependence, and DSM-IV criteria to define schizophrenia or schizoaffective disorders. All three studies included inpatients and outpatients, as well as patients with a dual diagnosis. In their review of these studies, the authors found that cannabis users performed better on various measures of cognition, including verbal learning and memory, attention and psychomotor, and global cognitive factor tests, than did non-cannabis users. The authors conducted a meta-analysis of the three studies and reported statistically significant associations between cannabis use and verbal learning and memory (Hedges g[7] = 0.351, 95% CI = 0.179–0.523), attention and psychomotor

[6] Negative symptoms of schizophrenia may include diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia.

[7] Hedges g reports the unbiased estimate of the effect size (the standardized difference between two means). It is commonly used for small sample sizes.

speed (Hedges g = 0.316, 95% CI = 0.144–0.488), and global cognitive factor (Hedges g = 0.237, 95% CI = 0.083–0.390). Tests of association with working memory and executive function were not statistically significant.

Rabin et al. (2011) conducted a meta-analysis on 8 cross-sectional studies, published between 2005 and 2010, with a total of 942 patients with schizophrenia. The 356 cannabis users among those patients had a mean age of 28.7 years, a mean education of 11.4 years, and 81.9 percent were male. Of the 942 patients, 586 were nonusers of cannabis and had a mean age of 32.4 years, a mean education of 12.2 years, and 65.8 percent were male. Limited information was provided about the statistical analysis, and the authors reported moderate associations with cannabis users performing better on general cognitive ability and intelligence; selective, sustained and divided attention; and visual-spatial and constructional abilities.

Yucel et al. (2012) searched the literature for the period between 1987 and March 2010 and included studies where cannabis was the predominant substance used by patients. They identified 10 studies involving 572 patients with schizophrenia; the studies were stratified by lifetime versus current or recent use. From their review, Yucel et al. (2012) found that patients with established schizophrenia and a history of cannabis use showed better performance on tests assessing cognitive abilities than did patients who did not use cannabis. For example, the meta-analysis conducted on 10 studies to assess global cognition resulted in a Cohen's d[8] of 0.35 (95% CI = 0.09–0.61; p = 0.009), showing small to moderate increases in performance in cannabis users compared to nonusers. Other small to moderate statistically significant effects were observed, again showing better performance by cannabis users compared to nonusers for processing speed, visual memory, and planning, despite the smaller number of studies available for these comparisons. The authors stated that tests for publication bias or heterogeneity were conducted, but these were only partially reported. No differences were reported for assessments of attention, verbal memory, or working memory.

Primary Literature

Positive Symptoms In a 2004 case-control study with schizophrenic patients, Rehman and Farooq (2007) determined that patients with cannabis abuse had higher rates of positive symptoms than nonusers. Seddon et al. (2016), in a case-control study examining cannabis use in the first year following a first-episode psychosis, found that cannabis use at baseline

[8] Cohen's d is an estimate of the effect size (the standardized difference between two means).

or the 1-year assessment was associated with greater severity of positive symptoms (as measured by the Positive and Negative Syndrome Scale [PANSS], 2.14; 95% CI = 1.41–2.88) and a decrease in global functioning (as measured by the Global Assessment of Functioning symptom scale [–3.27; 95% CI = -–6.04 to –0.49]). In contrast, Barrowclough et al. (2013) found no association between cannabis use and positive symptoms in patients with non-affective psychotic disorders, as assessed by PANSS (adjusted coefficient = 0.07; 95% CI = –0.21–0.34). Moreover, using a longitudinal analysis over 24 months, the researchers found that changes in cannabis dose did not predict changes in positive symptoms severity, even when patients became abstinent. In their study, the researchers conducted a cross sectional analysis of 160 patients with a clinical diagnosis of non-affective psychotic disorder and a DSM-IV diagnosis of drug and/or alcohol dependence or abuse. Notable strengths of this study are its dose–response analysis and its detailed quantification of cannabis use, with mean use in the sample being 4 days per week and an average of 2.4 grams per day. However, the results were not adjusted for confounders, including other drug use.

Another study, Dubertret et al. (2006) conducted a cross-sectional analysis on 205 patients with schizophrenia (n = 121 with no substance abuse; n = 38 cannabis users) and found that after controlling for other substance use, no association between cannabis use and positive symptoms was evident. A cross-sectional analysis by Tosato et al. (2013) (n = 311 patients) found no association between cannabis use and the severity of positive symptoms in a population of first-episode psychosis patients. Similarly, in a prospective, longitudinal cross-sectional study by Barrowclough et al. (2015), the authors found no specific association between cannabis dose and positive symptoms (n = 102; adjusted coefficient, 0.01; 95% CI = –0.24–0.25), and reductions in cannabis use during follow-up (longitudinal analysis up to 18 months) were not associated with improvements in positive PANSS symptoms in cannabis-using subjects after adjusting for confounders, including other drug use (n = 65; adjusted coefficient, –0.12; 95% CI = –0.45–0.22). After adjustment for confounders, abstinence from cannabis (90 days preceding the assessment) was found to be related to improved global functioning (adjusted coefficient, 4.95; 95% CI = 0.46–9.44). After controlling for confounders, van Dijk et al. (2012) found no difference between cannabis users (n = 68) and nonusers (n = 77) with schizophrenia with regard to the severity of baseline schizophrenia symptoms (p = 0.61; assessed by the Clinical Global Impression scale). The researchers also found no relationship between amount of cannabis used and the level of psychopathology (p = 0.676; as measured by PANSS).

Negative Symptoms Dubertret et al. (2006), using a cross-sectional analysis, found that after controlling for other drug substances, cannabis use was strongly associated with fewer negative symptoms of avolition—apathy ($p = 0.0001$)—as compared to non-cannabis users. Barrowclough et al. (2013), also using a cross-sectional analysis, found that previous 90-day cannabis use was not significantly associated with the severity of negative symptoms (adjusted coefficient, 0.12; 95% CI = –0.05–0.29). The longitudinal analysis of data from this cohort (up to 24 months) revealed no association between cannabis dose and negative symptom severity (adjusted coefficient, 0.18; 95% CI = –0.14–0.51). Similarly, a prospective longitudinal study by Barrowclough et al. (2015) found no association between cannabis dose and negative symptoms after adjustment for confounders, including other drug use (adjusted coefficient, 0.28; 95% CI = –0.04–0.61). Seddon et al. (2016) found that cannabis use at baseline or the 1-year assessment was not associated with differences in negative symptoms relative to nonusers (as measured by PANSS; –0.07; 95% CI = –1.11–0.97).

Cognition Power et al. (2015) found no association between lifetime cannabis use or cannabis dependence and cognitive function after controlling for confounding variables, including the onset of illness and comorbid cognitive functioning in Australian patients with an established *International Classification of Diseases-10* (ICD-10) diagnosis of psychotic disorder. Sanchez-Torres et al. (2013) used a longitudinal study to examine the impact of lifetime and current cannabis use on cognition in 42 patients with schizophrenia and found a negative effect of longitudinal cannabis use specifically in the social cognition domain (Pearson correlation, –0.34; $p < 0.05$). van Winkle et al. (2011) found that cannabis use before the onset of psychosis interacted significantly with the rs2494732 single nucleotide polymorphism of the AKT1 gene to affect patient reaction time and accuracy as measured by the Continuous Performance Test. Cannabis-using patients with the a priori vulnerability (i.e., homozygous for the polymorphism) were slower and less accurate on the CPT than nonusers.

Discussion of Findings

With regard to the effects of cannabis use on positive symptoms, the data are considered mixed. Studies report both worsening and no effect of cannabis use on positive symptoms in schizophrenia. The limitations observed in the reviewed studies included variable adjustment for other drug use and baseline symptom severity; issues with study design (observational); a reliance on self-reports; and variable analyses of cannabis use (i.e., dose/amount/frequency, current versus lifetime). However, these

studies, combined with human experimental studies demonstrating that cannabis can worsen positive symptoms in patients with schizophrenia, were also considered when determining the strength of evidence. With regard to negative symptoms, the data reviewed were generally more homogenous, with most studies reporting either an absence of association between cannabis use and negative symptoms or else reduced negative symptoms in cannabis users. Variable adjustments for other drug use and baseline symptom severity were noted as limitations in some studies. Overall, the data provide support for the conclusion that cannabis use does not worsen negative symptoms in patients with psychotic disorders. With regard to cognition in patients with psychotic disorders, the data reviewed in the systematic reviews suggest better cognitive performance in some cognitive domains in patients with psychotic disorders and cannabis use disorders, and in patients with a history of cannabis use, as compared to patients with psychotic disorders and no cannabis use disorder diagnosis. The limitations of two of the systematic reviews—Yucel et al. (2012) and Rabin et al. (2011)—include their study design (cross-sectional only); variable adjustments made for confounders, including other drug use; and variable definitions and inclusion criteria for cannabis using and non-using control groups. This study found better cognitive performance only in subjects with a lifetime history of cannabis use, but not recent cannabis use. The systematic review by Donoghue and Doody (2012) focused on longitudinal studies in schizophrenic subjects with and without comorbid cannabis use and found that cannabis users performed better on some measures of cognition, including verbal learning and memory, attention and psychomotor speed, and global cognitive factor tests, than non-cannabis users. The three reviewed studies showed similar effects; however, the largest study was more precise and had narrower confidence intervals. Estimates for the size of the effect are small to moderate. The primary articles reviewed indicate more mixed results than the systematic reviews.

Overall, the totality of data favor the conclusion that a history of, but not recent, cannabis use is associated with statistically significant performance improvement on measures of cognitive function in patients with psychotic disorders. It is not clear how the difference in scores might translate with respect to overall improved outcomes in functioning beyond the test setting. Furthermore, other data do not support the notion that acute cannabis exposure improves cognitive performance in patients with psychotic disorders, as acute intoxication is associated with impaired cognitive performance in cognitive domains of memory, learning, and attention (see Chapter 11). Among the multiple potential explanations of the data indicating better performance on certain measures of cognition in patients using cannabis are that these patients represent a higher-functioning sub-

group of psychotic patients or that cannabis users who achieve abstinence have better premorbid cognitive status. Additionally, it has been proposed that a history of cannabis use may have exerted neuroprotective effects in patients with psychotic disorders. Finally, we find insufficient data from which to draw conclusions regarding the effects of cannabis on risk for suicide in patients with psychotic disorders.

CONCLUSION 12-2

12-2(a) There is moderate evidence that, among individuals with psychotic disorders, there is a statistical association between a history of cannabis use and better cognitive performance.

12-2(b) There is limited evidence of a statistical association between cannabis use and an increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders.

12-2(c) There is moderate evidence for no statistical association between cannabis use and worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders.

BIPOLAR DISORDER

Bipolar and related disorders are categorized by episodes and/or symptoms of mania, hypomania, and depression (APA, 2013). The risk factors for developing bipolar disorder are not clear; however, research suggests that brain structure, genetics, and family history may contribute to its onset (NIMH, 2016). Given that cannabis is reportedly the most commonly used illicit drug by individuals with bipolar disorders (Zorrilla et al., 2015), it is worthwhile for this report to explore the potential association between cannabis use and the development and course of bipolar disorder.

Is There an Association Between Cannabis Use and the Development of Bipolar Disorder or Mania?

Systematic Reviews

The committee identified one systematic review, Gibbs et al. (2015), that assessed the association between cannabis use and bipolar disor-

der or mania. The authors searched multiple databases for English language studies published through 2014 and included studies that were experimental, prospective, cohort, or longitudinal. The overall search strategy yielded six studies with a total of 14,918 participants who met the inclusion criteria. Two of these studies, published in 2006 (n = 4815) and 2010 (n = 705), were used in the analysis. The meta-analysis showed an association between cannabis use and new onset of manic symptoms in individuals without preexisting bipolar disorder (OR, 2.97; 95% CI = 1.80–4.90). However, the researchers did not report information about the patient characteristics, the total number of subjects, age, gender, cannabis form, the ascertainment of mania symptoms, or other features of the two studies. Furthermore, due to the low number of studies that contributed to their research findings, the authors describe their conclusions as preliminary and tentative.

Primary Literature

Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)[9] (Feingold et al., 2014) found that any past-year use of cannabis was associated with the onset of bipolar disorder (OR, 2.24; 95% CI = 1.44–3.51) in unadjusted analyses. However, after adjusting for sociodemographic and clinical variables, the association was attenuated and no longer statistically significant (aOR, 1.17; 95% CI = 0.65–2.11).

Using the same NESARC dataset as Feingold, Cougle and colleagues (2015)[10] found that the risk of a past-year bipolar disorder diagnosis was elevated in regular (e.g., weekly use) cannabis users at Wave 2 follow-up: (OR, 1.37; 95% CI = 1.11–1.69). Cougle and collaborators (2015) reminded readers about the correlational nature of the study design and noted that causality could not be inferred from their conclusions. They also cautioned that the increased risk in bipolar disorders might be due to augmenting the psychotic features in frequent cannabis users (i.e., manic symptoms) that need further investigation. Also, Cougle and collaborators (2015) warned that in adjusting for other psychiatric comorbidities they only adjusted for those that fulfilled diagnostic thresholds, not other psychiatric symptoms that could explain the relationships of interest.

[9] The NESARC is a longitudinal and nationally representative survey. Data on psychiatric disorders and quality of life were assessed from two waves of subjects. Wave 1: 2001–2002, n = 43,093; Wave 2: 2004–2005, n = 34,653.

[10] Cougle et al. (2015) and Feingold et al. (2014) used the same dataset, but they chose to use different outcome variables: one analyzed past-year cannabis use, while the other examined past-year weekly cannabis use.

Discussion of Findings

Overall there is some evidence to support the association between cannabis use and the increased incidence of bipolar disorders. Although there is support for this association, more information is needed on the potential mediators that could explain the relationship as well as whether the risk is likely to occur only in conjunction with the use of other substances such as alcohol or nicotine. For example, panel studies that have evaluated the relationship found the magnitude of the relationship to be similar, but once alcohol or other substances were adjusted for in the statistical models, the associations diminished or became insignificant. This suggests that the constellation of behaviors that includes the use of cannabis, alcohol, and other substances might all play roles in the risk for bipolar disorders, with those different roles being difficult to disentangle. See Box 12-1 for additional discussion on the complex relationship between substance use and mental health disorders.

CONCLUSION 12-3 There is limited evidence of a statistical association between cannabis use and the likelihood of developing bipolar disorder, particularly among regular or daily users.

Is There an Association Between Cannabis Use and the Course or Symptoms of Bipolar Disorder?

Systematic Reviews

The committee identified Gibbs et al. (2015) as a systematic review that assessed the relationship between cannabis use and the course, symptoms, or other endpoints in individuals with bipolar disorder. Gibbs et al. (2015) concluded, based on their narratives of three studies, that cannabis use may worsen the course of bipolar disorder by increasing the likelihood, severity, or duration of manic phases. Their narrative summarizes the findings of the three studies: the duration of active cannabis use was associated with duration of mania syndrome/symptoms; cannabis use within a quarter (3-month time period) was associated with manic symptoms or episodes; and a report of "any cannabis use" was associated with mania symptoms over 1 year in a sample of 3,426 inpatients and outpatients. The three studies were published in 2000, 2008, and 2009. The studies used clinical samples of 50 new-onset bipolar patients ages 16 to 54, 166 first-episode DSM-IV bipolar I patients ages 18 to 72, and 3,426 bipolar inpatients and outpatients (age not reported). No other information (gender, country, etc.) about the study populations was reported.

Primary Literature

Zorrilla and colleagues (2015), using the European Mania in Bipolar Longitudinal Evaluation of Medication study (n = 1,922 patients), showed that previous users of cannabis had similar outcomes to never users (all $p > 0.05$) in terms of bipolar disorders, whereas current users had lower rates of recovery ($p = 0.004$) and remission ($p = 0.014$) and higher rates of recurrence of bipolar disorder ($p = 0.014$). They also demonstrated that the median time to remission was longer in the current cannabis use group (571 days, 95% CI = 539–588) compared with the other two groups (never users: 236 days, 95% CI = 209–345; previous users: 189 days, 95% CI = 1.5–357), while the times to relapse and recurrence were shorter in current use group. Using Cox regression models, Zorrilla and colleagues (2015) found that cannabis use (versus no use) was associated with time to recovery (HR, 0.53; 95% CI = 0.298–0.959), relapse (HR, 1.61; 95% CI = 1.116–2.316), and recurrence (HR, 1.67; 95% CI = 1.206–2.320). However, when alcohol and other substance use variables were included in the model as confounders, only the time to recurrence remained significantly associated with cannabis use (HR, 1.47; 95% CI = 1.030–2.092).

Using the NESARC data with two waves, Feingold et al. (2014) examined the relationship between weekly cannabis use and almost daily cannabis use and found a steady association with the incidence of mania/hypomania symptoms in all adjusted models (OR, 2.47; 95% CI = 1.03–5.92). In contrast, daily cannabis use was not associated with mania/hypomania symptoms (OR, 0.52, 95% CI = 0.17–1.55).

Discussion of Findings

The evidence on the association between cannabis use and the course and symptoms in patients with bipolar disorder is modest, but it is suggestive that cannabis use moderates the course of bipolar disorder by increasing the time to recovery, relapse, and recurrence of manic phases. As discussed in the section above, when adjustments for alcohol and other substance use variables are included in the model as confounders, only the time to recurrence remains as significantly associated to cannabis use. There is also moderate evidence that weekly cannabis use to almost daily cannabis use can lead to the onset of mania/hypomania symptoms in adjusted models, but there is less evidence of this association for daily users of cannabis. The authors report that, given the inconclusive nature of the relationship between very frequent cannabis use (daily/almost daily) or less than weekly cannabis use and the onset of mania/hypomania symptoms in adjusted models (i.e., dose–response), other factors that have not been identified might mediate the relationship. The authors suggest that part of the problem of being able to find a conclusive

relationship between the frequency of cannabis use and mania or hypomania symptoms might be due to the resemblance of mania and hypomania symptoms to psychotic symptoms, making it difficult to discriminate between these types of symptoms. It should also be noted that in some of the studies reviewed above, the analyzed patient populations were undergoing treatment for bipolar disorder, adding an additional layer of limitations to the research findings.

In reviewing the literature on the relationship between cannabis use and bipolar disorder, the committee identified various limitations in the studies discussed above, including a lack of biogenetic covariates that could relate to both cannabis use and bipolar disorders, as well as other psychological symptoms that are not adjusted in these studies. Many of these studies do not take into account the variance among the subtypes of cannabis or in the potency or route of administration, all of which could lead to difference in results. Also, the lack of precision in measuring the frequency of cannabis use at baseline and in measuring follow-up data remains a problem.

CONCLUSION 12-4 There is moderate evidence of a statistical association between regular cannabis use and increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders.

DEPRESSION

Depression is one of the nation's most common mental health disorders (ADAA, 2016). Across the many depressive disorders that exist (e.g., persistent depressive disorder, major depressive disorder, premenstrual dysphoric disorder) there are common symptomatic features of feelings of sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that affect the individual's capacity to function (APA, 2013, p. 155). The endocannabinoid system is known to play a role in mood regulation (NIDA, 2015); therefore, the committee decided to explore the association between cannabis use and depressive disorders or symptoms.

Is There an Association Between Cannabis Use and the Development of Depressive Disorders or Symptoms?

Systematic Reviews

The committee identified two systematic reviews that assessed the association between cannabis use and the risk of developing depressive

disorders or symptoms: Lev-Ran et al. (2013) and Moore et al. (2007). The most recent systematic review is discussed.

Lev-Ran et al. (2013) searched the published literature through 2012 and included studies with: population-based data that were collected longitudinally and prospectively; an exposure variable referring specifically to cannabis use (not "substance use"); outcome measures that referred specifically to depression—and not, for example, mixed anxiety–depressive symptoms; the outcome variable (depression) controlled for at baseline, or individuals with baseline depression being excluded; and data either presented as odds of developing depression following cannabis use or that allowed the OR to be calculated. When the authors identified multiple studies reporting on the same population cohort at different time points, only one study (the most recent) reporting on the respective cohort was included. The authors identified 14 studies published between 1977 and 2012. Seven were conducted in the United States, and one each were conducted in Australia, Canada, Colombia, the Netherlands, New Zealand, Norway, and Sweden. Sample sizes ranged from 736 to 45,087, with 10 of the samples having 1,000 or more participants. The ages of patients at cannabis assessment included high school age, subjects ages 12 to 17 or 12 to 16, and older groups ages 18 to 64. A wide range of measures were used to assess cannabis use: namely, any cannabis use in the previous 30 days; any previous cannabis use; cannabis use disorder; cannabis use one or more times per month; any cannabis use in the previous year or heavy use (at least once per week in the previous month); at least five previous occasions of cannabis use or heavy use (at least weekly); any use in the previous 6 months; or more than 4 occasions of use per month in a 5-year period. Studies also varied in the definition of comparison groups, with some studies contrasting any cannabis use to no cannabis use, and other studies comparing "heavy cannabis use" to a group with some or no cannabis use. Thus, the comparison group (lower level of exposure to cannabis) in the latter studies included nonusers, as well as individuals using cannabis less than weekly, or individuals not having a cannabis use disorder. Studies varied in their approaches to adjust for confounding factors, ranging from none to adjustment for more than 20 variables. One half of the studies accounted for other types of substance use and/or mental health issues as potential confounders. The analysis showed that cannabis use was associated with a small increase in risk for depressive outcome (pOR, 1.17; 95% CI = 1.05–1.30). The analysis further revealed a dose–response relationship, with a slightly higher OR observed in seven studies comparing heavy cannabis use to non-cannabis users (pOR, 1.62; 95% CI = 1.21–2.16).

Primary Literature

Although several primary research studies found a positive association, the confounding factors of polydrug use or unspecified cannabis use made it difficult for the committee to make conclusions on the overall findings (Brook et al., 2016; Nkansah-Amankra and Minelli, 2016; Rasic et al., 2013). Additional studies reviewed provided mixed findings on the association between cannabis use and depression or depressive symptoms (Crane et al., 2015; Gage et al., 2015; Silins et al., 2014; Wilkinson et al., 2016). A consideration of the confounding factors led to several of these mixed findings. For example, Sillins et al. (2014) published an analysis of interview data from three longitundal studies from Australia and New Zealand. The investigators sought to determine the association between the maximum frequency of cannabis use before age 17 and seven developmental outcomes, including depression. The number of participants varied by the outcome assessed but ranged from n = 2,537 to 3,765. Because this was an integrated study, the outcomes of depression were assessed by different measures (i.e., Composite International Diagnostic Interview, Clinical Interview Schedule, and short-form Depression Anxiety Stress Scale) and at different ages across the three studies. The investigators of this study created a dichotomous measure of moderate or severe depression in the past week to the past month between ages 17 and 25 years. Using combined data adjusted for study-specific effects, the investigators found a significant asssociation between adolescent cannabis use and the study's measure of depression (less than monthly use, OR, 1.12; 95% CI = 1.01–1.25; monthly or more, OR, 1.26; 95% CI = 1.02–1.56; weekly or more, OR, 1.42; 95% CI = 1.03–1.94; daily use OR, 1.59; 95% CI = 1.04–2.42), as well as an apparent potential dose–response relationship. However, after adjusting for relevant covariates in the analysis, this association became insignificant and negligible in size (less than monthly use, aOR, 1.01; 95% CI = 0.85–1.19; monthly or more, aOR, 1.01; 95% CI = 0.72–1.42; weekly or more, aOR, 1.02; 95% CI = 0.61–1.69; daily use, aOR, 1.02; 95% CI = 0.52–2.01). The authors noted that the confounding factors spanning the individual's background and functioning as well as parental and peer factors likely affected the change in the research findings.

Discussion of Findings

The evidence reported suggests that cannabis use, and particularly heavy cannabis use, is associated with a small increase in the risk of developing depressive disorders. This evidence is supported by a good-quality recent systematic review that included 10 longitudinal studies with sample sizes between 700 and 45,000. Although the supplemental studies from the primary literature reported mixed findings, the commit-

tee concludes that there is a strong enough evidence base to support the conclusion that there is an association between cannabis use and a small increased risk (pOR of 1.17; Lev-Ran et al., 2013) of developing depressive disorders, which increases with increased frequency of use (OR of 1.62; Lev-Ran et al., 2013). The possible relationship between heavy cannabis use and the development of depressive disorders or symptoms needs to be further explored.

Given that these relationships are associational and not necessarily causal, it is important to note possible alternative explanations for the mixed findings. For example, within the literature, a reverse association between cannabis use and depressive disorders has been documented, and the relationship may be bidirectional (Horwood et al., 2012; Wilkinson et al., 2016). This complex scenario is consistent both with the known protective roles of the endocannabinoid system in the control of mood and affect and with the propensity of cannabinoid receptors to undergo desensitization following prolonged activation. See Box 12-1 for an additional discussion on this topic.

To review the research on the potential therapeutic effects of cannabis or cannabinoids on major depression disorder, please refer to Chapter 4 (Therapeutic Effects of Cannabis and Cannabinoids).

CONCLUSION 12-5 There is moderate evidence of a statistical association between cannabis use and a small increased risk for the development of depressive disorders.

Is There an Association Between Cannabis Use and the Course or Symptoms of Depressive Disorder?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, or other endpoints in individuals with a depressive disorder.

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and the course, symptoms, or other endpoints in individuals with a depressive disorder and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

CONCLUSION 12-6 There is no evidence to support or refute a statistical association between cannabis use and changes in the course or symptoms of depressive disorders.

SUICIDE

Suicide is the act of purposely taking one's own life. It is the 10th most common cause of death in the United States, with an estimated 13 suicidal deaths per 100,000 individuals; it is often related to mental illness, substance abuse, or a major stressful event (CDC, 2014; MedlinePlus, 2016). Cannabis is widely used for both medical and recreational purposes (Azofeifa et al., 2016), and therefore, there is a public health interest to evaluate the possible association between cannabis use and suicide, suicidal attempts, and suicide ideation.

Is There an Association Between Cannabis Use and Suicidal Ideation, Suicide Attempts, and Suicide?

Systematic Reviews

Two systematic reviews were identified that assessed the association between cannabis use and suicidal ideation, attempts, and suicide (Borges et al., 2016; Moore et al., 2007). We report here on the most recent one. Borges et al. (2016) conducted a systematic review to address multiple questions concerning acute and chronic cannabis use, suicidal ideation, suicide attempts, and suicide. The authors reported the databases searched and their search terms, but they did not report the number of citations screened or the reasons for exclusions. The term "any cannabis use" was defined as: life-time use, use before or at age 15, ever used, any use in past 30 days, or any use in the last year. "Chronic use" was referred to as: cannabis use patterns, symptoms of cannabis use disorder, and heavy cannabis use. "Heavy cannabis use" was defined as: used 40 or more times, DSM-IIIR abuse/dependence, ≥6 times per month, >11 times in past year, >10 times, or daily.

The authors reviewed 12 studies that were relevant to the committee's research question. Their meta-analysis of six studies showed that any cannabis use was associated with an increased risk of suicidal ideation (pOR, 1.43; 95% CI = 1.13–1.83). Similarly, a review of five studies showed that heavy cannabis use was also associated with a larger increase of suicidal ideation (pOR, 2.53; 95% CI = 1.00–6.39). The six studies included in the meta-analysis of any cannabis use and suicide ideation were published between 1997 and 2014 and conducted in Canada, New Zealand, Norway, and the United States (four studies) in populations of male and

female young adults or adolescents. The five studies included in the meta-analysis of heavy cannabis use and suicidal ideation were published between 1997 and 2013 and conducted in Canada, New Zealand, Norway, and the United States (two studies) in male and female populations of all age groups.

The authors also assessed another subset of six studies to determine the association between any cannabis use and suicide attempts, reporting a pOR of 2.23 (95% CI = 1.24–4.00). The studies used reported on male and female adolescents or young adults in Canada, Ireland, and the United States (four studies). A review of a third subset of six studies found a higher risk of suicide attempt associated with heavy cannabis use (pOR, 3.20; 95% CI = 1.72–5.94). These six studies reported on male and female adolescents, young adults, or adults in Canada, New Zealand/Australia (two studies), Norway, and the United States (two studies).

The researchers reported that any cannabis use was associated with an increased risk of death by suicide (pOR, 2.56; 95% CI = 1.25–5.27), based on a meta-analysis of four nonoverlapping studies. The studies included two case-control studies and two longitudinal studies published between 2003 and 2012, which were conducted in Colombia, Denmark, Sweden, and the United States; the studies were carried out in young adults and in all age groups, in males and females, and in male-only study groups. Interestingly, the one study restricted to males only showed no association of cannabis with suicide, but the other studies that used mixed groups of males and females did show an association of cannabis with suicide.

Primary Literature

The committee identified one recent primary article published in 2016 (Shalit et al., 2016) that reported on the association between cannabis use and the risk of suicidality (suicidal ideation and suicide attempt). Shalit and collaborators presented their results using a general population sample of the NESARC (n = 34,653; 963 cannabis users versus 30,586 nonusers). They found that in the general population, any cannabis use in Wave 1 (baseline) was not statistically significantly associated with increased risk for developing suicidality in Wave 2 (follow-up) (aOR, 1.56; 95% CI = 0.98–2.46). However, when the results were stratified by gender, the researchers found significant differences in risk for suicidality. Among men, any cannabis use was significantly associated with the incidence of suicidality in fully adjusted models (aOR, 1.91; 95% CI = 1.02–3.56), but not for women (aOR, 1.19; 95% CI = 0.64–2.20). The magnitude of the relationship with the 3-year incidence of suicide ideation is larger in men (aOR, 4.28; 95% CI = 1.32–13.82) who are daily cannabis users, but this pattern is not observed for women (aOR, 0.75; 95% CI = 0.28–2.05).

However, in adjusted models neither cannabis use (aOR, –1.91; 95% CI = 0.85–4.28) nor daily cannabis use (aOR, 1.13; 95% CI = 0.42–3.05) was statistically significantly associated with the incidence of suicide attempts. Another finding of importance was that sex moderated the association between cannabis use, particularly daily use, and suicide attempts, with a significantly increased dose–response relationship in men (any cannabis use OR, 3.35; 95% CI = 1.07–10.47; daily cannabis use OR, 32.31; 95% CI = 2.59–402.88). However, there are several limitations, including that suicidality was only assessed in participants who reported a 2-week period of depressed mood or anhedonia, so the results might underestimate the effect for those that have suicidal ideation or suicide attempts without these symptoms. Other limitations include the use of dichotomous response categories for suicidality when there is some evidence that additional changes to the measures are needed; the lack of adjustment for some early traumatic life events associated with suicidality; and the lack of adjustments for psychotic disorders.

Discussion of Findings

The evidence reported suggests that any cannabis use is related with increased suicidal ideation, augmented suicide attempts, and greater risk of death by suicide. The studies presented demonstrate evidence of a dose–response effect, with heavy cannabis use being associated with a higher risk of suicidal ideation and suicidal attempts. Additionally, sex differences emerged from the research findings related to suicidality (Shalit et al., 2016) and death by suicide (Borges et al., 2016). These sex differences may have occurred due to differences in where the study samples were recruited (e.g., Australia, Canada, Denmark, New Zealand, Norway, Sweden, United States, etc.) or how the data were assessed. This might suggest that sample composition, gender, and the type of assessment could matter when examining these associations between cannabis use and suicidality and suicide completion.

Although the evidence seems to support a relationship between cannabis use and suicidality, particularly heavy cannabis use and suicidality, the limitations of the literature temper such findings. Several limitations should be noted, including the lack of homogeneity in the measurement of cannabis exposure, the lack of systematic controls for known risk factors, the short period of observation for suicidality, the variability in the covariates used to adjust for confounders, the differences in the dose–response analyses, and problems of small sample size. Additionally, as reported by the authors, some studies adjust for alcohol and other comorbidities, while in other studies there is no report of such adjustments. There is a strong need for new studies that discriminate between the acute and the

chronic use of cannabis and between suicidal ideation, suicide attempts, and completed suicides.

CONCLUSION 12-7

12-7(a) There is moderate evidence of a statistical association between cannabis use and increased incidence of suicidal ideation and suicide attempts, with a higher incidence among heavier users.

12-7(b) There is moderate evidence of a statistical association between cannabis use and increased incidence of suicide completion.

ANXIETY

Anxiety disorders share features of excessive fear and anxiety, which induce psychological and physical symptoms that can cause significant distress or interfere with social, occupational, and other areas of functioning (APA, 2013). In a given year, an estimated 18 percent of the U.S. adult population will suffer from symptoms associated with an anxiety disorder (NIMH, n.d.). Given the role of the endocannabinoid system in mood regulation, it is worthwhile for this report to explore the relationship between anxiety and cannabis.

Is There an Association Between Cannabis Use and the Development of Anxiety Disorders?

Systematic Reviews

One systematic review was identified that assessed the relationship between cannabis use and anxiety disorders (Kedzior and Laeber, 2014). The authors searched two databases for articles published through 2013 to identify studies that had been conducted in noninstitutionalized populations, with anxiety diagnoses based on DSM/ICD criteria, with odds ratios or data sufficient for the calculation of effects, and with comparison data from healthy nonusers. They then identified five studies that examined cannabis use at baseline and anxiety at follow-up. The five studies were all longitudinal, published between 1996 and 2013, and conducted in Australia, Colombia, the Netherlands, New Zealand, and the United States. Sample sizes were more than 2,000 or greater in four studies and more than 12,000 in the fifth study. Four studies were of adolescents and a fifth studied the general population (age unspecified). The five studies

adjusted for confounders such as demographics, prior anxiety disorder diagnosis, alcohol and tobacco use, and other mental health problems at age 15. In their review of the five studies, Kedzior and Laeber (2014) found that cannabis use at baseline was associated with the developmment of symptoms of anxiety at follow-up (OR, 1.28; 95% CI = 1.06–1.54) after adjusting for confounders (e.g., other substance use, psychiatric comorbidity, certain demographics).

Primary Literature

In a longitudinal U.S. study of a nationally representative sample of adults 18 years or older (NESARC; n = 34,653), Blanco and colleagues (2016) investigated the prospective associations of cannabis use in the past 12 months (Wave 1; years 2001–2002); with anxiety disorders 3 years later (Wave 2; years 2004–2005); and adjusted for sociodemographic characteristics, family history of substance use disorder, disturbed family environment, childhood parental loss, low self-esteem, social deviance, education, recent trauma, past and present psychiatric disorders, and respondent's history of divorce. The researchers found that cannabis use in the 12 months preceding the survey was not associated with an increased prevalence of anxiety disorders (OR, 1.0; 95% CI = 0.8–1.2) after adjustments for covariates. The researchers also reported no significant relationship of cannabis use (Wave 1) with the prevalence of panic disorder (OR, 0.8; 95% CI = 0.5–1.2), social anxiety disorder (OR, 1.2; 95% CI = 0.8–1.8), specific phobia (OR, 0.9; 95% CI = 0.7–1.2), or generalized anxiety disorder (OR, 1.0; 95% CI = 0.7–1.4) assessed 3 years later (Wave 2). The researchers also found no significant relationship between cannabis use and incident anxiety disorders (aOR, 0.9; 95% CI = 0.7–1.1). However, they did find that an increased frequency of cannabis use was related with significantly increased odds of incident social anxiety disorder (OR, 1.8; 95% CI = 1.1–2.8). Some of the limitations of this study are that cannabis use was ascertained by self-report, causality could not be established because of the possibility of residual confounding, and the follow-up period was limited to 3 years.

Feingold and colleagues (2016) used the same dataset as Blanco et al. (2016), NESARC, and also found no association of cannabis use with the increased incidence of any anxiety disorder (aOR, 1.12; 95% CI = 0.63–0.98) after adjusting for covariates. However, they did find a statistically nonsignificant association between daily or almost daily use of cannabis at Wave 1 (baseline) with the incidence of social anxiety at follow-up 3 years later (aOR, 1.98; 95% CI = 0.99–6.98). This relationship was found to be significant in older adults (aOR, 2.83; 95% CI = 1.26–6.35) but not for younger adults (aOR, 1.76; 95% CI = 0.44–6.98). They also found a

significant relationship between cannabis use disorder at baseline and incident social anxiety disorder among young adults (aOR, 2.45; 95% CI = 1.19–5.06) but not older adults (aOR, 1.38; 95% CI = 0.58–3.25). No other associations between cannabis use disorder and other anxiety disorders proved to be significant after adjustment for covariates.

Cougle et al. (2015) also used the NESARC to examine past-year regular cannabis use (defined as at least weekly use) and current and prospective presence of anxiety disorders 3 years later. These authors found no association (OR, 1.09; 95% CI = 0.90–1.32) in the prospective analyses that adjusted for psychiatric comorbidity and sociodemographic factors. However, when looking at specific anxiety disorders, Cougle and colleagues (2015) report finding a relationship between regular cannabis use and an increased risk of developing panic disorder with agoraphobia (OR, 1.56; 95% CI = 1.11–2.19) and social phobia (OR, 1.89; 95% CI = 1.54–2.32). As with other studies using the NESARC, the authors emphasize the nonrandomized nature of the study design, the possibility that the study was underpowered to find certain relationships, and the relatively short time period of observation.

Bechtold and colleagues (2015), using data from the oldest cohort of the Pittsburgh Youth Study, found that there were no differences among cannabis trajectory groups (categorized as low/nonusers, adolescence-limited users, increasing users, and early onset chronic users) related to a lifetime diagnosis of anxiety disorders for black or white men after controlling for confounders (e.g., socioeconomic status, co-occurring use of other substances, physical and mental health problems that predated cannabis use, and access to medical care). In this study cannabis use was evaluated with the Substance Use Questionnaire, with respondents (who were ages 15 to 26) initially indicating the number of days they had used cannabis in the previous 6 months and then, in each of the subsequent 10 annual follow-ups, reporting their use in the previous year. At age 36, respondents were assessed with the Diagnostic Interview Schedule to determine whether they had ever met the criteria for an anxiety disorder, and an analysis shows that the patterns of cannabis use from adolescence to young adulthood were not related to anxiety disorders. However, the authors mentioned several limitations, including the possibility of selection effects; the fact that cannabis use was determined by self-report; and the use of a limited sample that used cannabis from one geographic area and included only white and black men, implying that the results might not be generalizable to the general population. A recent study by Gage and colleagues (2015) found similar results. Using data from the Avon Longitudinal Study of Parents and Children (a UK birth cohort study), they found no evidence of an association between cannabis use at age 16 and anxiety disorder at age 18 (aOR, 0.96; 95% CI = 0.75–1.24) after

adjusting for pre-birth and childhood confounders (family history of depression, maternal education, urban living, IQ, borderline personality traits, victimization, peer problems, conduct disorder, and other substance use). The authors cite as limitations of their study the use of self-reported data, poor follow-up rates, and a limited power to detect small effects.

Brook and colleagues (2014), using the Harlem Longitudinal Developmental Study, assessed urban African American and Puerto Rican participants (n = 816) with four waves of data. In this study, Brook et al. (2014) found that participants with joint chronic cannabis, tobacco, and alcohol use were at an increased risk for generalized anxiety disorder in adulthood when compared to those with occasional alcohol use and no smoking and no cannabis use (OR, 4.35; 95% CI = 1.63–11.63). Again, this study's limitations, such as the use of self-reports, the use of proxies to determine earlier generalized anxiety disorder (depression in Time 1), and omitted variables (such as family substance use), could have explained such relationships.

Additional work by Brook and colleagues (2016) reported on a large community-based sample (the Children and Adults in Community study, n = 973 at Time 1), examining comorbid trajectories of substance use which included conjoint chronic cannabis with chronic alcohol and cigarette use as predictors of generalized anxiety disorder. According to their multivariate logistic regression analyses, the Bayesian posterior probability (BPP) of members who were chronic or moderate to heavy users of cannabis, alcohol, and cigarettes—when compared to the patterns of those with occasional alcohol use and no smoking and no cannabis—had an aOR of 6.39 (95% CI = 2.62–15.56). This suggests that the conjoint use of cannabis with alcohol and cigarettes could have biological or psychosocial effects that increased the risk for generalized anxiety disorder. However, the study had several limitations in the present study, including having a mostly white sample from upstate New York and not including environmental or social variables that could explain the relationship under study, such as family substance use or childhood psychiatric disorders.

Discussion of Findings

Studies examining the relationship between cannabis use and anxiety disorder show mixed results depending on whether they assessed the development of anxiety symptoms or the incidence of anxiety disorders; whether the explanatory variable was any cannabis use or cannabis use disorder; and whether there were adjustments for psychiatric comorbidity and sociodemographic factors. For example, Kedzior and Laeber (2014) found that cannabis use at baseline was associated with the development of symptoms of anxiety at follow-up. In contrast, the 2016 report

by Blanco and colleagues, the 2015 report by Cougle et al., and the 2015 report by Gage and colleagues all found no association between cannabis use and an increased prevalence of anxiety disorders in adjusted models. However, both Feingold et al.'s and Blanco et al.'s studies did find an association of daily or almost daily use of cannabis at Wave 1 with the incidence of social anxiety disorder at follow-up 3 years later. Age seemed to moderate this relationship since it was found to be significant in older adults but not in younger adults.

Some of the limitations of these studies are that cannabis use was ascertained by self-report; that causality cannot be established because of the possibility of residual confounding; that the follow-up period was limited to 3 years; and that there was a high loss in the follow-up and limited power to detect small effects. Further work needs to be done to examine why the outcomes differ depending on whether the assessment is done with anxiety symptoms or anxiety disorders and whether the explanatory variable is any cannabis use or cannabis use disorder. Morever, studies are needed to determine whether psychiatric comorbidity, sociodemographic factors, or the conjoint use of cannabis with alcohol and cigarettes have biological or psychosocial effects that increase the risk for generalized anxiety disorder.

To review the research on the potential therapeutic effects of cannabis or cannabinoids on anxiety, please refer to Chapter 4 (Therapeutic Effects of Cannabis and Cannabinoids).

CONCLUSION 12-8

12-8 (a) There is limited evidence of a statistical association between cannabis use and the development of any type of anxiety disorder, except social anxiety disorder.

12-8 (b) There is moderate evidence of a statistical association between regular cannabis use and increased incidence of social anxiety disorder.

Is There an Association Between Cannabis Use and the Course or Symptoms of Anxiety Disorders?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, and other endpoints of anxiety disorders.

Primary Literature

Recent work by Grunberg and collaborators (2015) conducted a prospective study to examine whether cannabis use (i.e., use during the past 30 days using the Time-Line Follow Back[11]) moderates the effects of temperament on the level of anxiety symptoms (measured with Achenbach's System of Empirically Based Assessment) within late adolescence and early adulthood (n = 338; 18- to 21-year-olds). While there was no association between cannabis use groups and anxiety symptoms among the college students in this prospective study, the researchers conducted simple slope analyses investigating the relationship between harm avoidance (characterized by heightened apprehension, shyness, pessimism, and inhibition of behaviors) and prospective anxiety symptoms for those subjects who rated low (zero days of use out of 30 days) and high (approximately 26 days of use out of 30 days) on cannabis use. The researchers found that harm avoidance measured at baseline was associated with more symptoms of anxiety measured 1 year later—but only for those low in cannabis use ($\beta = 0.15$, $t(329) = 2.69$, $p < 0.01$). When cannabis use was high, harm avoidance was unrelated to anxiety ($\beta = -0.14$, $t(329) = -1.40$, $p = 0.16$). Study participants with higher cannabis use showed a positive association between novelty seeking and anxiety symptoms ($\beta = 0.28$, $t(329) = 3.46$, $p = 0.001$), while those lower in cannabis use showed no relation between novelty seeking and anxiety symptoms ($\beta = -0.08$, $t(329) = -1.61$, $p = 0.11$).

Discussion of Findings

Grunberg and collaborators (2015) warned, however, that the findings discussed above should be taken with caution since the mechanisms underlying these relations are still not clear. In addition, although this study uses a prospective design in which cannabis use and temperament are evalutated at baseline to predict anxiety symptoms 1 year later, it is limited to college students (ages 18–21) in only one assessment site. The authors emphasized that the reason the relationship between cannabis use and anxiety symptoms is inconsistent is that there was no consideration of cannabis effects on other factors that influence anxiety symptoms such as temperament (i.e., levels of harm avoidance and novelty seeking) within the sample. Some limitations of this study are the use of a college student sample, the use of self-report for all assessments, and the use of correlational data—although cannabis use and temperament were measured 1 year before anxiety symptoms. Given the limited evidence of studies that

[11] Authors describe this as a calendar-assisted structured interview that allows participants to indicate the amount of cannabis used on each day over the past month.

address the relationship between cannabis use and anxiety symptoms, these findings need to be replicated in larger samples with appropriate controls.

CONCLUSION 12-9 There is limited evidence of a statistical association between near daily cannabis use and increased symptoms of anxiety.

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) falls within the broader trauma- and stressor-related disorders categorized by the DSM-V. The diagnostic criteria of PTSD include an exposure to a traumatic event (e.g., the threat of death, serious injury, or sexual violence) and exhibiting psychological distress symptoms that occur as a result of that exposure (e.g., intrusion symptoms, such as distressing memories; avoidance of stimuli that are associated with the traumatic event; negative alterations in mood and cognition; alterations in arousal and reactivity associated with the traumatic event; functional impairment) (APA, 2013, pp. 271–272). Given the known psychoactive effects of cannabis, the committee chose to explore the association between PTSD and cannabis use in this review.

Is There an Association Between Cannabis Use and the Development of PTSD?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the risk of developing PTSD.

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and the development of PTSD and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

CONCLUSION 12-10 There is no evidence to support or refute a statistical association between cannabis use and the development of posttraumatic stress disorder.

Is There an Association Between Cannabis Use and the Course or Symptoms of PTSD?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, and other endpoints in PTSD.

Primary Literature

Gentes et al. (2016) found that past 6-month cannabis use was associated with increased PTSD severity (Clinician Administered PTSD Scale; global severity score; aOR, 1.30; 95% CI = 1.01–1.66), depressive symptoms (Beck Depression Inventory; aOR, 9.25; 95% CI = 1.13–1.75), and suicidality (Beck Depression Inventory Item 9; aOR, 4.63; 95% CI = 1.02–1.54) in a population of treatment-seeking veterans (n = 719). In this study, the odds ratios were adjusted for age, race, service era, and combat exposure, but not co-occurring substance use. Conversely, Manhapra et al. (2015) found improvements in PTSD symptoms (Mississippi Scale for Combat-Related Posttraumatic Stress Disorder), violence, and suicidality after 4 months of abstinence from cannabis relative to symptoms upon entry to the study in a large population of veterans admitted for an intensive PTSD program (n = 22,948). Villagonzalo et al. (2011), in a small study of patients (n = 80; mean age 35 years) participating in a methadone maintenance program, found that the severity of cannabis use was associated with the occurrence of certain PTSD symptoms, as measured by the Posttraumatic Stress Disorder Checklist–Civilian Version. Significant findings were identified for measures of reexperiencing (i.e., repeated disturbing dreams, $\chi^2(2) = 6.351$; $p < 0.05$; physical reaction at reminder of event $\chi^2(2) = 7.053$; $p < 0.05$; hyperarousal (i.e., difficulty concentrating, $\chi^2(2) = 7.517$; $p < 0.05$; "super alert" $\chi^2(2) = 6.778$; $p < 0.05$; easily startled $\chi^2(2) = 9.645$, $p < 0.01$); and overall PTSD symptoms (1-way ANOVA, $F(2,65) = 3.705$; $p < 0.05$).

Of interest, the committee also identified two large observational studies that compared the effects of cannabis to controls. Both studies enrolled predominately male veterans. A large cohort study (Wilkinson et al., 2015) examined outcomes for 2,276 veterans who received specialized intensive PTSD services between 1992 and 2011. Assessments for substance use and PTSD symptoms were taken at intake and at 4 months after discharge. Veterans who continued to use or started using cannabis after discharge had significantly worse PTSD symptoms and greater drug abuse than those who had never used or who had stopped cannabis use at 4 months after discharge ($p < 0.0001$). Starters also had more violent behavior in the 4 months after enrollment compared to other groups

($p < 0.0001$). There were no significant differences among the groups on employment status. A second study (Johnson et al., 2016) was a matched, case-control cross-sectional study that was conducted in 700 veterans with probable PTSD, half of whom used cannabis and half who were nonusers. Cannabis users and nonusers did not differ on PTSD symptom severity ($p = 0.91$) or depression severity ($p = 0.07$) as measured by the PTSD Checklist–Civilian Version and the Patient Health Questionnaire, respectively. However, cannabis users were more likely to experience suicidal ideation ($p = 0.04$) and reported more alcohol use ($p < 0.001$) as measured by the Paykel questionnaire, an Alcohol Timeline Followback assessment, and the Alcohol, Smoking, and Substance Involvement Screening Test.

Discussion of Findings

Notable in this section relative to the others in this chapter is the lack of data addressing the key questions posed by the committee. For example, using the committee's specified search strategy, we found no relevant studies that directly addressed the question of whether cannabis use is associated with an increased risk of PTSD. Of the relevant studies reviewed, cannabis use appears to be associated with more severe symptoms, but limited sample sizes were an issue in certain studies; that issue, combined with the lack of adjustment for baseline symptom severity and other drug use and the examination of specialized patient populations, limits the strength of the conclusions that can be drawn. Overall, there is limited evidence for an association between cannabis use and increased PTSD symptom severity. The direction of the association is difficult to address, however. It has been argued that PTSD is a risk factor for cannabis use, and cannabis-using patients with PTSD often cite symptom-coping motives for cannabis use, which suggests that more severe PTSD may be driving patients to increase cannabis use in an effort to self-medicate.[12] In contrast, one study (Manhapra et al., 2015) found overall improvements in several symptom domains after 4 months of abstinence from cannabis, suggesting that cannabis use may be causally related to more severe PTSD symptoms. See Box 12-2 for a discussion on why it is often difficult to conclude causality in the associations between substance use and mental health.

To review the research on the potential therapeutic effects of cannabis or cannabinoids on PTSD, please refer to Chapter 4 (Therapeutic Effects of Cannabis and Cannabinoids).

[12] Studies examining PTSD as a risk factor for cannabis use and cannabis use disorders were identified and are discussed in Chapter 13 of this report.

CONCLUSION 12-11 There is limited evidence of a statistical association between cannabis use and increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder.

RESEARCH GAPS

As noted above, we found a paucity of studies relevant to our key questions. To address the research gaps relevant to PTSD, the committee suggests the following:

- More longitudinal studies to determine whether cannabis use is associated with an increased incidence of PTSD.
- In patients with PTSD, current data do not provide a very clear picture as to whether cannabis use affects PTSD symptoms. More longitudinal studies examining the effects of cannabis use on PTSD symptoms need to be conducted, with a specific emphasis placed on detailed measures of cannabis use (amounts, potency, routes of administration), controls for baseline symptom severity and the use of other substances, and temporality (excluding patients with cannabis use at study entry).
- From a cannabis therapeutics perspective, blinded, randomized, placebo-controlled studies in patients with PTSD need to be conducted to evaluate any potential therapeutic benefits of cannabis on PTSD symptoms and course.
- There is also a research need to investigate cannabis and cannabis constituents (tetrahydrocannabinol and cannabidiol) in animal models.

SUMMARY

This chapter outlines the committee's efforts to review the current evidence base for the association of cannabis use with prioritized mental health conditions. The health conditions reviewed in this chapter include schizophrenia and other psychotic disorders, bipolar disorder, depression, suicide, anxiety, and PTSD. The committee formed a number of research conclusions related to these health endpoints; however, it is critically important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections. See Box 12-3 for a summary list of the chapter's conclusions.

A conclusion weighted as substantial was reached for the research question addressing the statistical association between cannabis use and the development of schizophrenia or other psychoses. As noted in the

BOX 12-2
Special Considerations for Systematic Reviews of Observational Studies

The qua ty assessment of the systemat c rev ews n th s chapter fo owed the research methods used throughout th s report w th n the context of the menta hea th terature. Of note, the pr mary terature n menta hea th s most y observa- t ona (n contrast to the terature base n other fie ds, such as therapeut cs), and t was not poss b e to restr ct systemat c rev ews and meta-ana yses to those that synthes zed ev dence from random zed c n ca tr a s (RCTs). Accord ng y, the vast major ty of the stud es nc uded n the systemat c rev ews and meta-ana yses sum- mar zed n th s chapter were observat ona stud es. In add t on to rece v ng a ower- qua ty grad ng n most systems, the methodo og c sc ence around the synthes s of observat ona data s ess deve oped than t s for RCTs. The methodo ogy used for systemat c rev ews and meta-ana ys s or g nates n the synthes s of data from RCTs, where methodo ogy s h gh y standard zed and structured. The synthes s of observat ona stud es presents some cha enges that have not been fu y met, ar s ng out of the greater var ety n study des gn and conceptua zat on and the fact that there has been genera y ess exper ence n app y ng the methodo ogy of systemat c rev ews and meta-ana ys s to observat ona terature. For examp e, none of the systemat c rev ews d scussed n th s chapter ment oned a protoco , an eth cs rev ew board, or a pr or pub shed research object ves—features that have become ncreas ng y standard n systemat c rev ews of RCTs. Ma en and co eagues (2006, p. 765) noted: "Qua ty assessment does not rout ne y occur n systemat c rev ews of observat ona stud es. Where t does occur, there s no c ear consensus n the method used." Brugha and co eagues (2012, p. 450), n the r rev ew of systemat c rev ews and meta-ana yses of observat ona psych atr c ep dem o ogy stud es, found "a number of defic enc es n the conduct and report ng of systemat c rev ews and meta-ana yses of observat ona psych atr c ep dem o - ogy stud es that cou d have ser ous mp cat ons for nferences drawn or dec s ons made on the bas s of these rev ews. There were frequent om ss ons of descr pt ons of method of abstract on, study qua ty, pub cat on b as, b as and confound ng."

In assess ng the body of ev dence, t s tempt ng to corre ate the number of systemat c rev ews w th the strength of the ev dence; however, a number of con- cerns ar se when synthes z ng ev dence across systemat c rev ews. When mu - t p e systemat c rev ews address s m ar research quest ons or s ght var at ons on s m ar research quest ons, t s ke y that the rev ews w nc ude some of the

chapter's Discussion of Findings sections, there are common trends in the types of study limitations found in this evidence base. The most common are limitations in the study design (e.g., a lack of appropriate control groups, a lack of long-term follow-ups) variable analysis of cannabis use (i.e., dose/amount/frequency current versus. lifetime); small

same pr mary stud es. For examp e, n the Sch zophren a sect on above, the three systemat c rev ews assess ng the effects of cannab s on cogn t on—Donoghue and Doody (2012), Rab n et a . (2011), and Yuce et a . (2012)—each c te the pr mary study by Schne et a . (2009). Another four stud es were nc uded n two of the systemat c rev ews on cogn t on. G ven the use of some pr mary stud es n more than one systemat c rev ew, the number of systemat c rev ews or meta-ana yses may not, by themse ves, nd cate a stronger body of ev dence.

Wh e t s easy to understand how mu t p e rev ews m ght dent fy s m ar studes, t s a so of concern when rev ews dent fy d fferent stud es. For examp e, the systemat c rev ew on cogn t on by Rab n et a . (2011) dent fied four stud es that were not nc uded n the rev ews by Donoghue and Doody (2012) or by Yuce et a . (2012), and Yuce and co eagues (2012) a so dent fied four stud es that were not nc uded n the other systemat c rev ews. Th s may be exp a ned by a carefu exam nat on of the search strateg es and nc us on/exc us on cr ter a, but the reasons for such d fferences are not a ways transparent.

Exposure measurement s a ways of concern n observat ona stud es, and assessment of cannab s exposure s part cu ar y fraught because of ts ega status (n most sett ngs) and the re ance on se f-report. Inherent d fficu t es n accurate y assess ng the exposure n terms of dose, spec fic chem ca s, mode of ntake, durat on, frequency, and other var ab es resu t n the var ab ty n defin t ons used to operat ona ze cannab s exposure. For examp e, systemat c rev ews may nc ude stud es us ng great y d ffer ng defin t ons such as nondependent cannab s use n past week, a h story of 0.5 g cannab s/day, cannab s use n the ast 6 months, and >2g cannab s/week (Rab n et a ., 2011). In add t on, stud es focus ng on menta hea th may use med ca records show ng a d agnos s of cannab s use d sorder as the r exposure var ab e, e ther focus ng on the d sorder as a construct or as a proxy for cannab s exposure. Th s ast approach a ows researchers to cons der the construct of cannab s use d sorder, but t may resu t n exposure and non-exposure groups hav ng s m ar ntakes of cannab s. One can mag ne a scenar o where a person w th a cannab s use d sorder d agnos s has perhaps not consumed cannab s n the preced ng week, month, or other t me frame and where nd v dua s w thout a d agnos s of cannab s use d sorder had consumed cannab s n the same t me frame. In th s scenar o, m sc ass ficat on n both d rect ons wou d resu t n b ases toward the nu , a though d fferences between nd v dua s w th and w thout menta hea th d agnoses of cannab s use d sorder cou d be expected to be assoc ated w th other d fferences observed n the study groups.

sample sizes; and research gaps in the studies of depression and PTSD. These limitations highlight the enormous amount of available opportunity to advance the current research agenda, in the hopes of providing comprehensive and conclusive conclusions on the potential harms and therapeutic benefits of cannabis or cannabinoid use.

BOX 12-3
Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between cannabis use and:

- The deve opment of sch zophren a or other psychoses, w th the h ghest r sk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cogn t ve performance among nd v dua s w th psychot c d sorders and a h story of cannab s use (12-2a)
- Increased symptoms of man a and hypoman a n nd v dua s d agnosed w th b po ar d sorders (regu ar cannab s use) (12-4)
- A sma ncreased r sk for the deve opment of depress ve d sorders (12-5)
- Increased nc dence of su c da deat on and su c de attempts w th a h gher nc dence among heav er users (12-7a)
- Increased nc dence of su c de comp et on (12-7b)
- Increased nc dence of soc a anx ety d sorder (regu ar cannab s use) (12-8b)

There is moderate evidence of *no* statistical association between cannabis use and:

- Worsen ng of negat ve symptoms of sch zophren a (e.g., b unted affect) among nd v dua s w th psychot c d sorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An ncrease n pos t ve symptoms of sch zophren a (e.g., ha uc nat ons) among nd v dua s w th psychot c d sorders (12-2b)
- The ke hood of deve op ng b po ar d sorder, part cu ar y among regu ar or da y users (12-3)
- The deve opment of any type of anx ety d sorder, except soc a anx ety d sorder (12-8a)
- Increased symptoms of anx ety (near da y cannab s use) (12-9)
- Increased sever ty of posttraumat c stress d sorder symptoms among nd - v dua s w th posttraumat c stress d sorder (12-11)

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes n the course or symptoms of depress ve d sorders (12-6)
- The deve opment of posttraumat c stress d sorder (12-10)

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* Numbers in parentheses correspond to chapter conclusion numbers

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13

Problem Cannabis Use

Chapter Highlights

- Greater frequency of cannabis use increases the likelihood of developing problem cannabis use.
- Initiating cannabis use at a younger age increases the likelihood of developing problem cannabis use.

A recent national survey reported that 22.2 million Americans (ages 12 or older) identify as current users of cannabis (CBHSQ, 2015). A subgroup of these users, 4.2 million Americans, reported experiencing symptoms in the previous year that would qualify them for cannabis use disorder (CUD) (CBHSQ, 2015). Unfortunately, the literature remains unclear on the association or developmental link between varying levels of cannabis use and the development of "problem" cannabis use or cannabis use disorder, particularly at different age groups (e.g., 12 years or older).

In this chapter, the committee reviews the current research evidence that most directly addresses prioritized research questions related to the association between cannabis use and the development of problem cannabis use and to the risk and protective factors involved in the development or exacerbation of problem use. An initial search of the primary literature (see Appendix B) produced a substantial number of primary articles for the committee to review. Due to the time constraints of the study, additional search constraints were added to zero in on the types of studies

that would likely produce the clearest research conclusions. For example, literature searches were limited to articles that included the following search terms: longitudinal, prospective, and case-control. The primary literature was further limited to studies that included a sample size of >500 participants and to studies that investigated problem cannabis use as a function of the most relevant risk factors, including mental health, the age of initiation of cannabis use, risk factors during adolescence, biological sex, and other drug use. Large population-based studies that explored multiple demographic variables were also included.

It is of note, however, that due to the specific search restrictions outlined above, controlled laboratory studies with cannabis were not included in the committee's set of articles to review. There do, in fact, exist controlled lab studies that assess the direct effects of cannabis on behaviors relevant to cannabis use disorder and the dose-dependent effects of cannabis and that are related to its abuse liability. Unfortunately, because of the constraints of this study, these findings are not incorporated in the chapter's discussion. Furthermore, the committee's prioritized research questions did not examine the association between low-level cannabis use or infrequent cannabis use and the development of problem cannabis use.

To inform their research conclusions, the committee reviewed two of the most recent good- to fair-quality systematic reviews and 26 primary literature articles.

PROBLEM CANNABIS USE

As noted above, the literature is unclear on the association between cannabis use and the progression to the sort of cannabis use determined to be "problem" use. A major contributor to this issue is the lack of official distinction between "risky" or "problem" use of cannabis (Casajuana et al., 2016). In recent years, CUD[1] has been termed an official psychiatric disorder (APA, 2013; WHO, 2015). A current *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) diagnosis of CUD replaces the previous diagnoses of cannabis abuse and cannabis dependence. Although some progress has been made in standardizing terminology, explicit characterizations of cannabis use patterns that *precede* abuse or dependence still remain unclear (Casajuana et al., 2016). Given this context, for the purposes of this chapter the committee will use the broad term "problem cannabis use disorder" to encompass various levels of

[1] In brief, CUD is a diagnosable psychiatric disorder defined as a problematic pattern of cannabis use leading to clinically significant personal, social, physical, and/or psychological distress or impairment.

hazardous or potentially harmful cannabis use patterns, including those related to CUD, dependence, and abuse.

Which Characteristics of Cannabis Use Are Associated with the Progression to Developing Problem Cannabis Use?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and cannabis use disorder, dependence, abuse, or problem cannabis use.

Primary Literature

Several studies using large population-based surveys have explored the rates of cannabis use disorder and the variables that affect progression from the initiation of use to problem cannabis use. According to findings from Wave 1 (baseline; 2001–2002) and Wave 2 (follow-up; 2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a survey of a nationally representative sample of U.S. adults ages 18 years and older (n = 34,653 in Wave 2), cannabis use reported during the first wave was significantly associated with any cannabis use disorder during the second wave (adjusted odds ratio [aOR], 9.5; 95% confidence interval [CI] = 6.4–14.1); 14.1 percent of past-year cannabis users in Wave 1 met the criteria for cannabis abuse in Wave 2, and 5.1 percent met criteria for dependence, as compared with 0.7 percent of participants who reported no past-year cannabis use during Wave 1 who met the criteria for cannabis abuse and 0.2 percent who met the criteria for cannabis dependence (Blanco et al., 2016). This study accounted for multiple sociodemographic factors that may have affected the outcome.

The progression of cannabis use to developing cannabis use disorder as a function of the frequency of cannabis use was also explored using Waves 1 and 2 of the NESARC data (Cougle et al., 2016) Among the past-year weekly nondependent cannabis users in Wave 1 (n = 435), 9.7 percent progressed to cannabis dependence in Wave 2; however, an increased frequency of cannabis use per day only weakly predicted progression of cannabis use to CUD (odds ratio [OR], 1.08; CI = 1.04–1.13) in a prospective analysis. A cross-sectional analysis of Wave 1 data found that 8.0 percent of respondents who reported using cannabis at least once in the past year met the criteria for dependence, whereas among weekly and daily cannabis smokers, 17.0 percent and 18.8 percent, respectively, met the criteria for dependence.

Using data obtained from the U.S. National Household Survey on

Drug Abuse (NHSDA) conducted in 2001 with a representative sample of U.S. residents 12 years of age and older (n = 114,241), Chen and colleagues (2005) explored the rates of developing cannabis dependence syndrome after onset of use. Of the recent onset users (individuals that used cannabis within 24 months prior to assessment), an estimated 3.9 percent developed dependence during the interval since first use (median time = 1 year). Of those who initiated cannabis use more than 24 months before the assessment, and were also active cannabis users within the past year, 9.9 percent developed dependence (Chen et al., 2005).

Using data from two large U.S. surveys—the 1991 National Longitudinal Alcohol Epidemiologic Survey (NLAES) (n = 42,862) and the 2002 NESARC (n = 43,093)—Compton and colleagues (2004) assessed the rates of cannabis use disorder as a function of biological sex, ethnicity, and frequency of cannabis use. They found that the overall prevalence of DSM-IV cannabis abuse and dependence increased significantly from 1.2 percent to 1.5 percent between 1991 and 2001. The greatest increases in these rates were observed among young black men and women ($p < 0.001$), and young Hispanic men ($p = 0.006$). The increase in the rates of cannabis use disorder among cannabis users was observed in the absence of self-reported increases in frequency or quantity of use ($p = 0.002$); this suggests that the increases in cannabis use disorders may be due to the increased potency (percent tetrahydrocannabinol [THC]) of cannabis between 1991 and 2001.

Discussion of Findings

The limitations of these studies include the reliance on self-reported cannabis use, the fact that data were restricted to two time points of assessment separated by 3 years, and that the findings are based on epidemiological data obtained more than 10 years ago. A significant issue with relying on self-report methodologies to ascertain problem cannabis use is that this requires that the respondent have insight into the fact that cannabis is actually causing problems in order to meet criteria for cannabis abuse/dependence (as per the DSM-IV) or CUD (as per the DSM-V). Furthermore, while the primary literature indicates a weak association between the frequency of use and a greater risk of developing cannabis use disorder, it should be noted that the frequency of use in these studies was assessed in the absence of determining the amount of cannabis used per occasion, which is a primary variable hypothesized to affect the rates of developing problem cannabis use.

Cannabis use is increasing across the country and across age groups (Hasin et al., 2015); the strength of cannabis has increased (ElSohly et al., 2016); and different routes of cannabis administration have become popu-

lar, including vaping, dabs, and edibles (Daniulaityte et al., 2015; Kilmer et al., 2013; Pacula et al., 2016). These trends may reflect an increased vulnerability to developing problem cannabis use relative to what was estimated based on the Wave 1 and Wave 2 NESARC data collected in 2001–2001 and 2004–2005. Therefore, the estimated risk of developing problem cannabis use based on these data may not accurately reflect the risk now, given the current trends.

CONCLUSION 13-1 There is substantial evidence for a statistical association between increases in cannabis use frequency and the progression to developing problem cannabis use.

Are There Risk and Protective Factors for Developing Problem Cannabis Use?

Anxiety

Systematic Reviews Kedzior and Laeber (2014) searched two large databases for articles published from inception through 2013 to identify studies of cannabis use and anxiety. They included cross-sectional and longitudinal studies conducted in noninstitutionalized populations, with anxiety diagnoses based on DSM or *International Classification of Diseases* (ICD) criteria, odds ratios, or data sufficient for the calculation of a measure of effects, and they included comparison data from healthy nonusers. Their purpose was to examine both of the possible temporal relationships between cannabis use and anxiety (i.e., the effect of anxiety on cannabis use and the effect of cannabis use on anxiety). They identified 31 studies for their review. Five of these examined cannabis use at baseline and anxiety at follow-up, and the remainder considered the role of anxiety as a risk factor for cannabis use. Sample sizes were almost 2,000 or greater in four studies and more than 12,000 in a fifth study. After analyzing various subsets of the selected articles, the authors concluded that there was a small positive association between anxiety and CUD (OR, 1.68; 95% CI = 1.23–2.31, n = 13 studies). One study included in the analysis assessed anxiety at baseline and cannabis use at follow-up and did not find an association (OR, 0.94; 95% CI = 0.86–1.03), but it did not report on problem cannabis use at follow-up. The authors found little evidence of publication bias after their assessment, and they reported a moderate-high heterogeneity. They offered three possible explanations of this heterogeneity: differences in adjustment for confounding when calculating the OR, year of publication, and different methods for diagnosing anxiety. Based on this systematic review, it appears that while there is a small association between anxiety and CUD, anxiety does not seem to be a predisposing risk factor for developing CUD.

Primary Literature The committee did not identify any good-quality primary literature that reported on anxiety as a risk or a protective factor for developing problem cannabis use and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Stimulant Medication in Children Diagnosed with Attention Deficit Hyperactivity Disorder

Systematic Reviews Humphreys et al. (2013) conducted a systematic literature review and meta-analysis to assess the association between childhood treatment with stimulant medication and later substance use, abuse, or dependence. They searched the literature published between 1980 and 2012 and included published and unpublished studies with a longitudinal design, binary measures to identify children with attention deficit hyperactivity disorder (ADHD), binary substance use and abuse measures, and data allowing the calculation of odds ratios. Fifteen studies were included in the review; nine of these evaluated the association of stimulant medication with a lifetime history of ever using marijuana, and nine evaluated the association of stimulant medication with cannabis abuse or dependence. All study subjects were children at the time of enrollment, and the follow-up time ranged from 4 to 28 years in the group of 9 studies reviewed, with the mean age at follow-up ranging from 15 to 26 years. One of the studies in this systematic review included children as young as 4 years of age who would not be expected to develop CUD in the follow-up time period. The percentage of study subjects who were male ranged from 0 to 100, with the majority of the studies being more than 80 percent male. The researchers reported an OR of 1.01 (95% CI = 0.68–1.50) for the association between stimulant medication and marijuana abuse or dependence. Some suggestion of publication bias was noted, and heterogeneity was noted in the group of nine studies with data about marijuana abuse or dependence. These results suggest that medication for ADHD during childhood does not constitute a risk factor for developing problem cannabis use later in life.

Primary Literature The committee did not identify any good-quality primary literature that reported stimulant medication in children diagnosed with ADHD as a risk or a protective factor for developing problem cannabis use and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Psychopathology

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on psychopathology as a risk or a protective factor for developing problem cannabis use.

Primary Literature Data obtained from the 2001 and 2005 NESARC, a survey of a nationally representative sample of U.S. adults ages 18 years and older (n = 34,653 in Wave 2), explored anxiety as a risk factor for progression to cannabis use disorder. Using data from Wave 2 (comprised of 34, 653 participants from Wave 1), Feingold and colleagues (2016) found that anxiety disorders were not associated with an increased incidence of cannabis use disorders (aOR, 0.68; 95% CI = 0.41–1.14). Similarly, a prospective analysis using Wave 1 and Wave 2 NESARC data also found that anxiety disorders failed to predict progression from cannabis use to cannabis dependence in weekly cannabis users (Cougle et al., 2016).

Another analysis used these data to determine the association between baseline major depressive disorder (MDD) as a risk factor for cannabis use disorders (Pacek et al., 2013). A positive relationship was observed between baseline MDD and cannabis use disorders (OR, 2.01, 95% CI = 1.09–3.68); baseline MDD also increased the risk of co-occurring alcohol and cannabis use disorders (OR, 5.23; 95% CI = 1.28–21.34) when compared to individuals without baseline MDD. When adjusting the model to account for potential confounding variables, the association between baseline MDD and the development of cannabis use disorders alone, and co-occurring with alcohol use disorders was retained (aOR, 2.28; 95% CI = 1.28–4.05 for cannabis use disorders alone and aOR, 4.51, 95% CI = 1.31–15.60 for comorbid alcohol and cannabis use disorders). These findings support a strong association between MDD and the development of cannabis use disorders. According to a later prospective analysis (Cougle et al., 2016), among weekly, nondependent cannabis users in Wave 1, depressive disorders did not significantly predict progression to cannabis dependence in Wave 2 (OR, 0.89; 95% CI = 0.58–1.38) (Cougle et al., 2016). The discrepancy between these two findings may be due to the former study assessing respondents who met the criteria for MDD. Also, the pool of respondents in the earlier study was not limited to those who reported weekly cannabis use during Wave 1, as was the case with the later study.

Another study assessing the impact of baseline depressive symptoms on developing cannabis abuse used data from a longitudinal study involving 1,980 participants (the 1980 Baltimore Epidemiologic Catchment Area study). In this study, a subset of participants (n = 1,837) were assessed for cannabis use disorders 14 to 16 years after initial assessment (Bovasso, 2001). Depressive symptoms failed to predict cannabis abuse at follow-up assessments, which indicated that among the population

studied, depression was not a risk factor for later cannabis abuse. The long duration between the initial assessment and the follow-up and the presence of significant attrition were significant limitations to this study.

In order to determine the effects of psychotic disorders on the risk for heavy cannabis use, data obtained from the Genomic Psychiatric Cohort—a clinically assessed multiethnic sample of participants (n = 9,142) with a diagnosis of schizophrenia, bipolar disorder with psychotic features, or schizoaffective disorders—were compared to a control population (n = 10,195) (Hartz et al., 2014). Relative to the control population, individuals with chronic psychotic disorders were found to have an increased risk for heavy cannabis use, defined by the researchers as cannabis use more than 21 times per year (OR, 3.5; 95% CI = 3.2–3.7). It is important to note, however, that it remains difficult to determine how heavy cannabis use translates to problem cannabis use, cannabis dependence, or CUD.

A prospective analysis using data from Waves 1 and 2 of the NESARC found that personality disorders failed to predict a progression from past-year, weekly nondependent cannabis use in Wave 1 to cannabis dependence in Wave 2 (OR, 0.91; 95% CI = 0.62–1.34). This same analysis demonstrated that bipolar disorder was associated with a lower risk for developing CUD (OR, 0.43; 95% CI = 0.36–0.52) (Cougle et al., 2016).

Biological Sex

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on biological sex as a risk or a protective factor for developing problem cannabis use.

Primary Literature Data from the NLAES (n = 42,862) were analyzed in effort to determine the effect of biological sex on the risk of developing cannabis use disorders (Grant et al., 2006). Of the participants that reported cannabis use at least 12 times, women were less likely to be categorized with cannabis "abuse/moderate dependence" relative to men (8 percent versus 14 percent) or "severe abuse/dependence" (3 percent versus 6 percent). While men were consistently more likely to report hazardous cannabis use relative to women, women were more likely to report withdrawal and to have higher rates of four symptoms of dependence (i.e., emotional problems, giving up activities, using more cannabis than intended, withdrawal) in the "abuse/moderate dependence" category than men. These findings may suggest either that men and women differ in cannabis dependence symptomatology or that they differ in their willingness to self-report the symptoms.

Using data obtained from Wave IV of the National Longitudinal Study of Adolescent Health—a nationally representative population-

based survey of young adults ages 24 to 32 (n = 15,500; interviewed from 2008–2009)—lifetime prevalence rates of cannabis dependence were determined to be 8.3 percent, and they were higher among males than among females (Haberstick et al., 2014). However, a prospective analysis using data from Wave 1 and Wave 2 of the NESARC failed to find that biological sex predicted a progression from cannabis use to cannabis dependence in weekly nondependent cannabis users (OR, 1.17; 95% CI = 0.75–1.81) (Cougle et al., 2016).

Progression from the onset of cannabis use to the development of cannabis dependence as a function of biological sex was explored using data obtained from the NHSDA, which was conducted in 2001 with a representative sample of U.S. residents 12 years of age and older (n = 114,241) (Chen et al., 2005). The rate for developing cannabis dependence 24 months after onset of use was 3.9 percent for both men and women. However, it is not known if differences between men and women would have emerged if a shorter time frame from cannabis use onset had been explored.

Other Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on other drug use as a risk or a protective factor for developing problem cannabis use.

Primary Literature To explore the impact of other drug use as a risk factor for developing problem cannabis use, data obtained from the NHSDA conducted in 2001 with a representative sample of U.S. residents 12 years of age and older (n = 114,241) were analyzed. The rate of developing cannabis dependence within 24 months of first cannabis use was doubled among respondents who had experience with three or more other drugs (tobacco, alcohol, and other drugs) prior to cannabis use (adjusted risk ratio [aRR] = 2.2; 95% CI = 1.1–4.3; p = 0.03) (Chen et al., 2005). However, a prospective analysis using data from Waves 1 and 2 of the NESARC failed to find that alcohol or nicotine dependence predicted progression from cannabis use to cannabis dependence (OR, 0.88; 95% CI = 0.58–1.32 and OR, 0.77; 95% CI = 0.52–1.13, respectively) (Cougle et al., 2016).

Age—Older Population

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on older age as a risk or a protective factor for developing problem cannabis use.

Primary Literature Based on the large population-based U.S. National Survey on Drug Use and Health, the prevalence of cannabis use in the United States was assessed in a population more than 50 years of age (n = 10,953; data from 2005 and 2006). Only 0.12 percent of the population met the criteria for cannabis abuse and dependence demonstrating that, at the time of this survey, this is an age group that is at low risk for developing CUD (Blazer and Wu, 2009).

Age of Initiation of Cannabis Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the age of initiation of cannabis use as a risk or a protective factor for developing problem cannabis use.

Primary Literature The age of initiation of cannabis use as a risk factor for developing cannabis dependence has been explored in many studies. Chen et al. (2005) used data obtained from the NHSDA conducted in 2001 with a representative sample of U.S. residents 12 years of age and older (n = 114,241). Adolescent onset cannabis users were more likely to become dependent than respondents who had initiated cannabis use during adulthood. Using data obtained from adult onset users of cannabis (21 years of age and older) as a reference, Chen and colleagues found a strong association between an onset of cannabis use between 11 and 13 years of age and the relative risk of becoming dependent (aRR = 10.8; 95% CI = 2.5–47.1). The estimated risk ratio of developing cannabis dependence when initiating cannabis use at 14 to 15 years of age was 12.0 (95% CI = 2.9–50.3).

Another study exploring early, frequent cannabis use as a risk factor for developing cannabis use disorder used data from three long-running surveys in Australia and New Zealand[2] (Silins et al., 2014). Compared to individuals who had never used cannabis, those who were daily users before 17 years of age had significantly greater odds of later developing cannabis dependence (n = 2,675; aOR, 17.95; 95% CI = 9.44–34.12). This study controlled for 53 covariates, including socio-demographic factors and other potential antecedents to the development of problem cannabis use that may have affected the findings.

A longitudinal study of a community-based sample of adolescents and young adults surveyed between 14 and 24 years of age in Munich, Germany, with four waves of assessments over a 10-year period (n = 3,021 at baseline) ascertained the prevalence rates of DSM-IV cannabis

[2] These surveys include the Australian Temperament Project, the Christchurch Health and Development Study, and the Victorian Adolescent Health Cohort Study.

dependence as a function of cannabis use (Perkonigg et al., 2008). During the first assessment (at baseline), 1.5 percent of the sample met the criteria for DSM-IV cannabis dependence. Among those who reported using cannabis at that time, 4.3 percent met the criteria for dependence. At the 10-year follow-up, 6.1 percent of those who reported using cannabis at baseline met the criteria for dependence. The authors concluded that the higher rates of cannabis dependence during the 10-year follow-up assessment suggested that cannabis use early in life may be indicative of increased vulnerability to developing CUD. However, there are other factors (as discussed below) that may explain why an increase in cannabis dependence was observed at the 10-year follow-up.

A later study using these data evaluated the probability and speed of going from first cannabis use to developing cannabis dependence as a function of the age of first use. The conditional probability of transition from cannabis use to dependence was estimated to be 6.2 percent (Behrendt et al., 2009). The authors also compared the time of transition from first substance use (nicotine, alcohol, or cannabis) to the development of the specific substance use disorder and found that the transition from first cannabis use to the development of CUD occurred at a faster rate than for those with alcohol or nicotine use disorders.

Other Variables Specific to Adolescents

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on variables that protect against or increase the risk of developing cannabis use disorders among adolescents.

Primary Literature Longitudinal data from the above-described community-based sample from Munich, Germany, were analyzed to determine whether the age of first alcohol and nicotine affects the risk of transition from cannabis use to cannabis dependence (Behrendt et al., 2012). This analysis took into account externalizing disorders (mental disorders characterized by disruptive behaviors that are directed toward an individual's external environment) and parental substance use disorders as potential factors that may affect the trajectory to cannabis dependence. Using multiple models, the authors found that (1) a younger age of cannabis use (hazard ratio [HR], 0.77), (2) paternal alcohol dependence (HR, 1.47), and (3) externalizing disorders (HR, 1.69) were all associated with a higher risk of developing cannabis dependence. Externalizing disorders were associated with a slower transition from initial cannabis use to cannabis dependence (HR main effect, 1.14; HR interaction effect, 1.17; 95% CI = 1.03–1.33; $p = 0.013$). A younger age of first alcohol use was also associated with a higher risk for developing cannabis dependence (HR, 0.88).

In participants who used nicotine first, younger age of cannabis use and maternal alcohol dependence were associated with a higher risk of developing cannabis dependence. As such, the age of first alcohol and nicotine use interacted with other risk factors, including the age of first cannabis use, externalizing disorders, and parental alcohol use, in contributing to the risks of developing CUD.

In a population-based longitudinal study of children between the ages of 6 and 12 with yearly assessments, CUD was assessed at ages 19 to 21 (n = 1,803) to define the overall prevalence rates of the disorder (Pingault et al., 2013). The authors further determined whether childhood inattention and hyperactivity symptoms of ADHD, including oppositional behaviors (e.g., hostile, disobedient, or defiant behaviors), and anxiety and depressive behaviors served as risk factors for developing CUD. Overall, cannabis abuse or dependence (high, moderate, or severe) affected 9.1 percent of the participants during young adulthood. Only oppositional behaviors contributed to the risk of developing CUD (OR, 2.33; 95% CI = 1.4–3.87), whereas anxiety and depressive disorders did not.

To determine early life-course predictors of problem cannabis use in early adulthood, data obtained from a population-based birth cohort study of 2,493 young adults who had been included in the Mater Hospital and University of Queensland Study of Pregnancy (MUSP) were assessed (Hayatbakhsh et al., 2009). In this population, 21 percent of those who ever used cannabis were classified as having a CUD at the 21-year follow-up assessment. Males were 2.5 times more likely to have a CUD than females; children living in a family with the mother reporting more frequent changes in marital status had an increased risk of CUD (OR, 2.9; 95% CI = 1.7–5.0); aggressive and delinquent children were 5.4 times more likely to develop CUD; those with poor school performance at 14 years of age were more likely to have CUD (OR, 3.4; 95% CI = 2.3–4.9); and maternal smoking when the child was 14 years of age also increased risk of CUD (OR, 2.0; 95% CI = 1.6–2.5). Childhood anxiety and depression were not risk factors for developing CUD.

In an effort to determine the association between cannabis use by 18 years of age and risk for CUD at 24 years of age, the frequency of cannabis use was evaluated in a 10-year representative cohort study set in Australia (n = 1,520 participants included in the final assessment), which included six surveys during adolescence (15–17.5 years of age) and two follow-up assessments during young adulthood (at 21 and 24 years of age) (Swift et al., 2008). One-third of the population reported having used cannabis during adolescence, and 37 percent of the adolescent cannabis users were using at least weekly when interviewed at 24 years of age. After adjusting for potential confounding factors, problem cannabis use at 24 years of age was associated with adolescent cannabis use, tobacco

use, and persistent mental health problems. The frequency of cannabis use was evaluated in a follow-up analysis that sought to determine whether moderation of cannabis use among adolescent cannabis users protected against the risk of CUD in young adulthood (Swift et al., 2009). In this study, participants were grouped into one of six categories that reflected their maximum level of adolescent use (i.e., nonusers, occasional to abstinence, occasional persisting, weekly to abstinence, weekly to occasional, and weekly persisting). The study's outcome measures were the level of cannabis use and DSM-IV cannabis dependence in youth adulthood. While 31 percent of the population reported having ever used cannabis, 71 percent of occasional users and 28 percent of weekly users were abstinent in young adulthood. Adolescent weekly or daily users who persisted with regular use (rather than decreased use or becoming abstinent) were at the greatest risk for developing CUD in young adulthood. Therefore, this suggests that moderating adolescent cannabis use can protect against the later problem use that is observed in persistent users. However, regardless of whether the adolescent users moderated their intake, the risk for developing CUD in young adulthood was still significantly greater for adolescent users than for those who never used cannabis.

The Christchurch Health and Development longitudinal birth cohort study (n = 1,265) from New Zealand assessed the probability of developing CUD by young adulthood as a function of various social and demographic factors (Boden et al., 2006). By 18 years of age, 4.7 percent of the population met criteria for cannabis dependence; that number increased to 12.5 percent by 25 years of age. The primary risk factors that predicted the development of CUD included being male and having poor academic performance. Respondents with four or more of the following risk factors had a 50 percent risk of developing cannabis dependence: (1) peer substance use, (2) parental history of a substance use disorder, (3) novelty seeking, (4) cigarette smoking, (5) childhood sexual abuse, and (6) conduct problems.

A longitudinal study of probands from the Oregon Adolescent Depression Project (final n = 816) assessed the prevalence and age of onset of CUD over four assessments between the ages of 16 and 30 (Farmer et al., 2015). The weighted lifetime prevalence of CUD before the age of 30 was estimated to be 19.1 percent; 81.8 of these participants achieved recovery from CUD, and the recurrence rate of CUD was 27.7 percent, which likely occurred within 36 months following the offset of the first CUD diagnosis. Males were more likely to have been diagnosed at some point during their lives than females.

The association between psychopathology and problem cannabis use was also assessed in a longitudinal prospective study of adolescents (n = 1,395) that were 14 to 17 years of age at baseline and who were assessed

at three different time points over the course of 10 years (Wittchen et al., 2007). A prospective analysis determined that mood disorders (OR, 2.5; 95% CI = 1.3–4.7), including bipolar disorder (hypomania and mania) (OR, 2.7; 95% CI = 1.1–6.2), but not including dysthymia (chronic depression) (OR, 2.3; 95% CI = 0.7–6.7), predicted progression to CUD. Generalized anxiety disorder and specific phobias were also associated with CUD (OR, 3.9; 95% CI = 1.1–13.8 and OR, 1.8; 95% CI = 1.1–3.0, respectively). Of note, ADHD, posttraumatic stress disorder (PTSD), and panic/anxiety all failed to predict the development of CUD.

Data from a longitudinal survey of a representative sample (n = 2,032) of secondary students in the Australian state of Victoria who were assessed for cannabis disorders six times between the ages of 14 and 17 from 1992–1995 and again at 20 years of age were evaluated to determine the adolescent precursors of young adult cannabis dependence (Coffey et al., 2003). Variables that independently predicted cannabis dependence in young adulthood included being male (OR = 2.6; $p < 0.01$), regular cannabis use during adolescence (weekly use: OR = 4.9; daily use: OR = 4.6; $p = 0.02$), persistent antisocial behavior (linear effect $p = 0.03$), and persistent cigarette smoking (linear effect $p = 0.02$). Psychiatric comorbidity did not predict cannabis dependence (linear effect, $p = 0.26$). Regular cannabis use during adolescence only increased the risk for CUD in the absence of persistent problem alcohol use.

Discussion of Findings

Overall findings suggest that both biological sex and the age of initiation of cannabis use are positively associated with the development of problem cannabis use. There is also evidence that being male and smoking cigarettes are risk factors that contribute to the progression to problem cannabis use. Additional risk factors for the development of CUD during adolescence that are supported by moderate evidence include frequency of use, oppositional behaviors, younger age of first alcohol use, nicotine use, parental substance use, poor school performance, and childhood sexual abuse. The strength of association between the risk factors for developing problem cannabis use, including other drug use and psychopathology, differs between adult and adolescent onset of cannabis use. It is important to highlight that the studies reviewed above vary in their age grouping and generally include populations that cross from late adolescence into young adulthood. Therefore, the conclusions below pertain to a mixture of age subgroups, including older adolescents and young adults.

One significant limitation of any conclusions drawn from the current literature is that the data on cannabis use, other drug use, and the symptoms of problem cannabis use are derived from self-reports. Another

concern is that the structured interviews used to assess baseline dependent variables (i.e., mental health) and outcomes (i.e., problem cannabis use) vary between studies, and even for some longer longitudinal studies, within individual studies. Also, as mentioned in the first section, understanding the conclusions drawn from the currently available literature should take into account the fact that trends in cannabis use have evolved over the last 10 years and that the strength of cannabis has increased, which likely affects the strength of associations between risk factors and developing problem cannabis use. It is also important to note that there is biological plausibility for many of the risk factors noted above. Specifically, there is preclinical literature that speaks to the sex-dependent effects, exposure to nicotine as a risk factor for CUD, and the age of initiation of use affecting CUD.

CONCLUSION 13-2

Anxiety and Depression

13-2(a) There is limited evidence that childhood anxiety and childhood depression are risk factors for the development of problem cannabis use.

13-2(b) There is moderate evidence that anxiety, personality disorders, and bipolar disorders are not risk factors for the development of problem cannabis use.

13-2(c) There is moderate evidence that major depressive disorder is a risk factor for the development of problem cannabis use.

ADHD

13-2(d) There is moderate evidence that adolescent attention deficit hyperactivity disorder (ADHD) is not a risk factor for the development of problem cannabis use.

13-2(e) There is substantial evidence that stimulant treatment of ADHD during adolescence is not a risk factor for the development of problem cannabis use.

Biological Sex

13-2(f) There is moderate evidence that being male is a risk factor for the development of problem cannabis use.

Other Drug Use

13-2(g) There is moderate evidence that exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use.

13-2(h) There is moderate evidence that neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use.

13-2(i) There is substantial evidence that being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use.

Age

13-2(j) There is substantial evidence that initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use.

13-2(k) There is moderate evidence that during adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use.

Are There Risk and Protective Factors for Severity or Persistence of Problem Cannabis Use?

Psychopathology

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on psychopathology as a risk or a protective factor for the severity or persistence of problem cannabis use.

Primary Literature A case-control study sought to determine the association between a history of psychiatric treatment and persistent cannabis

use disorder (Arendt et al., 2007). Data from the Danish Psychiatric Case Register (n = 3,114; mean age at start of treatment = 25.7 years) were compared to a representative control group that was randomly selected from the general population and matched to the patient population for age and biological sex (n = 15,570). The authors determined that a history of psychiatric treatment was associated with increased rates of reentry into substance abuse treatment for cannabis dependence (OR, 1.26; 95% CI = 1.07–1.48) relative to the control population.

In an Israeli population (n = 1,317; ages ranged from 21–45 years and older), Walsh et al. (2014) conducted in-person structured interviews to examine the association between traumatic exposure and substance dependence (alcohol, nicotine, and marijuana) and to assess whether PTSD accounted for this association. After controlling for alcohol and nicotine dependence, investigators found that PTSD symptoms were associated with increased odds of marijuana dependence (OR, 1.1; 95% CI = 1.04–1.24) and concluded that the severity of PTSD symptoms may increase the risk for substance dependence. It should be noted, however, that these are cross-sectional data and that the directionality and causality of these associations cannot be determined.

A study by Boden et al. (2013) was outside the scope of our primary literature search due to its small sample size, but it was included because of its potential relevance to the committee's prioritized research question. In this study, researchers found that in a small population of cannabis-dependent military veterans (n = 37; mean age of starting sample = 51.3 years), a diagnosis of PTSD was significantly associated with the use of cannabis to cope with PTSD symptoms, the severity of cannabis withdrawal, and three factors of cannabis drug craving (i.e., compulsivity, emotionality, and anticipation) relative to a cannabis-dependent population without a diagnosis of PTSD (n = 57). Furthermore, the severity of PTSD symptoms was associated with an increased severity of cannabis withdrawal and factors of cannabis craving (i.e., compulsivity, emotionality, and anticipation).

Biological Sex

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on biological sex as a risk or a protective factor for the severity or persistence of problem cannabis use.

Primary Literature Data from the NLAES (n = 42,862) were analyzed in an effort to determine the effect of biological sex on the risk and severity of cannabis use disorders (Grant et al., 2006). Of the participants who reported cannabis use at least 12 times, women were less likely to be cat-

egorized with cannabis "abuse/moderate dependence" than men (8 percent versus 14 percent) or "severe abuse/dependence" (3 percent versus 6 percent). While men were consistently more likely than women to report hazardous cannabis use, women were more likely to report withdrawal and to have higher rates of four symptoms of dependence in the "abuse/moderate dependence" category.

A longitudinal study of probands from the Oregon Adolescent Depression Project (final n = 816) assessed recovery from CUD as a function of biological sex (Farmer et al., 2015). Females achieved recovery from CUD at a significantly faster rate than males (females = 24.2 months, standard deviation [SD] = 24.8; males = 41.2 months, SD = 42.7; p = .006), although recurrence rates of CUD did not differ between males and females (30.0% of males, 25.4% of females, p = 0.564).

Discussion of Findings

In addition to the limitations cited for the first two sections such as issues with self-reported cannabis use, the respondents' reporting of symptoms of problem cannabis use, and data restricted to trends of cannabis use and cannabis strength that do not accurately reflect current trends, the current findings are additionally restricted to limited follow-up with participants and to only a few of the risk factors highlighted in the second section, including biological sex. The impact of the primary risk factors for developing problem cannabis use identified in the second section of this chapter, including the age of initiation of use, biological sex, and other drug use, should be explored as risk factors for both the severity and the recurrence of problem cannabis use over extended periods of time.

CONCLUSION 13-3

13-3(a) There is moderate evidence of a statistical association between the persistence of problem cannabis use and a history of psychiatric treatment.

13-3(b) There is substantial evidence of a statistical association between being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females.

13-3(c) There is moderate evidence of a statistical association between problem cannabis use and increased severity of posttraumatic stress disorder symptoms.

RESEARCH GAP

To address the research gaps relevant to problem cannabis use, the committee suggests the following:

- The impact of the primary risk factors for developing problem cannabis use needs to be explored as risk factors for both the severity and the recurrence of problem cannabis use over extended periods of time.

SUMMARY

This chapter outlines the committee's efforts to review the current evidence base (1) to determine likelihood of developing problem cannabis use and (2) to identify the potential risk and protective factors involved in the development or exacerbation of problem use. The vast majority of the conclusions formed within this chapter were of moderate evidence; however, the conclusions that were determined to have substantial evidence were formed by research that examined the impact of biological sex, cannabis use at an early age, and past use of cannabis on problem cannabis use. Many of the chapter conclusions pertain to a mixture of age groups, including older adolescents and young adults. See Box 13-1 for a summary list of the chapter's conclusions.

These research conclusions may have important public health implications; however, it is important that the conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections above. It is also important to understand that the conclusions drawn from the currently available literature should take into account the fact that trends of cannabis use have evolved over the past 10 years and note that the strength of cannabis has increased, which likely has affected strength of associations between risk factors and developing problem cannabis use. Greater attention to the research limitations (e.g., reliance on self-reported cannabis use, limited detail on the amount of cannabis used per occasion, polydrug use, limited follow-up, and so on) and improvements to study design and methodological approach would bolster the evidence base and help ensure that substantial evidence concerning problem cannabis use is available.

BOX 13-1
Summary of Chapter Conclusions*

There is substantial evidence that:

- St mu ant treatment of attent on defic t hyperact v ty d sorder (ADHD) dur- ng ado escence s *not* a r sk factor for the deve opment of prob em cannab s use (13-2e)
- Be ng ma e and smok ng c garettes are r sk factors for the progress on of cannab s use to prob em cannab s use (13-2)
- In t at ng cannab s use at an ear er age s a r sk factor for the deve opment of prob em cannab s use (13-2j)

There is substantial evidence of a statistical association between:

- Increases n cannab s use frequency and the progress on to deve op ng prob em cannab s use (13-1)
- Be ng ma e and the sever ty of prob em cannab s use, but the recurrence of prob em cannab s use does not d ffer between ma es and fema es (13-3b)

There is moderate evidence that:

- Anx ety, persona ty d sorders, and b po ar d sorders are *not* r sk factors for the deve opment of prob em cannab s use (13-2b)
- Major depress ve d sorder s a r sk factor for the deve opment of prob em cannab s use (13-2c)

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- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)
- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, opposition behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

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* Numbers in parentheses correspond to chapter conclusion numbers

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14

Cannabis Use and the Abuse of Other Substances

Chapter Highlight

- Cannabis use is likely to increase the risk for developing substance dependence (other than cannabis use disorder).

Since the 1970s, researchers have debated about the role that cannabis may play in the "gateway hypothesis," which suggests that individuals rarely use certain substances, such as heroin or cocaine, without first having used "gateway" substances, such as alcohol, tobacco, or cannabis (Kandel, 1975; Vanyukov et al., 2012). While some research has shown an association between cannabis use and the subsequent use of other illicit drugs, the predictors of progression from cannabis use to other illicit drugs remain largely unknown (Secades-Villa et al., 2015). Emerging animal studies have begun to explore the hypothesis that cannabis exposure may enhance the susceptibility to the addictive effects of other drugs (Panlilio et al., 2012). Researchers have also begun to explore the "reverse gateway hypothesis." This hypothesis posits that cannabis use is a reverse gateway to the initiation of other addictive drugs such as nicotine and alcohol (Agrawal et al., 2008).

In the United States, the number of individuals 12 years and older using illicit drugs rose each year between 2002 and 2013. In 2014 alone, the National Survey on Drug Use and Health reported that in this age range 27 million individuals—or almost 1 in every 10 Americans—were found

to have used illicit drugs within the past 30 days, 66.9 million were current users of tobacco, and another 139.7 million were past-month alcohol drinkers (CBHSQ, 2015). With illicit drug use on the rise, the need for understanding and addressing when and how individuals start using illicit drugs is of the utmost importance. Of similar importance is understanding the role that cannabis might play in the use of other addictive substances such as tobacco and alcohol.

The committee responsible for the 1999 Institute of Medicine (IOM)[1] report *Marijuana and Medicine: Assessing the Science Base* discussed the "gateway hypotheses" but did not make any specific conclusions about its relevance to cannabis use. That report questioned the designation of cannabis as a "gateway" drug because its use is often preceded by underage drinking and tobacco use, and no conclusive evidence supporting a causal link between cannabis use and the use of other illicit drugs was found at that time (IOM, 1999).

In this chapter, the committee reviews the research evidence that most directly addresses the prioritized research questions related to the associations among cannabis use and (1) the initiation of use of other substances, (2) changes in the rates and use patterns of other substances and, (3) and the development of other substance dependence or substance abuse disorder. Due to the time constraints of the study, additional search constraints were added to prioritize the types of studies that would likely produce the clearest research conclusions. For example, literature searches were limited to articles that included the search terms "longitudinal," "prospective," and "case-control," and the committee did not review controlled laboratory studies with cannabis. Although the committee did not find any fair- or good-quality systematic reviews covering these issues, 12 primary articles published since the 1999 IOM report were identified and are reviewed in this chapter.

ABUSE OF OTHER SUBSTANCES

Is There an Association Between Cannabis Use and the Initiation of Use of Other Substances?

Tobacco/Nicotine

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the initiation of tobacco/nicotine use.

[1] As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

Primary Literature Mayet and colleagues (2016) conducted a retrospective cohort study of the transitions between tobacco, cannabis, and other illicit drugs initiations. Data on 16,421 adults ages 18 to 34 were collected from two French nationwide health and behavior studies conducted in 2005 and 2010. The data used included the age of initiation of substance use (cannabis, tobacco, alcohol, other illicit drugs), current use, and a number of other variables (e.g., gender, socioeconomic level). A total of 436,206 observations based on yearly measures were provided by the study subjects, including 17,510 transitions from one state of use to another. A Markov multistate model was constructed to examine transitions from cannabis use to the use of other drugs. The model's results show that the probability of initiating tobacco after cannabis use (10.39 percent) was significantly greater ($p < 0.001$) than the probability of initiating cannabis after tobacco use (3.47 percent). The primary study limitations include potential recall bias on the age of initiation and the usual issues surrounding the self-reporting of substance use.

Mayet and colleagues (2011) analyzed data collected from a cross-sectional survey of 29,393 17-year-old adolescents attending a compulsory military information session to assess transitions from cannabis use to the use of other substances. Data from study participants were captured via a self-administered questionnaire on substance use; thus, participants were considered followed from birth through 2011 by way of recall data. Substance use was categorized as "no lifetime use of tobacco and cannabis," "tobacco initiation only," "cannabis initiation only," "daily use of tobacco only," "daily use of cannabis only," or "daily use of both tobacco and cannabis" (Mayet et al., 2011, p. 1102). A Markov multistate model was constructed to examine the transition states among the first-substance-use cohorts from no use/initial substance use to other substance use states.

Study participants were more likely to use tobacco (72.2 percent) than cannabis (49.4 percent), and only 2 percent of those using both tobacco and cannabis reported having used cannabis before tobacco (Mayet et al., 2011). With respect to transitions from initial substance use, the risk of initiating tobacco use from no lifetime use was 17.6 times greater (95% confidence interval [CI] = 16.5–18.9) than first initiating cannabis use. Among individuals initiating use with cannabis, the transition to first tobacco use was 3.2 times greater (95% CI = 2.9–3.6) than the transition from no lifetime use of cannabis to first tobacco use (Mayet et al., 2011). However, the transition of first tobacco use to cannabis was 42.1 times greater (95% CI = 39.3–45.1) than the transition from no lifetime use of tobacco to first cannabis use. The transition from daily use of cannabis to daily use of both cannabis and tobacco was 3.0 times greater (95% CI = 2.0–4.4) than the transition from daily tobacco use to daily use of both cannabis and tobacco (Mayet et al., 2011). The authors also found that

cannabis initiation did not increase the risk of a tobacco user transitioning to a daily cannabis smoker. The study's limitations include potential problems with recall bias and self-reporting of substance use.

Opioids

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the initiation of use of opioids.

Primary Literature In the retrospective cohort study described earlier, Mayet and colleagues (2016) also explored the transition from cannabis use to the use of other illicit drugs. They found that the probability of initiating other illicit drugs after cannabis did not differ significantly from the probability of starting with other illicit drugs.

Mixed Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the initiation of use of other substances.

Primary Literature Novins and Barón (2004) reported on risk factors for the initiation of substance use and transition to other substance use among American Indian adolescents living west of the Mississippi. Survey data collected as part of the Voices of Indian Teens longitudinal study from 1993 to 1996 were used to calculate the conditional probability that an adolescent who reported lifetime use of cannabis (Stage 1) would progress to report a lifetime use of stimulants, sedatives, cocaine, or other drugs such as hallucinogens, phencyclidine, or heroin (Stage 2).

For analysis purposes, the initial sample of 2,356 adolescents was reduced to 1,244 adolescents due to exclusions related to continued lifetime abstention or transition to Stage 2 before the study began and to inconsistent responses between the two waves of data collection, as well as those lost to follow-up (Novins and Barón, 2004). The hazard ratio (HR) for the progression of cannabis use (Stage 1) to a harder substance (Stage 2) was 2.737 ($p < 0.01$). The authors noted that the study had a number of limitations, including generalizability to other populations, the self-reporting of substance use data, an inability to include tobacco use in the analysis because the survey did not differentiate between ceremonial and non-ceremonial tobacco use, and the potential for underestimating the results because of the potential bias created by individuals lost to

follow-up who may have had different (higher) patterns of substance use than those remaining in the study.

Discussion of Findings

The small number of studies reviewed provide limited evidence that cannabis use increases the rates of initiation of other drug use, mainly tobacco. Two studies had relatively large samples. The data do not provide compelling evidence that cannabis is associated with the initiation of other drugs of abuse, although this is one possibility. Other possibilities that could explain these findings include easier access to cannabis than to other illicit substances and common risk factors for both cannabis use and the use of other substances. Although cannabis use is associated with increased odds of transitioning to tobacco use relative to non-cannabis users, tobacco use was associated with far greater odds of transitioning to cannabis use relative to non-tobacco users. These data highlight tobacco use as a key risk factor for the initiation of cannabis use.

CONCLUSION 14-1 There is limited evidence of a statistical association between cannabis use and the initiation of tobacco use.

Is There an Association Between Cannabis Use and the Rates and Use Patterns of Other Substances?

Alcohol

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of drinking alcohol.

Primary Literature Buu and colleagues (2015) conducted a secondary data analysis of eight waves of data collected from 850 high-risk adolescents participating in the longitudinal Flint Adolescent Study to assess risk and protective factors for substance use and other health risk behaviors through adulthood (i.e., ages 14–24 years). The impact of early or later onset (i.e., age at first use) and of the quantity and frequency of cannabis use on heavy drinking were specific research questions. A linear mixed model was used to determine the longitudinal effects of nicotine and marijuana on heavy drinking while controlling for the early onset of alcohol use. Model results indicate that both early onset cannabis users (β, 0.2263; standard error [SE] = 0.0445; $p < 0.0001$), late onset cannabis users (β, 0.1838; SE = 0.0461; $p < 0.0001$), and those who used cannabis more

frequently (β, 0.2667; SE = 0.0119; p <0.0001) were all at a higher risk of heavy alcohol drinking than those who did not use cannabis at all (Buu et al., 2015). Among this population, about 80 percent of the study participants were black and had grade point averages of 3.0 or below and thus are not representative of the general youth population. Furthermore, the lifetime prevalence of substance use was higher in the study population than in the general population. The impact of cannabis use on nicotine use was not reported.

Opioids

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of opioids.

Primary Literature In a longitudinal study of a random sample of 120 adolescents ages 12 to 18 years who were admitted to a level 1 trauma center or an emergency department for injury, Whiteside and colleagues (2016) found that preinjury cannabis use was an independent predictor of continued prescription opioid use up to 12 months after discharge (relative risk, 1.69; 95% CI = 1.09–2.6). Cannabis use was assessed via a single-item question regarding cannabis use (yes/no) in the year before the injury, and the use of a range of prescription opioids (codeine, hydrocodone, oxycodone, etc.) was assessed and categorized as yes or no at months 2, 5, and 12. At 1 year post injury, 12.5 percent of adolescents were still using prescribed opioids. The study's limitations include the use of self-reported data to determine preinjury cannabis use and opioid use, the reliance on a small study sample, and the fact that the sample was collected at an urban academic trauma center, which thus limited the generalizability of the findings.

Tobacco/Nicotine

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of tobacco and nicotine dependence.

Primary Literature Agrawal and colleagues (2008) studied women cannabis users and patterns of smoking and nicotine dependence. Data were collected as part of the Missouri Adolescent Female Twin Study (MOAFTS), a cohort study of 3,787 young adult twin females ages 18 to 29 years, who were originally interviewed in 1994–1999 and subsequently reinterviewed in 2002–2005. Data collection included lifetime cannabis

use (ever used cannabis and other measures of frequency and use) and cannabis dependence (determined by a lifetime history of one or more of four *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV] abuse critera or one or more of six DSM-IV dependence criteria). Regular cigarette smoking among participants was determined by responding positively to having smoked 100 or more cigarettes lifetime and smoking 20–99 cigarettes at least once per week for a period of 2 months or longer. Nicotine dependence was defined using the seven DSM-IV dependence criteria, with at least three symptoms clustering within the same 12-month period. Data on a number of covariates were also collected, including measures of behavioral disinhibition, negative affect regulation, and other measures of psychopathology. In this sample, 44.2 percent of the participants were cannabis users, 34.7 percent were classified as regular cigarette smokers, and 17.4 percent were designated as nicotine dependent based on DSM-IV criteria. It is also important to note that only 6.8 percent of participants reported smoking their first cigarette before using cannabis for the first time.

Survival analyses were used to examine whether women who smoked cannabis were at an increased risk of moving from experimenting with smoking (but not first time smoking) to becoming a regular smoker. After adjusting for covariates, the results indicate that women with a prior history of cannabis use were 4.4 times more likely (HR, 4.41; 95% CI = 3.57–5.44) to transition from experimenting with smoking to becoming regular smokers. An additional analysis was conducted to assess spurious associations caused by the onset of cannabis use and regular smoking in the same year. The results of this analysis showed a diminished effect size; the effect size of the hazards of regular smoking in cannabis users was reduced to 1.8 (95% CI = 1.5–2.2) for those meeting this condition.

Mixed Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of substances other than cannabis.

Primary Literature To examine trajectories of adolescent cannabis and alcohol users Patton and colleagues (2007) analyzed data from a 10-year cohort study of health in 2,032 adolescents and young adults living in Victoria, Australia. Data were collected in eight waves over the study period from an initial study sample of adolescents who were in mid-secondary school in 1992. About 95 percent of students from the initial study sample participated in Waves 1 through 6, and 75 percent of the students participated in Wave 8. The frequency of cannabis and alcohol

use was categorized in three categories: "any alcohol or cannabis use," "at least moderate-risk alcohol or cannabis use," and "high-risk alcohol or cannabis use" (Patton et al., 2007, p. 609). Logistic regression modeling was used to explore the associations between substance use in adolescence (at about 15 years old in Wave 1) and later substance use in early adulthood (at about 25 years old in Wave 8).

After adjusting for a number of social and behavioral factors and persistent substance use measures, the researchers found that adolescents with moderate-risk cannabis use were seven times as likely to develop high-risk cannabis use (odds ratio [OR], 7.4; 95% CI = 3.3–17) and twice as likely to develop high-risk alcohol use in early adulthood (OR, 2.2; 95% CI = 1.1–4.5) compared with students with no hazardous alcohol use or daily cannabis use (Patton et al., 2007).

Among this population, the risk was also elevated for daily cigarette smoking (OR, 3.0; 95% CI = 1.7–5.4), for the use of amphetamines (OR, 6.0; 95% CI = 3.6–10.0), for the use of ecstasy (OR, 7.2; 95% CI = 4.3–12.0), and for the use of cocaine (OR, 4.7; 95% CI = 2.3–9.7) within the past 12 months, as reported in Wave 8 (Patton et al., 2007). The study's limitations include a 25 percent reduction in the initial sample between Wave 1 and Wave 8 (imputation techniques were used to mitigate potential bias related to students missing waves of the survey), the use of self-reports to determine substance use, and questions about the generalizability of the study to other populations.

The use of cannabis and relapse after discharge from a substance abuse program were the focus of a study conducted by Aharonovich and colleagues (2005). This longitudinal study followed 349 patients who had undergone and successfully completed inpatient treatment for a DSM-IV diagnosis of alcohol, cocaine, or heroin dependence; patients had not experienced mania or non-affective psychosis. Patients were followed up after discharge at months 6, 12, and 18 to update the Psychiatric Research Interview for Substance and Mental Disorders. Responses were analyzed to assess cannabis use and return to substance abuse, sustained remission from substance abuse, and relapse to substance abuse after sustained remission. Of the 349 patients participating in the study, 250 contributed data through at least one follow-up interview; the study results are based on this subset of patients. Of the 250 patients dependent on alcohol, cocaine, or heroin at baseline who did not achieve sustained remission from using these substances, 41.4 percent used cannabis during follow-up after hospital discharge compared to 15.4 percent of those who had achieved remission ($p < 0.0001$) (Aharonovich et al., 2005). Among the patients dependent on alcohol at baseline who failed to achieve sustained remission, 38.7 percent used cannabis ($p < 0.004$), and among patients dependent on cocaine at baseline who failed to achieve sustained remis-

sion, 52.5 percent used cannabis during follow-up after hospital discharge ($p < 0.03$). Relapse after sustained remission was also seen among patients who used cannabis during follow-up.

A Cox proportional model that adjusted for sociodemographic variables and diagnoses of substance dependence and a number of psychiatric symptoms and disorders was developed to examine the effects of cannabis use on a number of outcomes, including the return to substance use (multiple substance use, alcohol only, cocaine only, and heroin only), sustained remission from substance use, and relapse to substance use. HRs were significant ($p < 0.0001$) for cannabis use and a return to the use of multiple substances, alcohol only, and cocaine only. Cannabis use was associated with a statistically significant reduced hazard of achieving a sustained remission from multiple substance use and cocaine use specifically ($p < 0.05$). In addition, cannabis use was found to increase the hazard of relapse to alcohol use ($p < 0.05$).

Discussion of Findings

The primary literature reviewed present limited evidence that cannabis use affects the rates and patterns of the use of other substances. With regard to alcohol use, cannabis users were found to be at a higher risk for heavy drinking than nonusers. With regard to opioids, cannabis use predicted continued opioid prescriptions 1 year after injury. Finally, cannabis use was associated with reduced odds of achieving abstinence from alcohol, cocaine, or polysubstance use after inpatient hospitalization and treatment for substance use disorders. The limitations of these studies include their lack of generalizability due to their use of restricted study populations, their limited assessment of cannabis use, the lack of dose–response relationships, and the potential for self-report bias.

CONCLUSION 14-2 There is limited evidence of a statistical association between cannabis use and changes in the rates and use patterns of other licit and illicit substances.

Is There an Association Between Cannabis Use and the Development of Other Substance Dependence or Other Substance Abuse Disorder?

Alcohol

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the development of alcohol dependence or alcohol use disorder.

Primary Literature Buu and colleagues (2014) assessed the long-term effects of cannabis use on alcohol problems and alcohol use disorder (AUD) using data from the Michigan Longitudinal Study. The researchers followed a sample of 160 female–male sibling pairs from high-risk families (sample total of 320 individuals) from ages 3–5 to 21–23 years, assessing the participants every 3 years using the Drinking and Drug History Questionnaire, Diagnostic Interview Schedule, Diagnostic Interview Schedule for Children, and the Health and Daily Living Questionnaire. Data were collected on age at first use of alcohol, cannabis, and nicotine as well as the quantity and frequency of use and were analyzed using a linear mixed model. The authors concluded that a higher frequency of cannabis use was related to greater odds of developing drinking problems (β, 0.55; SE = 0.08; $p < 0.05$) and to meeting an AUD diagnosis (β, 0.59; SE = 0.09; $p < 0.05$) (Buu et al., 2014). However, the odds were not as high as those associated with the frequency of alcohol consumption on the odds of developing drinking problems (β, 1.90; SE = 0.10; $p < 0.05$) and the odds of meeting an AUD diagnosis (β, 1.75; SE = 0.31; $p < 0.05$) (Buu et al., 2014). Furthermore, an early onset of cannabis use was not found to contribute to AUD. A major limitation of this study is that the participant population included children who had intact families in early childhood, families that were at high risk for developing AUD, and families of minority race/ethnicity, thus limiting the generalizability of the study results.

Tobacco/Nicotine

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the development of tobacco or nicotine dependence or tobacco or nicotine abuse disorder.

Primary Literature Timberlake and colleagues (2007) conducted a study to examine the role of cannabis use in adolescence and the likelihood of developing nicotine dependence and initiating daily tobacco smoking at an earlier age. Survey data were collected from 90,118 students participating in the National Longitudinal Study of Adolescent Health conducted in 132 U.S. schools (public and private) between September 1994 and April 1995. A subsample of participants was followed up at three points with more in-depth surveys, a baseline survey (Wave I), and two subsequent surveys (Wave II, 1 year after the baseline survey, and Wave III, 6 years later). Of these, 5,963 unrelated participants formed the primary sample and included individuals who had not smoked cigarettes by the baseline survey (Wave I) but smoked at least one cigarette by Wave III. Participants ranged in age from 18.3 to 27.7 years. Data on lifetime use of

cannabis and prior-month use at Wave I, age at daily cigarette smoking, and lifetime and current nicotine dependence at Wave III were available for these participants. A smaller sample of 1,447 participants who had tried cannabis by Wave I and for which data on the age of first use was available was used to examine lifetime and current nicotine dependence 6 years later. Cannabis use was classified as no lifetime use, experimental use (1–10 times), and regular use (greater than 10 times). Age at first use was also collected from adolescents who had experimented with cannabis by Wave I of the survey. Nicotine dependence was defined using the Fagerstrom Test for Nicotine Dependence. Demographic risk factor data were also collected. Survey-based logistic regression analysis and censored regression techniques were used to predict outcomes.

Results from this study indicate that regular lifetime users of cannabis at Wave I were 1.89 times more likely to develop lifetime nicotine dependence ($t = 2.3$ $p < 0.05$, adjusted odds ratio [aOR], 1.89; 95% CI = 1.09–3.30) than nonusers. Past-month users (both experimental and regular) at Wave I were 1.83 times more likely to develop lifetime nicotine dependence ($t = 2.3$ $p < 0.05$, aOR, 1.83; 95% CI = 1.08–3.11) than nonusers. Furthermore, lifetime users who began using at later ages (23–27) were less likely to develop nicotine dependence at Wave III compared to those who began using at earlier ages ($t = -3.3$ $p < 0.01$, aOR, 0.82; 95% CI = 0.73–0.93). Limitations associated with this study include self-reported data on substance use, and recall bias.

Agrawal and colleagues (2008), as described in the above section, studied women cannabis users and patterns of smoking and nicotine dependence. Survival analyses were used to examine whether women who smoked cannabis were at an increased risk of moving from regular smoker to nicotine dependent. After adjusting for covariates, the results indicate that women with a prior history of cannabis use were 2.8 times more likely (HR, 2.80; 95% CI = 1.84–4.26) to transition from regular smoking to nicotine dependence. Limitations associated with this study include the lack of generalizability to men, self-reported data on substance use, and recall bias.

Mixed Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the development of substance dependence or substance abuse disorder.

Primary Literature In a longitudinal U.S. study of a nationally representative sample of 34,653 adults 18 years or older, Blanco and colleagues

TABLE 14-1 Cannabis Use in the Past 12 Months and Incident Psychiatric Disorders in Wave 2

Incident Psychiatric Disorders in Wave 2	Adjusted OR (95% CI)
Any substance use disorder (includes cannabis use disorder)	6.2 (4.1–9.4)
Any alcohol use disorder	2.7 (1.9–3.8)
Alcohol abuse	1.5 (1.1–2.0)
Alcohol dependence	1.9 (1.4–2.7)
Other drug use disorder	2.6 (1.6–4.4)
Other drug abuse	3.4 (2.5–5.4)
Other drug dependence	2.7 (1.6–4.5)
Nicotine dependence	1.7 (1.2–2.4)

NOTE: CI = confidence interval; OR = odds ratio.
SOURCE: Adapted from Blanco et al., 2016.

(2016) examined the association between cannabis use and the risk of developing substance abuse and other mental health disorders. This study investigated the potential association between cannabis use in the past year (Wave 1) with incident substance use disorders, alcohol abuse and dependence, other drug abuse and dependence, and nicotine dependence 3 years later (Wave 2). Both Wave 1 and Wave 2 adjusted for sociodemographic characteristics, a family history of substance use disorder, a disturbed family environment, childhood parental loss, low self-esteem, social deviance, education, recent trauma, past and present psychiatric disorders, and the respondent's history of divorce. The researchers found that, after adjusting for covariates, cannabis use in the 12 months preceding the interview was associated with an increased risk of developing any substance use disorders, including Cannabis Use Disorder (OR, 6.2; 95% CI = 4.1–9.4) (Blanco et al., 2016). The adjusted ORs for all incident psychiatric disorders in Wave 2 are presented in Table 14-1.

The frequency of cannabis use in Wave 1 was also associated with an incidence of any substance use disorder in Wave 2 (aOR, 1.9; 95% CI = 1.7–2.1), indicating a dose–response association between cannabis use and substance use disorder.[2] Some of the limitations of this study included the fact that substance use was ascertained by self-report, that there was a possibility of residual confounding, and that the follow-up period was limited to 3 years (Blanco et al., 2016).

Palmer and colleagues (2009) analyzed the substance use experiences

[2] Frequency of cannabis use was measured as "no use," "some use but less than one use per month," and "one or more uses per month."

of 1,733 individuals (ages 12–25) who participated in the Colorado Community Twin Study. Data on substance use experimentation and repeated use were collected via self-reported questionnaires and psychiatric interviews in two waves about 5 years apart. Substance abuse and dependence were assessed using the Composite International Diagnostic Interview–Substance Abuse Module (CIDI–SAM) structured interview. With respect to substance use, experimentation was defined as "having used a substance one or more times in a person's lifetime"; repeated marijuana use was defined as having used cannabis "six or more times in a respondent's lifetime"; and cannabis abuse and dependence were defined based on the DSM-IV as having compulsive use without generally developing physiological dependence (APA, 1994, p. 216; Palmer et al., 2009, pp. 79–80).

Results show that the risks of alcohol abuse/dependence (OR, 3.44; 95% CI = 1.93–6.12) and tobacco dependence (OR, 4.12; 95% CI = 2.26–7.51) were greater in individuals who used cannabis more than once in their lifetime (without meeting a diagnosis of cannabis substance use disorder) compared to those who did not use cannabis (Palmer et al., 2009). Individuals diagnosed with cannabis use disorder had higher odds of being diagnosed with alcohol abuse/dependence (OR, 8.78; 95% CI = 3.15–24.53) and tobacco dependence (OR, 8.61; 95% CI = 3.15–23.56) than those who did not use cannabis. However, once the logistic regression models were adjusted for the individuals' involvement with alcohol and tobacco, the ORs no longer reached significance (Palmer et al., 2009).

The researchers found that individuals with cannabis use disorder were not at higher risk for alcohol abuse/dependence (OR, 1.77; 95% CI = 0.54–5.78) or tobacco dependence (OR, 2.61; 95% CI = 0.78–8.72) compared with those who had used cannabis more than once in their lifetime but did not have cannabis use disorder (Palmer et al., 2009). They note that the cannabis and other substance use results indicate "a model of generalized risk since substance use disorders on any substance in young adulthood could be predicted by involvement with any of the three substances in adolescence" (Palmer et al., 2009, p. 78). Study limitations include the difficulty capturing the more severe cases in the cohort, as they are generally not reported; questions about the reliability of self-reporting; of the fact that covariates of substance abuse were not included in the logistic regression models; and the failure of the authors to impose clustering criteria or to distinguish between dependence with or without physiological symptoms (Palmer et al., 2009).

Using data from 1,265 participants of the Christchurch Health and Development longitudinal birth cohort study, Fergusson and colleagues (2008) explored factors associated with illicit drug use, abuse, or dependence among study participants at ages 16 to 25. Cannabis use data were collected for each year and were classified into four levels of frequency:

"did not use cannabis," "used less than monthly on average (1–11 times)," "used at least monthly on average (12-50 times)," and "used at least weekly (>50 times)" (Fergusson et al., 2008, p. 169). Annual frequency of cannabis use was the strongest predictor of illicit drug use (β, 1.58; SE = 0.06, p <0.0001) and drug abuse or dependence (β, 1.73; SE = 12, p <0.0001) across age groups (Fergusson et al., 2008). The interaction between cannabis use and age was also explored and the association was found to diminish with increasing age. The adjusted odds ratios for the risk of illicit drug use and abuse/dependence for participants who used cannabis at least weekly are presented in Table 14-2 below. Study limitations include questions about the generalizability of the study and the fact that the assessments were based on self-reported data. The confidence intervals for some results are wide.

Discussion of Findings

Most of the studies reviewed indicate an association between cannabis use and use of or dependence on other substances, with some data indicating this effect is more pronounced in younger individuals and is dependent on the dose or frequency of cannabis use. The strengths of some studies cited include the study designs (longitudinal cohort stud-

TABLE 14-2 Adjusted Odds Ratios (and 95% Confidence Intervals) for at Least Weekly Cannabis Use and Risk Factors for Cannabis Use and Illicit Drug Abuse/Dependence, at Ages 16–17, 20–21, and 24–25

Adjusted Odds Ratios for at Least Weekly Frequency of Use of Cannabis and the Risk of Illicit Drug Use at Specific Ages		
Age	aOR	95% CI
16–17	92.20	46.53–182.72
20–21	26.31	17.50–39.69
24–25	7.53	4.48–12.43
Adjusted Odds Ratios for at Least Weekly Frequency of Use of Cannabis and Risk of Illicit Drug Abuse/Dependence		
16–17	117.92	26.31–523.74
20–21	27.61	11.24–67.90
24–25	6.49	2.19–19.20

NOTE: CI = confidence interval; aOR = adjusted odds ratio.
SOURCE: Adapted from Fergusson et al., 2008.

ies), the existence of large sample sizes, and the fact that adjustments were made for a variety of confounders. The magnitude of the associations appears in the moderate range. The limitations of the studies include, in most cases, the use of self-report for cannabis use, recall bias, and, in some cases, the limited duration of follow-up.

CONCLUSION 14-3 There is moderate evidence of a statistical association between cannabis use and the development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs. The development of problem cannabis use is described in Chapter 13 of this report.

RESEARCH GAPS

To address the research gaps relevant to cannabis use and the abuse of other substances, the committee suggests the following:

- Additional studies are needed to determine whether cannabis use is an independent risk factor for, or causally contributes to, the initiation or use of and dependence on other drugs of abuse later in life.
- In states with legalized recreational cannabis, there need to be longitudinal studies that examine whether the prevalence of use of other drugs parallels the increase in prevalence of cannabis use.

SUMMARY

This chapter summarizes current research evidence on the association between cannabis use and the potential for abusing other substances. Several important research conclusions were reached (see Box 14-1); however, it is important that these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections above.

BOX 14-1
Summary of Chapter Conclusions*

There is moderate evidence of a statistical association between cannabis use and:

- The deve opment of substance dependence and/or a substance abuse d sorder for substances, nc ud ng a coho , tobacco, and other c t drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The n t at on of tobacco use (14-1)
- Changes n the rates and use patterns of other c t and c t substances (14-2)

* Numbers in parentheses correspond to chapter conclusion numbers

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Part IV

Research Barriers and Recommendations

15

Challenges and Barriers in Conducting Cannabis Research

Several states have legalized cannabis for medical or recreational use since the release of the 1999 Institute of Medicine (IOM)[1] report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999). As of October 2016, 25 states and the District of Columbia had legalized the medical use of cannabis, while 4 states and the District of Columbia had also legalized recreational cannabis use (NCSL, 2016; NORML, 2016a).[2] In November 2016, voters in California, Maine, Massachusetts, and Nevada approved ballot initiatives to legalize recreational cannabis, while voters in Arkansas, Florida, Montana, and North Dakota approved ballot initiatives to permit or expand the use of cannabis for medical purposes (NORML, 2016b).

Policy changes are associated with marked changes in patterns of cannabis use. In recent years, the number of U.S. adolescents and adults ages 12 and older who reported using cannabis increased by 35.0 percent and 20.0 percent for use in the past month and in the past year, respectively (Azofeifa et al., 2016). Revenue from the sale and taxation of cannabis can serve as a proxy measure for cannabis use and suggests that the scope of cannabis use in the United States is considerable. For example, the total estimated value of legal cannabis sales in the United States was $5.7 bil-

[1] As of March 2016, the Health and Medicine Division continues the task of producing consensus studies and convening activities previously undertaken by the Institute of Medicine (IOM).

[2] The count of states where cannabis is legalized for medical use includes Ohio and Pennsylvania, where medical cannabis laws were not operational as of October 2016 (NCSL, 2016).

lion in 2015 and $7.1 billion in 2016 (Arcview Market Research and New Frontier Data, 2016). At the state level, the Colorado Department of Revenue reported that sales and excise taxes on recreational and medical cannabis sales totaled $88,239,323 in fiscal year 2015 (CDOR, 2016a, p. 29),[3] and in Washington, state and local sales taxes and state business and occupation taxes on recreational and medical cannabis totaled $53,410,661 in fiscal year 2016 (WDOR, 2016a,b).[4]

Despite these changes in state policy and the increasing prevalence of cannabis use and its implications for population health, the federal government has not legalized cannabis and continues to enforce restrictive policies and regulations on research into the health harms or benefits of cannabis products that are available to consumers in a majority of states. As a result, research on the health effects of cannabis and cannabinoids has been limited in the United States, leaving patients, health care professionals, and policy makers without the evidence they need to make sound decisions regarding the use of cannabis and cannabinoids. This lack of evidence-based information on the health effects of cannabis and cannabinoids poses a public health risk.

In order to promote research on cannabis and cannabinoids, the barriers to such research must first be identified and addressed. The committee identified several barriers to conducting basic, clinical, and population health research on cannabis and cannabinoids, including regulations and policies that restrict access to the cannabis products that are used by an increasing number of consumers and patients in state-regulated markets, funding limitations, and numerous methodological challenges. The following sections discuss these barriers in detail.

REGULATORY AND SUPPLY BARRIERS

Regulatory Barriers

Investigators seeking to conduct research on cannabis or cannabinoids must navigate a series of review processes that may involve the National Institute on Drug Abuse (NIDA), the U.S. Food and Drug Administration (FDA), the U.S. Drug Enforcement Administration (DEA), institutional review boards, offices or departments in state government, state boards

[3] $22,225,750 (Marijuana Sales Tax [2.9%]) + $42,017,798 (Retail Marijuana Sales Tax [10%]) + $23,995,775 (Retail Marijuana Excise Tax [15%]) = $88,239,323.

[4] Medical Cannabis: $5,236,536 (State Retail Sales Tax) + $792,906 (State Business and Occupation Tax) + $ 2,084,323 (Local Retail Sales Tax) = $8,113,765. Recreational Cannabis: $30,017,823 (State Retail Sales Tax) + $4,050,212 (State Business & Occupation Tax) + $11,228,861 (Local Retail Sales Tax) = $45,296,896. $8,113,765 (Total Medical Cannabis Taxes) + $45,296,896 (Total Recreational Cannabis Taxes) = $53,410,661.

of medical examiners, the researcher's home institution, and potential funders. A brief overview of some of these review processes is discussed.

Researchers conducting clinical research on biological products such as cannabis must submit an investigational new drug (IND) application to the FDA. As a next step, the investigator may contact NIDA, an important source of research-grade cannabis, to obtain an administrative letter of authorization (LOA). An LOA describes the manufacturer's facilities, as well as the availability and pertinent characteristics of the desired cannabis product (e.g., strains, quality, strength, pharmacology, toxicology). To safeguard against the acquisition of cannabis or cannabinoids for nonresearch purposes, investigators must also apply for a DEA registration and site licensure before conducting studies involving cannabis or any of its cannabinoid constituents, irrespective of their pharmacologic activity.[5] The investigator must submit the IND and LOA to the FDA and the DEA for review (FDA, 2015).

After submitting an IND application, researchers must wait at least 30 days before initiating research, during which period the FDA reviews the application to ensure that research participants will not be exposed to unreasonable risk (FDA, 2016a). If the FDA determines that the proposed research would expose study participants to unreasonable risk or that the IND application is in some other way deficient, a clinical hold postponing the research may be imposed. This hold is not lifted until and unless the sponsoring researchers have resolved the deficiencies (FDA, 2016b).

It is important to note that the Controlled Substances Act of 1970 classified cannabis as a Schedule I substance, the highest level of drug restriction.[6] As defined by the Act, Schedule I substances are those that (1) have a high potential for abuse; (2) have no currently accepted medical use in treatment in the United States; and (3) have a lack of accepted safety for their use under medical supervision.[7] Other substances classified in Schedule I include heroin, LSD, mescaline, hallucinogenic amphetamine derivatives, fentanyl derivatives (synthetic opioid analgesics), and gammahydroxybutyrate (GHB).[8] By contrast, Schedule II substances—though they also have a high potential for abuse and may lead to severe psychological or physical dependence—are defined as having a currently

[5] Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.11 and Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11.

[6] Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11; United States Code, Schedules of Controlled Substances, Title 21, § 812.

[7] United States Code, Schedules of Controlled Substances, Title 21, § 812(b)(1).

[8] Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11.

BOX 15-1
Illustrative Examples of the Current Research Barriers to Colorado Researchers

As a concrete examp e of the mpact of the d v de between federa and state po cy, cannab s concentrate sa es doub ed n Co orado from 2015 to 2016, reach- ng $60.5 m on n the first quarter of 2016 (Mar juana Bus ness Da y Staff, 2016), and yet current federa aw prevents chem sts from exam n ng the compos t on of those products as t may re ate to safety, neurosc ent sts from test ng the effects of those products on the bra n or phys o ogy n an ma mode s, and c n ca sc ent sts from conduct ng research on how these products may he p or harm pat ents. And wh e between 498,170 and 721,599 un ts of med ca and recreat ona cannab s ed b es were so d per month n Co orado n 2015 (CDOR, 2016b, p. 12), federa aw a so proh b ts sc ent sts from test ng those products for contam nants, under- stand ng the effects of these products n an ma mode s, or nvest gat ng the effects n pat ent popu at ons.

accepted medical use and can be prescribed with a controlled substance prescription (DEA, 2006).[9]

In some states, researchers conducting clinical research on cannabis or cannabinoid products must also apply for and receive a controlled substance certificate from a state board of medical examiners or a controlled substance registration from a department of the state government in order to conduct clinical trials or any other activity involving Schedule I substances (Alabama Board of Medical Examiners, 2013; MDHSS, n.d.). Some state governments require additional approvals. For example, California requires that all trials involving Schedule I or II controlled substances be registered with and approved by the Research Advisory Panel of California (CADOJ/OAG, 2016). When the necessary approvals are secured, only then can the investigator apply for a DEA registration and site licensure to conduct research on a Schedule I controlled substance (see Box 15-1 for examples of research barriers).

Researchers conducting trials of Schedule I substances must additionally submit a research protocol to the DEA that includes details regarding the security provisions for storing and dispensing the substance.[10] Previously, nonfederally funded studies on cannabis were also required to undergo an additional review process conducted by the Public Health

[9] United States Code, Schedules of Controlled Substances, Title 21, § 812(b)(2).

[10] Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.18.

Service. This review process was determined to unnecessarily duplicate the FDA's IND application process in several ways and, as of June 2015, is no longer required.[11]

To ensure that controlled substances obtained for research purposes will be stored and accessed in accordance with DEA security requirements, local DEA officials may perform a preregistration inspection of the facility where the proposed research will take place (University of Colorado, 2016). DEA security requirements include storing cannabis in a safe, a steel cabinet, or a vault, and limiting access to the storage facility to "an absolute minimum number of specifically authorized employees.[12] The extent of the security measures required by DEA varies with the amount of cannabis being stored,[13] and among local DEA jurisdictions (Woodworth, 2011). Funders must bear the costs of meeting the necessary security requirements.

Additionally, as with any human clinical trial, approval from an institutional review board must be sought.[14] Obtaining this approval confirms that an appropriate plan to protect the rights and welfare of human research subjects has been outlined in the proposed research efforts. If a study is being conducted in a clinical research center, a separate review may be required by this entity's medical or research advisory committee.

In summary, basic and clinical researchers seeking to obtain cannabis or cannabinoids from NIDA for research purposes—including efforts to determine the value of cannabis or cannabinoids for treating a medical condition or achieving a therapeutic end need—must obtain a number of approvals from a range of federal, state, or local agencies, institutions, or organizations. This process can be a daunting experience for researchers. The substantial layers of bureaucracy that emerge from cannabis's Schedule I categorization is reported to have discouraged a number of cannabis researchers from applying for grant funding or pursuing additional research efforts (Nutt et al., 2013). Given the many gaps in the research of the health effects of cannabis and cannabinoids, there is a need to address these regulatory barriers so that researchers will be

[11] Office of the Secretary, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services. Notice. "Announcement of Revision to the Department of Health and Human Services Guidance on Procedures for the Provision of Marijuana for Medical Research as Published on May 21, 1999," *Federal Register*, 80, no. 120 (June 23, 2015): 35960, https://www.gpo.gov/fdsys/pkg/FR-2015-06-23/pdf/2015-15479.pdf (accessed November 25, 2016).

[12] Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.72 (a) and (d).

[13] Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.71 (c).

[14] Code of Federal Regulations, Institutional Review Boards, Title 21, § 56.103.

better able to address key public health questions about the therapeutic and adverse effects of cannabis and cannabinoid use.

CONCLUSION 15-1 There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research.[15]

Barriers to Cannabis Supply

In the United States, cannabis for research purposes is available only through the NIDA Drug Supply Program (NIDA, 2016a). The mission of NIDA is to "advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health," rather than to pursue or support research into the potential therapeutic uses of cannabis or any other drugs (NIDA, 2016b). As a result of this emphasis, less than one-fifth of cannabinoid research funded by NIDA in fiscal year 2015 concerns the therapeutic properties of cannabinoids (NIDA, 2016c).[16] Because NIDA funded the majority of all the National Institutes of Health (NIH)-sponsored cannabinoid research in fiscal year 2015 (NIDA, 2016c),[17] its focus on the consequences of drug use and addiction constitutes an impediment to research on the potential beneficial health effects of cannabis and cannabinoids.

All of the cannabis that NIDA provides to investigators is sourced from the University of Mississippi, which is currently the sole cultivator of the plant material and has been since 1968 (NIDA, 1998, 2016a).[18] In the past, the varieties of cannabis that were available to investigators through NIDA were limited in scope and were not of comparable potency to what patients could obtain at their dispensaries (Stith and Vigil, 2016). Because

[15] The committee was specifically directed in its statement of task not to comment on cannabis policy issues, such as regulatory options for legalization, taxation, or distribution. While the committee has identified the Schedule 1 classification of cannabis as posing a significant barrier to the conduct of scientific research on the health effects of cannabis, the committee is aware that any decision on the regulation of cannabis involves many factors far outside the committee's remit and expertise. Specifically, the committee did not comment on the abuse or dependency liability or accepted medical use of cannabis compared to other scheduled drugs.

[16] In fiscal year 2015, NIDA's investment in cannabinoid research totaled $66,078,314, of which $10,923,472 was allocated for therapeutic cannabinoid research (NIDA, 2016c).

[17] In fiscal year 2015, NIH's investment in cannabinoid research totaled $ $111,275,219, of which $66,078,314 was allocated to NIDA (NIDA, 2016c).

[18] NIDA contracts with the University of Mississippi through an open solicitation process. Although the University of Mississippi is currently NIDA's only supplier of research-grade cannabis, other groups can compete for the contract (NIDA, 2015, 2016a).

of restrictions on production and vicissitudes in supply and demand, federally produced cannabis may have been harvested years earlier, is stored in a freezer (a process that may affect the quality of the product) (Taschwer and Schmid, 2015; Thomas and Pollard, 2016), and often has a lower potency than cannabis sold in state-regulated markets (Reardon, 2015; Stith and Vigil, 2016). In addition, many products available in state-regulated markets (e.g., edibles, concentrates, oils, wax, topicals) are not commonly available through federal sources (NIDA, 2016d). Since the products available through the federal system do not sufficiently reflect the variety of products used by consumers, research conducted using cannabis provided by NIDA may lack external validity. In July 2016, NIDA posted a formal request for information on the varieties of cannabis and cannabis products of interest to researchers (NIDA, 2016e). Reflecting the perceived shortcomings of cannabis and cannabis products currently provided by NIDA, a summary of the comments received in response to this request states that "the most consistent recommendation was to provide marijuana strains and products that reflect the diversity of products available in state dispensaries" (NIDA, 2016e).

Naturally, it is difficult for a single facility at the University of Mississippi to replicate the array and potency of products available in dispensaries across the country. It is worth noting, however, that NIDA has been increasingly responsive to the needs of clinical investigators. For example, NIDA has contracted with the University of Mississippi to produce cannabis strains with varying concentrations of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (NIDA, 2016d), and NIDA has previously authorized development of cannabis extracts, tinctures, and other dosage formulations for research purposes (Thomas and Pollard, 2016). As mentioned above, NIDA has sought public comment on the needs of cannabis researchers in order to inform efforts to "expand access to diverse marijuana strains and products for research purposes" (NIDA, 2016e). In addition, cannabis is made available to research investigators funded by NIH at no cost.[19] Finally, the DEA has adopted a new policy that increases the number of entities that may be registered under the Controlled Substances Act (CSA) to grow (manufacture) marijuana to supply legitimate researchers in the United States.[20] Under this new policy, the DEA will facilitate cannabis research by increasing the number of private

[19] In December 2016, cannabis provided by NIDA was generally free for NIH-sponsored research. For research not funded by the federal government, the cost of non-placebo cannabis was $10.96 per cigarette and $1,133 per pound ($2,497 per kilogram) (NIDA, 2016d).

[20] DEA, U.S. Department of Justice. Policy Statement. "Applications to Become Registered Under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States," *Federal Register*, 81, no. 156 (August 12, 2016): 53846, https://www.gpo.gov/fdsys/pkg/FR-2016-08-12/pdf/2016-17955.pdf (accessed January 7, 2017).

entities allowed to cultivate and distribute research-grade cannabis. As of December 2016, the University of Mississippi remains the sole cultivator of cannabis provided to researchers by NIDA (NIDA, 2016a).

Although new plans are being made to provide a wider array of more clinically relevant cannabis products for research, at present this issue is still a significant barrier for conducting comprehensive research on the health effects of cannabis use. How the proposed changes will affect cannabis research in the future remains to be seen.

CONCLUSION 15-2 It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use.

Funding Limitations

Funding for research is another key barrier; without adequate financial support, cannabis research will be unable to inform health care or public health practice or to keep pace with changes in cannabis policy and patterns of cannabis use. NIH is responsible for funding research across a number of health domains. In 2015, NIH spending on all cannabinoid research totaled $111,275,219 (NIDA, 2016c). NIDA, a member institute of NIH, has as its mission to study factors related to substance abuse and dependence and conducts research on the negative health effects and behavioral consequences associated with the abuse of cannabis and other drugs (NIDA, 2016b). Because cannabis was historically perceived to have only negative effects, the majority of cannabis research has been conducted under the auspices of NIDA.

In fiscal year 2015, studies supported by NIDA accounted for 59.3 percent ($66,078,314) of all NIH spending on cannabinoid research; however, only 16.5 percent ($10,923,472) of NIDA's spending on cannabinoid research supported studies investigating therapeutic properties of cannabinoids (NIDA, 2016c).[21,22] As demonstrated in Chapter 4 of this report, a growing body of evidence suggests that cannabis and cannabinoids also have therapeutic health effects. In light of these findings, a comprehen-

[21] $66,078,314 (Total NIDA spending on cannabinoid research in fiscal year 2015)/ $111,275,219 (Total NIH spending on cannabinoid research in fiscal year 2015) = 0.593. $10,923,472 (Total NIDA spending on therapeutic cannabinoid research in fiscal year 2015)/ $66,078,314 (Total NIDA spending on cannabinoid research in fiscal year 2015) = 0.165.

[22] By contrast, NIH spending on tobacco research totaled $300 million in 2015, and spending on research related to the harms and benefits of alcohol use totaled $473 million in 2015 (NIH, 2016).

sive research agenda that investigates both the potential adverse and the potential therapeutic health effects of cannabis use is needed.

However, it may be unrealistic to expect NIDA to have the resources or interest to fund this broader research agenda, which could involve investigating the health effects of cannabis use on a diverse range of conditions (e.g., metabolic syndrome, cardiovascular disease, cancer, obesity and sedentary behavior, Alzheimer's disease) that are targeted by other institutes and centers of NIH. While it is not clear how these studies might be funded, almost assuredly the changing norms and the changing legal status of cannabis will have an impact on conditions that are targeted by institutes other than NIDA, and it will become increasingly important to have a funding mechanism to better understand the comprehensive health effects of cannabis so that consumers and policy makers can respond to changing trends accordingly.

CONCLUSION 15-3 A diverse network of funders is needed to support cannabis and cannabinoid research that explores the harmful and beneficial health effects of cannabis use.

METHODOLOGICAL CHALLENGES

Drug Delivery Challenges

Another challenge in investigating the potential health effects of cannabis and cannabinoids is the identification of a method of administering the drug that is accepted by study participants, that can be performed at most research sites, and that ensures standardized dosing. Smoking as a route of administration is particularly challenging, as some study participants may not view it as an acceptable method of drug administration, and academic medical centers or other locations where cannabis or cannabinoid research takes place may lack facilities where study participants can smoke under controlled conditions. Furthermore, variations among individuals in terms of their cannabis smoking techniques make it difficult to ensure that study participants reliably receive the targeted dose of the drug. Devices for providing a metered dose of cannabis via inhalation exist (Eisenberg et al., 2014), but the FDA has not approved such devices for use. Standardized smoking techniques have also been developed (Foltin et al., 1988) but can be difficult to perform correctly. These difficulties are due, in part, to differences among individuals in their tolerance of the potential psychoactive effects of the drug (D'Souza et al., 2008; Ramaekers et al., 2009), which may prevent the receipt of equal doses by all study participants.

Researchers have also explored vaporization as a method for adminis-

tering cannabis (Abrams et al., 2007). Cannabinoids vaporize at lower temperatures than the temperature at which pyrolytic toxic compounds are created through combustion; as a result, levels of some carcinogenic compounds are lower in cannabis vapor than in cannabis smoke (Eisenberg et al., 2014). However, there is a paucity of research on the effectiveness of these devices as a mode of drug administration. For example, data on the plasma concentrations of cannabinoids achieved through use of vaporizers exists, but they are limited (Abrams et al., 2007; Zuurman et al., 2008). In addition, even less is known about the long-term pulmonary effects of inhaling a vaporized liquid than about the effect of inhaling plant material. As vaporizing devices proliferate and evolve, researchers may benefit from advances in their portability and usability, but they will also have to account for clinically relevant differences in the functioning and the effectiveness of an increasingly wide range of models.

To circumvent the practical and methodological challenges involved in administration of cannabis through smoking or vaporization, investigators may choose to study the health effects of orally administered dronabinol or nabilone, which offer a more controlled method of drug delivery. However, the effects generated by these isolated cannabinoids might, at least in part, be different from those produced by the use of the whole cannabis plant, which also contains CBD and other cannabinoids, as well as terpenoids and flavonoids. As a result, extrapolating from the observed health effects associated with use of an isolated cannabinoid such as dronabinol or nabilone in order to predict the health effects associated with the use of cannabis may lead to erroneous conclusions.

The Placebo Issue

The gold standard of drug development is the prospective, randomized, double-blind, placebo-controlled clinical trial. Placebo cannabis produced by solvent extraction is available from NIDA and has a potency of 0.002 percent THC by weight and 0.001 percent CBD by weight (NIDA, 2016d).[23] The extraction process seems to retain the terpenoids and flavonoids so that the combusted placebo material smells similar to the true cannabis, thus helping to preserve the blinding to some extent. However, the psychoactive and vasoactive effects of cannabis pose a considerable challenge for effective blinding, since study participants who feel such

[23] In December 2016, placebo cannabis provided by NIDA was generally free for NIH-sponsored research. For research not funded by the federal government, the cost of placebo cannabis was $13.94 per cigarette and $1,133 per pound ($2,497 per kilogram) (NIDA, 2016d).

effects will surmise that they are receiving cannabis or cannabinoids, and not a placebo.

Strategies to promote the effectiveness of blinding exist. For example, if the cannabis being studied has a very low THC content, study participants—especially those who, through regular use of more potent cannabis strains, are inured to the psychoactive effects of cannabis with low THC content—may not notice the psychoactive effects of the cannabis and therefore be unable to reliably determine whether they are using cannabis or a placebo. There is also a possibility that cannabis products with a lower ratio of the concentration of THC to the concentration of CBD may have less psychoactivity than products with a comparatively higher ratio of the concentration of THC to the concentration of CBD (Hindocha et al., 2015; Jacobs et al., 2016). Using these strains with diminished psychoactive effects could promote more effective blinding. Researchers may also try treating both study arms in a placebo-controlled cannabis trial with a mildly psychoactive or sedating drug, the effects of which may help to ensure that study participants are unable to determine whether they are receiving a placebo or cannabis. However, by introducing another active agent, the investigators risk obfuscating the results of their study.

A potential method for assessing the effectiveness of blinding in a cannabis trial is to ask study participants to guess whether they are receiving true cannabis or a placebo. If most or all of the participants correctly guess their assignment, it can be inferred that the blinding was ineffective. Whether or not such methods are employed, investigators risk undermining their study results. On the one hand, conducting the test carries the risk of discovering that attempts at blinding were ineffective, thereby rendering the study results invalid. On the other hand, not conducting the test may lead journal reviewers aware of the challenges of blinding in cannabis trials to assume that blinding was ineffective and to discount the study results accordingly. Thus, research to address the challenge of achieving reliably effective blinding in a cannabis trial is of marked importance.

Exposure Assessment

In order to arrive at valid and meaningful results, population studies on the health effects of cannabis require as detailed an ascertainment of exposure to cannabis as possible. However, obtaining such a detailed exposure history can be difficult. This is especially true for recreational cannabis use due to the lack of a standardized dose and the existence of diverse routes of administration, including multiple modes of inhalation (Schauer et al., 2016). In addition, known pharmacological biomarkers of cannabis use may be unreliable in some circumstances, while population

studies to identify novel pharmacological biomarkers of cannabis exposure are limited (Hartman et al., 2016; Schwope et al., 2011). Furthermore, the wide variety of different cannabis strains developed through a long and ongoing process of cultivation and the associated variation in the concentration of active substances in cannabis further complicate the characterization of cannabis exposure (ElSohly and Gul, 2014; Elsohly et al., 2016; Mehmedic et al., 2010). Finally, recreational cannabis may contain chemical contaminants or adulterants (Busse et al., 2008). Cannabis users may be unaware of the presence of these chemicals, making it unlikely that such chemicals would be identified through toxicological evaluation unless the user became involved in a forensic investigation.

Most observational studies, particularly case-control and cohort studies, depend on self-report in order to assess cannabis exposure. These reports may be incomplete, inaccurate, or imprecise due to failure on the part of investigators to ask cannabis users detailed questions about their cannabis exposure history, including the source of their cannabis exposure (e.g., smoking, edibles, vaping), or because users themselves may have limited knowledge of some aspects of their exposure or may be resistant to reporting some information. Personal recall of substance use may also be affected by other factors. For example, memory problems have been identified as a cause of inaccuracies in reporting drug use (Johnson and Fendrich, 2005; Pedersen, 1990). In other cases, study participants may not report illicit substance use in an attempt to conform to perceived social norms (Johnson and Fendrich, 2005). Similarly, individuals with substance dependency syndromes may have psychiatric comorbidity that affects the accuracy of reporting.

Finally, important information often missing from cannabis exposure histories is the extent of other substance use. As noted in Chapter 14, there is limited evidence that cannabis use is associated with the use of other licit or illicit substances. Despite this association and the confounding effect of polysubstance use on evaluations of the health effects of cannabis use, surveys used to characterize cannabis exposure histories do not always assess for the presence of other substance use. Since secondhand exposure to cannabis smoke can have minor health effects, there may also be value in assessing for such exposure as part of larger assessments of cannabis exposure (Herrmann et al., 2015).

Cannabis-Related Study Designs

In researching the health outcomes of cannabis use, the committee identified a number of studies, particularly cohort studies, of general health outcomes such as all-cause mortality or important chronic illnesses such as cancers or cardiovascular diseases. For both cohort and

case-control studies, a better assessment of cannabis use would offer more valuable information, such as years of use and age at first use. Particularly for cohort studies, this would offer better ascertainment of the duration and net burden of use as well as more insight into period and age effects. As discussed in the proceeding health outcomes chapters of the report, in many of the existing cohort studies cannabis use was often queried only at baseline, and thus there was little information on interval use over time or on the variation or cessation in that use. There was also very limited information on interval health events as the cohorts progressed, impeding a summarization of long-term use and the consequent health effects. Attention to these issues will likely improve the precision of study findings.

CONCLUSION 15-4 To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed.

BOX 15-2
Summary of Chapter Conclusions*

There are several challenges and barriers in conducting cannabis and cannabinoid research, including

- There are spec fic regu atory barr ers, nc ud ng the c ass ficat on of canna- b s as a Schedu e I substance, that mpede the advancement of cannab s and cannab no d research (15-1)
- It s often d fficu t for researchers to ga n access to the quant ty, qua ty, and type of cannab s product necessary to address spec fic research quest ons on the hea th effects of cannab s use (15-2)
- A d verse network of funders s needed to support cannab s and canna- b no d research that exp ores the harmfu and benefic a hea th effects of cannab s use (15-3)
- To deve op conc us ve ev dence for the effects of cannab s use on short- and ong-term hea th outcomes, mprovements and standard zat on n re- search methodo ogy (nc ud ng those used n contro ed tr a s and obser- vat ona stud es) are needed (15-4)

* Numbers in parentheses correspond to chapter conclusion numbers

SUMMARY

The methodological challenges and the regulatory, financial, and access barriers described above markedly affect the ability to conduct comprehensive basic, clinical, and public health research on the health effects of cannabis use, with further consequences for the many potential beneficiaries of such research. In the absence of an appropriately funded and supported cannabis research agenda, patients may be unaware of viable treatment options, providers may be unable to prescribe effective treatments, policy makers may be hindered from developing evidence-based policies, and health care organizations and insurance providers lack a basis on which to revise their care and coverage policies. In short, such barriers represent a public health problem. See Box 15-2 for a summary of the chapter conclusions.

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16

Recommendations to Support and Improve the Cannabis Research Agenda

This is a pivotal time in the world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. The committee has put forth a substantial number of research conclusions on the health effects of cannabis or cannabinoids. Based on their research conclusions, the members of the committee formulated four specific recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers. The report's full recommendations are described below.

ADDRESS RESEARCH GAPS

To address the research gaps outlined throughout this report, a comprehensive national research agenda will be required. The aspirational goal and organizing principle of this agenda should be to maximize the population-health impact of cannabis research. Achieving this objective will require coordination and collaboration among researchers and research groups; support from stakeholders at the local, state, and national levels; and the concurrent pursuit of several distinct research streams, including clinical and observational research and research in the areas of health policy, health economics, public health, and public safety.

The research agenda should include basic science studies to help inform efforts to minimize harms and maximize benefits associated with

the acute and chronic use of cannabis and cannabinoids, as well as health policy and public health research to examine the health effects of broader social and behavioral changes associated with the legalization of recreational and/or medical cannabis and other changes in cannabis policy. To support the statistical associations identified in epidemiological research, the research agenda should also include basic science research that identifies plausible mechanisms by which cannabis affects specific health endpoints. Furthermore, translational research should be embedded in each of these research streams to ensure that research findings will be of practical use to help inform health care practices, public health priorities, national and state policy, and public safety standards.

***Recommendation 1*: To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both harmful and beneficial effects), public agencies,[1] philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:**

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or understudied populations, such as children and youths (often described as less than 18 years of age) and older populations (generally over 50 years of age), pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and tetrahydrocannabinol (THC) or other cannabinoids.
- Determine the harms and benefits associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential harmful and beneficial health effects of using different forms of cannabis, such as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.

[1] Agencies may include the Centers for Disease Control and Prevention (CDC), relevant agencies of the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA).

- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other high-priority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.
- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

IMPROVE RESEARCH QUALITY

In order to effectively guide health care decisions and inform public policy, the proposed cannabis research agenda must produce conclusive, actionable evidence. This will require research studies to be carefully designed and rigorously conducted and to have their data results accurately and comprehensively reported.

Ensuring that cannabis research is of uniformly high quality will require the development of guidelines for data collection, standards for research design and reporting, standardized terminology, and a minimum dataset for clinical and epidemiological studies.

Data collection guidelines could prioritize alternate methods for assessing cannabis use, such as whole blood or urine analysis, over those based on self-report or prescriptions. Standards for research design and methodology could require that researchers attempt to account for the confounding effects of alcohol, tobacco, or other relevant substances of abuse. Standards for research reporting could require that authors of systematic reviews report the key demographic characteristics of the study

population, as well as information related to cannabis dose, frequency of use, and route of administration. A universal, standardized terminology would help to create standard units for describing cannabis use. Because much of the existing epidemiological research on cannabis use fails to distinguish between cannabis that is smoked and cannabis that is administered orally, topically, or via other routes, health effects associated with cannabis use may be conflated with those associated with smoking per se. To correct this, future research will need to employ data collection methods that distinguish between different types of cannabis and different routes of cannabis administration.

Wherever possible, these efforts should adapt existing tools to the particular needs and constraints of cannabis research. For example, workshop participants could build on commonly used guidelines and standards for conducting and reporting research, including Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Consolidated Standards of Reporting Trials (CONSORT), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), and Cochrane guidelines for systematic reviews.

Adequately addressing these topics will require input from numerous stakeholders, including clinical and public health cannabis researchers; research methodologists; representatives from working groups that have developed research reporting guidelines; organizations engaged in standards development; representatives from scientific publications; and representatives from government agencies directly or indirectly involved in the research process, including the U.S. Department of Health and Human Services (HHS), including CDC and NIH, and FDA.

> *Recommendation 2*: **To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both harmful and beneficial effects), agencies of the U.S. Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention, should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research. Workshop objectives should include, but need not be limited to:**
>
> - The development of a minimum dataset for observational and clinical studies, standards for research methods and design, and guidelines for data collection methods.
> - Adaptation of existing research-reporting standards to the needs of cannabis research.

- The development of uniform terminology for clinical and epidemiological cannabis research.
- The development of standardized and evidence-based question banks for clinical research and public health surveillance tools.

IMPROVE SURVEILLANCE CAPACITY

The development of a comprehensive and conclusive evidence base on the health effects of cannabis must begin with data collection. In turn, data collection on a scale sufficient to guide state and national policy will require a diverse array of powerful surveillance tools and technologies.

In many cases, existing surveillance tools can be adapted to further the cannabis research agenda. For example, a recurrent and comprehensive set of cannabis-related questions could be added to existing national health surveys. Researchers could use the Behavioral Risk Factor Surveillance System to track changes in the prevalence of medical and recreational cannabis use; the Medical Expenditure Panel Survey to assess the impact of medical cannabis laws on health care treatments and costs; and the National Vital Statistics System to monitor changes in the incidence rate of cannabis-related overdose deaths.

In other cases, novel diagnostic technologies will need to be developed to aid data collection efforts. For example, the growing incidence of cannabis poisonings among children and the demonstrated risks associated with driving under the influence of cannabis underscore the need for rapid and noninvasive methods of assessing for acute cannabis intoxication.

Multiple stakeholders can contribute to these efforts. CDC's Center for Surveillance, Epidemiology and Laboratory Services, the Questionnaire Design Research Laboratory at the National Center for Health Statistics, and the Center for Behavioral Health Statistics and Quality at the Substance Abuse and Mental Health Services Administration (SAMHSA) can aid in the design and evaluation of survey questions that accurately capture key data points relating to cannabis use. State public health departments can collaborate with Association of Public Health Laboratories to use existing public health laboratories to provide diagnostic tools and other laboratory resources to meet the needs of clinical and public health professionals engaged in cannabis research. Because of differences in cannabis product type, availability, access, and regulation, such surveillance efforts need to be state based, for the time being.

In their potential role as conveners, the National Association of County and City Health Officials (NACCHO) and the Association of State and Territorial Health Officials (ASTHO) can aid federal agencies

and state and local health departments in assessing the capacity to expand the resources of public health surveillance systems, as well as in articulating strategies and prioritizing the actions necessary to meet the needs of a comprehensive cannabis research agenda.

> *Recommendation 3*: **To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both harmful and beneficial effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, the National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts. Potential efforts should include, but need not be limited to:**
>
> - The development of question banks on the harmful and beneficial health effects of therapeutic and recreational cannabis use and their incorporation into major public health surveys, including the National Health and Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System, National Survey on Drug Use and Health, Youth Risk Behavior Surveillance System, National Vital Statistics System, Medical Expenditure Panel Survey, and National Survey of Family Growth.
> - Determining the capacity to collect and reliably interpret data from diagnostic classification codes in administrative data (e.g., *International Classification of Diseases-10*).
> - The establishment and utilization of state-based testing facilities to analyze the chemical composition of cannabis and products containing cannabis, cannabinoids, or THC.
> - The development of novel diagnostic technologies that allow for rapid, accurate, and noninvasive assessment of cannabis exposure and impairment.
> - Strategies for surveillance of harmful effects of cannabis for therapeutic use.

ADDRESS RESEARCH BARRIERS

The designation of cannabis as a Schedule I substance imposes numerous regulatory barriers that limit access to the funding and material

resources necessary to conduct cannabis research. Unless these barriers are directly addressed, or creative solutions are developed to circumvent the challenges they pose, a comprehensive national cannabis research agenda will remain an elusive goal.

The evidence discussed in this report suggests that cannabis has both therapeutic value and public health risks. The public health case for pursuing cannabis research, which is premised on this potential for both harm and benefit, is sharpened by the increased prevalence of cannabis use in states where medical and recreational cannabis has been legalized.

To ensure that policy makers are better informed to make decisions on cannabis research and policy, and to explore and characterize the full scope of political and nonpolitical strategies for resolving regulatory barriers to cannabis research, an objective and evidence-based analysis of cannabis policy is necessary.

***Recommendation 4*: The Centers for Disease Control and Prevention, National Institutes of Health, U.S. Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda. Committee objectives should include, but need not be limited to:**

- Proposing strategies for expanding access to research-grade marijuana, through the creation and approval of new facilities for growing and storing cannabis.
- Identifying nontraditional funding sources and mechanisms to support a comprehensive national cannabis research agenda.
- Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products.

Appendix A

Glossary

Δ^9-tetrahydrocannabinol (THC)—the main psychoactive constituent of cannabis.

adjusted odds ratio (aOR)—an odds ratio that controls for confounding variables.

Ashworth scale—a clinical measure of muscle spasticity based on an assessment of a patient's muscle tone in different muscle groups.

association—the statistical relation between two or more events, characteristics, or other variables.

cannabidiol (CBD)—a constituent of cannabis that has been traditionally considered non-psychoactive.

cannabinoid—one of a class of chemical compounds that act on cannabinoid receptors, cannabinoids can be naturally derived from the cannabis plant or manufactured.

cannabis—a broad term that can be used to describe the various products and chemical compounds derived from the *Cannabis sativa* or *Cannabis indica* species.

cannabis use disorder (CUD)—according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, a problem-causing pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two distinguishing symptoms (e.g., cannabis is taken in larger amounts or for longer periods than intended; experience of craving; continued cannabis use despite the experience of physical, social, or interpersonal problems caused by cannabis use) occurring within a 12-month period.

case series—an analysis of a series of people with the disease (there is no comparison group in case series). Case series studies provide weaker evidence than case-control studies.

case-control study—an observational analytic study that enrolls one group of persons with a certain disease, chronic condition, or type of injury (case-patients) and a group of persons without the health problem (control subjects) and compares differences in exposures, behaviors, and other characteristics to identify and quantify associations, test hypotheses, and identify causes.

cohort study—an observational analytic study in which enrollment is based on one's status of exposure to a certain factor or membership in a certain group. Populations are followed, and disease, death, or other health-related outcomes are documented and compared. Cohort studies can be either prospective or retrospective.

comparator—the agent to which the experimental arm of a study is compared (e.g., placebo, usual care, active control).

control—comparator against which the study treatment is evaluated (e.g., concurrent [placebo, no treatment, dose–response, active], and external [historical, published literature]).

cross-sectional study—a study in which a sample of persons from a population are enrolled and their exposures and health outcomes are measured simultaneously; a survey.

cultivar—a plant variety that has been produced in cultivation by selective breeding.

dose—the quantity of a drug that is used at one time or in fractional amounts during a given period of time.

dronabinol—a synthetic cannabinoid for oral administration, similar to tetrahydrocannabinol (THC). It is the active ingredient in Marinol®.

evidence—information on which a conclusion about a cause-effect relationship is based. The most direct evidence for health effects in humans is usually based on studies of health endpoints that are conducted in humans, including randomized trials and nonrandomized epidemiologic studies. Additional evidence can be provided by studies of intermediate endpoints or markers in humans as well as by nonhuman studies. The committee has developed a strength-of-evidence table so that the level of evidence is expressed in uniform terms and calibrated throughout the report (see Appendix B).

exclusion criteria—a list of characteristics in a protocol, any one of which may exclude a potential subject from participation in a study.

hazard ratio (HR)—the weighted relative risk of an outcome (e.g., death) during the entire study period; often reported in the context of survival analysis.

health effects—the positive and negative health outcomes resulting from exposure to cannabis or cannabis-derived products.

incidence—the number of new cases of a condition, symptom, death, or injury that develop during a specified period of time.

inclusion criteria—the criteria in a protocol that prospective subjects must meet to be eligible for participation in a study.

marijuana—a *Cannabis sativa* plant-derived product typically composed from the plant's dried leaves, stems, seeds, and buds.

meta-analysis—a statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a more precise summary estimate of the effect on a particular outcome. Meta-analyses are frequently used in systematic reviews.

morbidity—any departure, subjective or objective, from a state of physiological or psychological health and well-being (e.g., disease, injury, disability).

mortality—death or loss of life.

nabilone—a synthetic cannabinoid for oral administration, similar to tetrahydrocannabinol (THC). It is the active ingredient in Cesemet®.

narrative review—narrative reviews tend to be mainly descriptive, do not involve a systematic search of the literature, and thereby often focus on a subset of studies in an area chosen based on availability or author selection. Generally, narrative reviews offer lower-quality evidence than systematic reviews. For this reason, and for the purpose of the report, narrative reviews are classified as primary literature.

observational study—a study in which the investigator observes rather than influences exposure and disease among participants. Case-control and cohort studies are examples of observational studies.

odds ratio (OR)—one measure of treatment effectiveness. It is the odds of an event happening in the experimental group expressed as a proportion of the odds of an event happening in the control group. The closer the OR is to 1, the smaller the difference in effect is between the experimental intervention and the control intervention. If the OR is greater (or less) than 1, then the effects of the treatment are more (or less) than those of the control treatment. Note that the effects being measured may be adverse (e.g., death or disability) or desirable (e.g., survival). When events are rare, the OR is analogous to the relative risk (RR), but as event rates increase, the OR and RR diverge.

outcome—events or experiences that clinicians or investigators examining the impact of an intervention or exposure measure because they believe such events or experiences may be influenced by the intervention or exposure.

pooled estimate—an average derived from multiple studies with varying data but with a common measurement. Typically found in systematic reviews and meta-analyses.

potency—the amount of drug required to produce a specific level of effect.

preclinical—research studies that use cell culture or animal models to test scientific hypotheses. These studies are performed prior to clinical studies that use human subjects.

prevalence—the number or proportion of individuals within a given population who share a specific characteristic.

primary literature—peer-reviewed accounts of original research that contribute new evidence to science. By comparison, systematic reviews and literature reviews analyze existing evidence. Examples of the types of primary literature used in the report are randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, and case series.

problem cannabis use—a symptom of cannabis use disorder. Problem cannabis use includes the experience of persistent or recurrent social, interpersonal, occupational, academic, recreational, psychological, or physical problems caused or exacerbated by cannabis use.

randomized controlled trial (RCT)—a trial in which participants are randomly assigned to one of two or more groups, at least one of which (the experimental group) receives an intervention that is being tested and another (the comparison or control group) receives an alternative treatment or placebo. This design allows assessment of the relative effects of interventions.

relative risk (RR)—a ratio of the risk of an event among an exposed population to the risk among the unexposed.

route of administration—the path by which a drug is taken into the body.

systematic review—research that summarizes the evidence on a clearly formulated question according to a predefined protocol. Systematic and explicit methods to identify, select, and appraise relevant studies and to extract, collate, and report their findings are used. Statistical meta-analysis may or may not be used. Systematic reviews were the optimal data source for identifying associations between cannabis exposure and all of the health endpoints discussed in this report.

Appendix B

Study Approach

In response to its charge, the committee developed a process defined by discrete actions building toward an evidence base that would eventually inform the committee's findings and conclusions. This process is depicted in Figure B-1.

The following sections detail the process by which the committee came to their conclusions about the weight of evidence regarding the association between cannabis and specific health endpoints. The steps include the literature search, the refinement of the specific health endpoints of medical and public health importance to be assessed, the identification and assessment of relevant literature (including published systematic reviews and primary literature), and the development of consistent and specific language to describe the integration of the literature to reflect the weight of evidence.

LITERATURE SEARCH

A professional research librarian worked with the committee to conduct the literature searches used to identify relevant research. Six searches were conducted. An initial search (Search 1) of Medline, Embase, and the Cochrane Database of Systematic Reviews found 19,189 total articles reporting on associations between cannabis exposure and health endpoints. Search 1 included articles that were published between January 1999 and June 2016 and that included a cannabis search term and search terms relevant to health effects of interest in at least one of several search

FIGURE B-1 Summary of the committee's process.

fields (e.g., title, abstract, subject heading). A partial review of the search results found a large number of irrelevant documents. For this reason, a second and more limited search strategy was developed.

Search 2 involved the same databases as Search 1 but used different search terms to identify articles associated with specific health endpoints, and it excluded articles with specific terms (e.g., "animal," "spice") in the title or abstract. Search 2 produced 2,092 articles between 1999 and the 2016. The substantial reduction in articles indicated that the more limited search strategy caused relevant research to be excluded; consequently, a third and broader search strategy was developed.

Search 3 of the same databases produced 7,198 total articles reporting on associations between cannabis exposure and any health endpoint. This search included articles published between 1999 and 2016, excluded articles with specific terms (e.g., "mice," "spice") in the title or abstract, and limited articles by study design (e.g., clinical trial, observational study, systematic review).

The results of Search 2 and Search 3 were combined, and three additional searches were conducted in order to address potential gaps in the overall search results. Search 4 identified 1,396 articles in the PsycINFO database, filling gaps in the committee's collection of literature on the effects of cannabis exposure on mental health and psychosocial endpoints. Using the search term "Nabilone" (a synthetic cannabinoid), Search 5 identified 33 articles in Medline, Embase, and the Cochrane Database of Systematic Reviews that previous searches had not included. Search 6 identified 389 articles and brought the literature up to date by extending the date of publication parameter to August 2, 2016, and including articles published electronically ahead of print. The terms and strategies used in these searches are provided on page 419 of this appendix. In addition to these six searches, committee members also reviewed their personal libraries, and added potentially relevant articles from these collections to the combined search results.

The results from searches 2 through 6 were combined to create a master library containing 10,759 unique articles, including 1,488 articles initially categorized as systematic reviews. These articles were then sorted into seven major health endpoint topic areas: injury and mortality; car-

diovascular and respiratory symptoms and conditions; cancer, immune function, and infections; mental health symptoms and conditions; prenatal, perinatal, and postnatal health effects; psychosocial health effects; and therapeutic health effects.[1] Upon further reflection and review of the available literature, the committee decided to separate the original cardiovascular and respiratory topic area into two individual research topics, as well as to separate out two additional research topics—problem cannabis use, and cannabis use and abuse of other substances—from the original mental health topic area. This final list of topic areas was subsequently divided into the 11 health endpoint topic areas covered in the chapters that comprise parts II and III of the report. Within each of these topic areas the committee identified specific research questions relating to health endpoints of medical and public health importance that would be the focus of the report. They based this list on their public health and medical expertise, their knowledge of the cannabis literature, input from the sponsors at the first meeting, and other key reviews about the health effects of cannabis. This process, which reduced the total number of articles to be reviewed by the committee, was necessary to make the scope of the report manageable, but it may have resulted in the exclusion of certain health outcomes of interest to health professionals, researchers, policy makers, or the public. Below, Box B-1 lists the health topic areas and specific health endpoints selected for review by the committee.

After filtering the original search results for articles relevant to the health endpoints of interest, 6,540 primary literature articles and 288 systematic reviews were left to be reviewed by the committee. Given the large number of potentially relevant articles, the committee decided to begin by reviewing the identified systematic reviews. To accomplish this, the committee modified previously developed approaches for evaluating the quality of the systematic reviews and primary literature. These approaches are described in the systematic review: identification and quality review, "Primary Literature: Identification and Quality Review," and "Data Synthesis and Strength of Evidence Assessment" sections below.

The committee identified articles as possibly being systematic reviews based on abstracts or keyword searches, and then they evaluated each of the identified articles for the presence of the key elements of a systematic review by asking the following questions:

[1] The organization of Search 2 results involved different search terms and tools than the organization of Search 3 results. Search 2 topic groups were developed using unique search terms, online databases (Medline, Embase, Cochrane Database of Systematic Reviews), and Ovid search functions. Search 3 topics groups were developed using unique search terms, the Search 3 EndNote library, and the EndNote full-text keyword search function.

BOX B-1
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects

- Chron c pa n; cancer, chemotherapy- nduced nausea/vom t ng; anorex a and we ght oss; rr tab e bowe syndrome; ep epsy; spast c ty re ated to mu t p e sc eros s or sp na cord njury; Tourette syndrome; amyotroph c atera sc eros s; Hunt ngton's d sease; Park nson's d sease; dyston a; de-ment a; g aucoma; traumat c bra n njury; add ct on; anx ety; depress on; s eep d sorders; posttraumat c stress d sorder; sch zophren a and other psychoses

Cancer

- Lung cancer; head and neck cancer; test cu ar cancer; esophagea cancer; other cancer

Cardiometabolic risk

- Acute myocard a nfarct on; stroke; metabo c dysregu at on, metabo c syndrome, pred abetes, and d abetes me tus

Respiratory disease

- Pu monary funct on; chron c obstruct ve pu monary d sorder; resp ratory symptoms (nc ud ng chron c bronch t s); asthma

Immunity

- Immune funct on; nfect ous d sease

1. Does the article describe a search involving at least two databases?
2. Does the article describe a search involving appropriate search terms?
3. Does the article describe a search involving prespecified eligibility criteria?
4. Does the article include a risk-of-bias discussion and/or quality assessment?
5. Does the article include a meta-analysis or qualitative synthesis of findings?
6. Does the article report on one or more health effects of cannabis on humans?

Injury and death

- A -cause morta ty; occupat ona njury; motor veh c e crash; overdose njury and death

Prenatal, perinatal, and postnatal exposure to cannabis

- Pregnancy comp cat ons for the mother; feta growth and deve opment; neonata cond t ons; ater outcomes for the nfant

Psychosocial

- Cogn t on (earn ng, memory, attent on, nte gence); academ c ach eve-ment and educat ona outcomes; emp oyment and ncome; soc a re at on-sh ps and other soc a ro es

Mental health

- Sch zophren a and other psychoses; b po ar d sorders, depress on; su -c de; anx ety; posttraumat c stress d sorder

Problem cannabis use

- Cannab s use d sorder

Cannabis use and abuse of other substances

- Abuse of other substances

Articles that were deemed true systematic reviews using the above questions as a guideline were then assessed for quality based on five attributes adapted from other sources (Higgins et al., 2011). In their assessment of the quality of a systematic review, committee members considered the study eligibility criteria, how studies were identified and considered for inclusion, how data were collected and appraised by the authors, the methods by which study findings were selected and synthesized, and whether any conflict of interests were addressed. Box B-2 lists the specific questions committee members were asked to consider in the quality assessment.

Based on the responses to these questions, the overall quality of the systematic review was rated as good, fair, or poor. To ensure the accuracy

BOX B-2
Quality Assessment Questions

QUESTION

Rate your level of concern (high or low) regarding study eligibility criteria. Your response should be informed by the following questions:

Study eligibility criteria

- Was an "a pr or" des gn prov ded?
- Were study e g b ty cr ter a c ear y spec fied?
- Were restr ct ons n e g b ty cr ter a appropr ate?

Identification and collection of studies

- Was a comprehens ve terature search performed?
- Were the terms and structure of the search strategy ke y to retr eve as many e g b e stud es as poss b e?
- Were restr ct ons based on date, pub cat on format, or anguage appropr ate?
- Was se ect on b as avo ded?

Data collection and study appraisal

- Were at east two nd v dua s nvo ved n study se ect on and data extract on?
- Were the character st cs of the nc uded stud es prov ded?
- Was the sc ent fic qua ty of the nc uded stud es assessed and documented?

Synthesis and findings

- Was the sc ent fic qua ty of the nc uded stud es used appropr ate y n formu at ng conc us ons?
- Were the methods used to comb ne the find ngs of stud es appropr ate?
- Was between-study var at on (heterogene ty) m n ma or addressed n the synthes s?
- Was the ke hood of pub cat on b as assessed?
- Are the stated conc us ons supported by the data presented?

Conflict of interest

- Was the confl ct of nterest for the systemat c rev ew stated?

Overall quality

- Rate the overa qua ty of the systemat c rev ew

of quality assessments, all systematic reviews were rated independently by at least two committee members. Disagreements among committee members regarding the overall quality of a systematic review were resolved through deliberation or by the assessment of a third committee member. Only those systematic reviews rated as good or fair quality were used to inform the report's findings, conclusions, and recommendations.

PRIMARY LITERATURE: IDENTIFICATION AND QUALITY REVIEW

For those health endpoints addressed by more than one good- or fair-quality systematic review, the committee gave primacy to the most recently published systematic reviews (since 2011). Any deviations in this process are detailed in the chapter text. For every health endpoint with an associated good- or fair-quality systematic review, the committee also reviewed relevant primary literature published after the cutoff date of the literature search used in that systematic review. For endpoints not addressed by at least one good- or fair-quality systematic review, the committee reviewed all relevant primary literature published between January 1, 1999, and August 2, 2016.

Committee members first reviewed article abstracts to identify and remove editorials, opinion pieces, grey literature, and other documents that were not peer-reviewed cross-sectional studies, case-control studies, cohort studies, randomized controlled trials (RCTs), or nonsystematic literature reviews. During this preliminary review, committee members also assessed the relevance of the article to the health endpoint question.

In their in-depth review of the primary literature, committee members were guided by the Cochrane Quality Assessment for randomized controlled trials and the Newcastle–Ottawa Scale for cohort and case-control studies.[2] For a depiction of the flow of articles through the search and selection process, see Figure B-2.

DATA SYNTHESIS AND STRENGTH OF EVIDENCE ASSESSMENT

After completing the identification and quality-assessment process described above, the committee formulated its findings and conclusions.

[2] The Cochrane Risk Assessment Tool was designed to assess for a risk of bias consequent to flaws in the design, conduct, analysis, and reporting of randomized trials (Higgins, 2011). The Newcastle–Ottawa Scale (NOS) was designed to assess the quality of nonrandomized trials to be included in a systematic review. The NOS assesses studies along three dimensions: selection of study groups, comparability of study groups, and determination of endpoints and exposures (Wells et al., 2011).

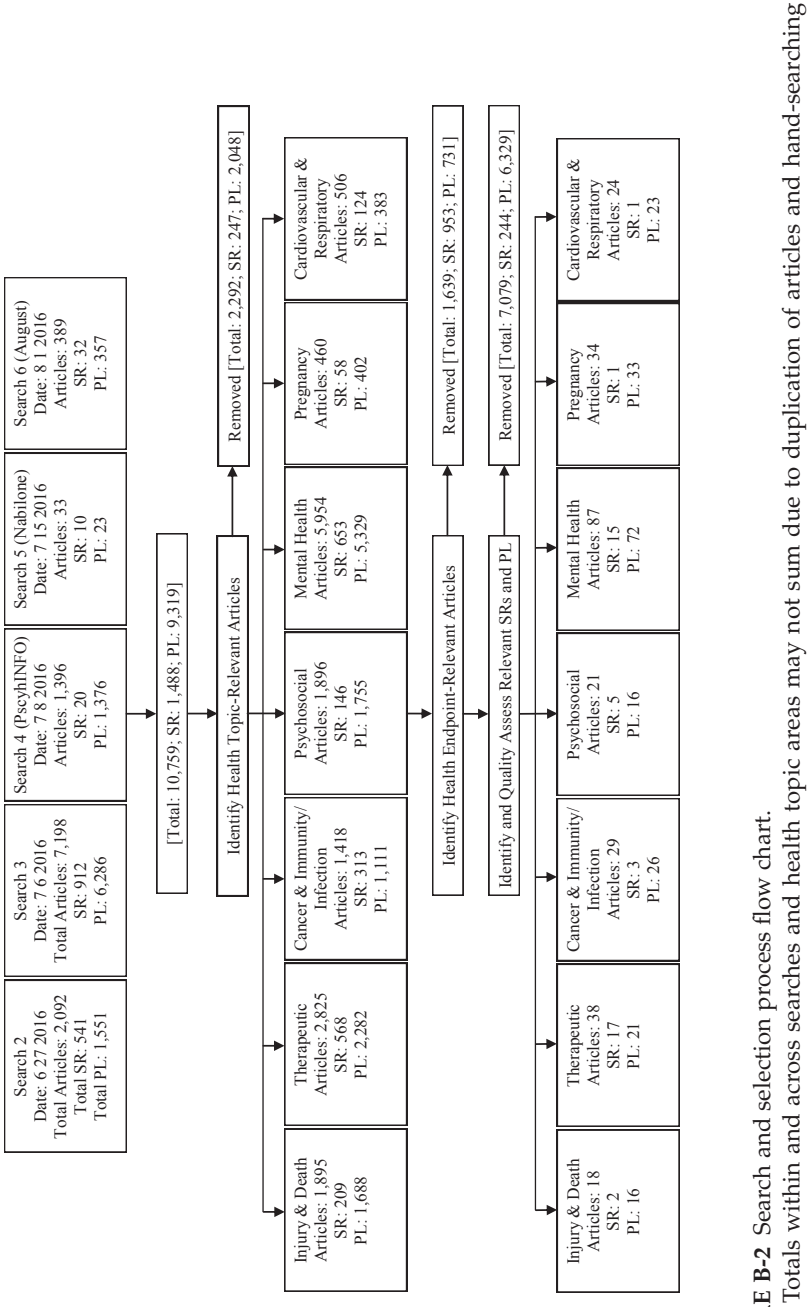

FIGURE B-2 Search and selection process flow chart.
NOTE: Totals within and across searches and health topic areas may not sum due to duplication of articles and hand-searching efforts.

The committee employed two strategies to ensure that report conclusions and recommendations were based on the best available evidence and that the strength of the evidence informing the conclusions was explicitly articulated. First, the committee privileged evidence drawn from RCTs, followed by nonrandomized controlled trials, prospective controlled studies, and case-control studies. Case series and case studies were referenced only in the absence of higher-quality studies. Second, the committee developed a set of standardized terms to describe the strength of the evidence informing every conclusion. Informed by the reports of previous Institute of Medicine (IOM)[3] committees, the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoid use (for therapeutic purposes) is an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) is statistically associated with the prioritized health endpoints of interest. The weight of the evidence was determined during private deliberations of subgroups of the committee. This hierarchy of evidence does not imply the magnitude of the observed effect or the importance of the health effect from an individual or population standpoint. Instead, these terms reflect the quality, quantity, and consistency of the evidence supporting a conclusion. See Box B-3 for the terms and their descriptions.

DISCUSSION

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited time frame, while adhering to the National Academies of Sciences, Engineering, and Medicine's high standards for the quality and rigor of committee reports. Some limitations to these strategies and processes are discussed below.

First, the committee was not tasked to conduct a systematic review, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search, assessments by more than one person of the quality (risk of bias) of key literature and the conclusions, prespecification of the questions of interest before conclusions were formulated, standard language to allow comparisons between conclusions, and declarations of conflict of interest via the National Academies conflict of interest policies. Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was

[3] As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

BOX B-3
Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeut c effects: There s strong ev dence from random zed contro ed tr a s to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s strong ev dence from random zed contro ed tr a s to support or refute a stat st ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are many support ve find ngs from good-qua ty stud es w th no cred b e oppos ng find ngs. A firm conc us on can be made, and the m tat ons to the ev dence, nc ud ng chance, b as, and confound ng factors, can be ru ed out w th reasonab e confidence.

SUBSTANTIAL EVIDENCE

For therapeut c effects: There s strong ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s strong ev dence to support or refute a stat st - ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are severa support ve find ngs from good-qua ty stud es w th very few or no cred b e oppos ng find ngs. A firm conc us on can be made, but m nor m tat ons, nc ud ng chance, b as, and confound ng factors, cannot be ru ed out w th reasonab e confidence.

MODERATE EVIDENCE

For therapeut c effects: There s some ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

manageable within the time frame available to the committee. Furthermore, very good research may not be reflected in this report because it did not directly address the health endpoint questions that the committee formulated.

For other hea th effects: There s some ev dence to support or refute a stat st - ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are severa support ve find ngs from good- to fa r-qua ty stud es w th very few or no cred b e oppos ng find ngs. A genera conc u- s on can be made, but m tat ons, nc ud ng chance, b as, and confound ng factors, cannot be ru ed out w th reasonab e confidence.

LIMITED EVIDENCE

For therapeut c effects: There s weak ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s weak ev dence to support or refute a stat st - ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are support ve find ngs from fa r-qua ty stud es or m xed find ngs w th most favor ng one conc us on. A conc us on can be made, but there s s gn ficant uncerta nty due to chance, b as, and confound ng factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeut c effects: There s no or nsuffic ent ev dence to support the conc us on that cannab s or cannab no ds are an effect ve or neffect ve treatment for the hea th endpo nt of nterest.

For other hea th effects: There s no or nsuffic ent ev dence to support or re- fute a stat st ca assoc at on between cannab s or cannab no d use and the hea th endpo nt of nterest.

For th s eve of ev dence, there are m xed find ngs, a s ng e poor study, or hea th endpo nt has not been stud ed at a . No conc us on can be made because of substant a uncerta nty due to chance, b as, and confound ng factors.

SEARCH STRATEGIES

Search 2
Date: June 27, 2016

Total citations:
Systematic reviews: 541
Primary literature: 1,551
Total: 2,092

Databases (search engine): Medline (Ovid); Embase (Ovid); Cochrane (Ovid)

Note: Ovid command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MESH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The fields searched by a .mp in Embase and Medline include title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, and unique identifier. The fields searched by a .mp in Cochrane include title, short title, abstract, full text, keywords, caption text.

Search No.	Search Syntax
	Beneficial
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	10 not 13
15	Rats/ or rats.ti,ab.
16	Mice/ or mice.ti,ab.
17	animals/ or animals.ti,ab.
18	or/15–17
19	14 not 18
20	Therapeutics/
21	"therapeutic use".mp.
22	benefits.mp.
23	treatment.mp.
24	therapy.mp.
25	Palliative Care/ or palliation.mp.
26	"Quality of Life"/
27	or/20–26

Search No.	Search Syntax
28	19 and 27
29	Nausea/ or nausea.mp.
30	Vomiting/
31	vomiting.mp.
32	or/28–30
33	28 and 31
34	limit 32 to (abstracts and English language and humans and yr="1999–Current")
35	Analgesia/ or Analgesia.mp.
36	28 and 35
37	limit 36 to (English language and humans and yr="1999–Current")
38	Anxiety/ or anxiety relief.mp. or Anxiety Disorders/
39	28 and 38
40	limit 39 to (English language and humans and yr="1999–Current")
41	irritable bowel syndrome.mp. or Irritable Bowel Syndrome/
42	28 and 41
43	limit 42 to (English language and humans and yr="1999–Current")
44	improved sexual function.mp. or Sexual Behavior/
45	sexual function.mp.
46	or/44–45
47	28 and 46
48	limit 47 to (English language and humans and yr="1999–Current")
49	Interpersonal Relations/ or social relationships.mp.
50	28 and 57
51	limit 50 to (English language and humans and yr="1999–Current")
52	increased appetite.mp. or Appetite/ or Eating/
53	wasting.mp. or Wasting Syndrome/
54	or/52–53
	28 and 54
55	limit 54 to (English language and humans and yr="1999–Current")
56	Substance-Related Disorders/ or addiction.mp.
57	28 and 56
58	limit 57 to (English language and humans and yr="1999–Current")
59	intraocular pressure.mp. or Intraocular Pressure/
60	28 and 59
61	limit 60 to (English language and humans and yr="1999–Current")
62	PTSD.mp. or Stress Disorders, posttraumatic/
63	trauma.mp.
64	or/62–63
65	28 and 64
66	limit 65 to (English language and humans and yr="1999–Current")

Search No.	Search Syntax
67	Premenstrual Syndrome/ or Premenstrual Dysphoric Disorder/ or premenstrual.mp.
68	28 and 67
69	limit 68 to (English language and humans and yr="1999–Current")
70	Epilepsy/ or seizure control.mp. or Seizures/
71	28 and 70
72	limit 71 to (English language and humans and yr="1999–Current")
73	sleep disorders.mp. or Sleep Wake Disorders/
74	insomnia.mp. or "Sleep Initiation and Maintenance Disorders"/
75	or/73–74
76	28 and 75
77	limit 76 to (English language and humans and yr="1999–Current")
78	Muscle Spasticity/ or Spasticity.mp.
79	Pain/
80	Multiple Sclerosis/
81	or/78–80
82	28 and 81
83	limit 82 to (English language and humans and yr="1999–Current")
84	cancer treatment.mp.
85	cancer prevention.mp.
86	or/84–85
87	28 and 86
88	limit 87 to (English language and humans and yr="1999–Current")
89	brain injury.mp. or Brain Injuries/
90	28 and 89
91	limit 90 to (English language and humans and yr="1999–Current")
92	34 or 37 or 40 or 43 or 48 or 51 or 55 or 58 or 61 or 66 or 69 or 72 or 77 or 83 or 88 or 91
93	limit 92 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
94	34 or 37 or 40 or 43 or 48 or 51 or 55 or 58 or 61 or 66 or 69 or 72 or 77 or 83 or 88 or 91
95	limit 94 to (meta-analysis or systematic reviews)

Search No.	Search Syntax
	Cancer
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/

Search No.	Search Syntax
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	cancer.mp. or Neoplasms/
20	lung cancer.mp. or Lung Neoplasms/
21	Esophageal Neoplasms/ or Pharyngeal Neoplasms/ or Laryngeal Neoplasms/ or "Head and Neck Neoplasms"/ or upper aerodigestive tract cancer.mp. or Mouth Neoplasms/
22	testicular cancer.mp. or Testicular Neoplasms/
23	childhood cancer.mp.
24	immune system.mp. or Immune System/
25	Immunity/
26	immunity.mp.
27	or/19–26
28	18 and 27
29	28 not 17
30	limit 29 to (human and English language and yr="1999–Current")
31	limit 30 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
32	limit 30 to (meta analysis or systematic reviews)

Search No.	Search Syntax
	Cardiovascular
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/

Search No.	Search Syntax
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	Cardiovascular Abnormalities/ or Cardiovascular Diseases/ or cardiovascular.mp.
12	cerebrovascular.mp. or Cerebrovascular Disorders/
13	Peripheral Vascular Diseases/ or peripheral vascular.mp.
14	heart attack.mp. or Myocardial Infarction/
15	Stroke/ or stroke risk.mp.
16	thromboangiitis obliterans.mp. or Thromboangiitis Obliterans/
17	spice.ti,ab.
18	K2.ti,ab.
19	or/17–18
20	10 not 19
21	Rats/ or rats.ti,ab.
22	Mice/ or mice.ti,ab.
23	animals/ or animals.ti,ab.
24	or/21–23
25	or/11–16
26	20 and 25
27	26 not 24
28	27
29	limit 28 to (English language and humans and yr="1999–Current")
30	limit 29 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
31	limit 29 to (meta analysis or systematic reviews)

Search No.	Search Syntax
	Injury
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.

Search No.	Search Syntax
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	injury.mp. or "Wounds and Injuries"/
19	10 and 18
20	19 not 13
21	20 not 17
22	21
23	limit 22 to (English language and humans and yr="1999–Current")
24	Accidents, Traffic/ or motor vehicle accident.mp.
25	motor vehicle crash.mp.
26	or/24–25
27	10 and 26
28	27 not 13
29	28 not 17
30	29
31	limit 30 to (English language and humans and yr="1999–Current")
32	all-cause death.mp.
33	Death/
34	or/32–33
35	10 and 34
36	35 not 13
37	36 not 17
38	37
39	limit 38 to (English language and humans and yr="1999–Current")
40	Drug Overdose/
41	overdose death.mp.
42	or/40–41
43	10 and 42
44	43 not 13
45	44 not 17
46	45
47	limit 46 to (English language and humans and yr="1999–Current")
48	limit 23 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)

Search No.	Search Syntax
49	limit 31 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
50	limit 39 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
51	limit 47 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
52	limit 23 to (meta analysis or systematic reviews)
53	limit 31 to (meta analysis or systematic reviews)
54	limit 39 to (meta analysis or systematic reviews)
55	limit 47 to (meta analysis or systematic reviews)

Search No.	Search Syntax
	Mental Health
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	mental disease/ or mental health/
20	18 and 19
21	20 not 17
22	21
23	limit 22 to (human and English language and yr="1999–Current")

Search No.	Search Syntax
24	limit 23 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
25	limit 24 to (journal and article)
26	limit 24 to (meta analysis or "systematic review")
27	limit 26 to (journal and (article or review))
28	cannabis addiction/
29	drug abuse/ or drug misuse/
30	cannabis dependence.mp.
31	or/28–30
32	18 and 31
33	32 not 17
34	33
35	limit 34 to (human and english language and yr="1999–Current")
36	limit 35 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
37	limit 36 to (journal and article)
38	limit 35 to (meta analysis or "systematic review")
39	limit 38 to (journal and (article or review))
40	alcohol abuse/
41	tobacco dependence/ or tobacco consumption/
42	"tobacco use"/
43	drug abuse/
44	drug dependence/
45	or/40–44
46	18 and 45
47	46 not 17
48	47
49	limit 48 to (human and English language and yr="1999–Current")
50	limit 49 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
51	limit 50 to (journal and article)
52	limit 49 to (meta analysis or "systematic review")
53	limit 52 to (journal and (article or review))
54	schizophrenia/
55	psychosis/
56	psychotic disorder.mp.
57	or/54–56
58	18 and 57
59	58 not 17

Search No.	Search Syntax
60	59
61	limit 60 to (human and English language and yr="1999–Current")
62	limit 61 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
63	limit 62 to (journal and article)
64	limit 61 to (meta analysis or "systematic review")
65	limit 64 to (journal and (article or review))
66	depression/
67	18 and 66
68	67 not 17
69	68
70	limit 69 to (human and English language and yr="1999–Current")
71	limit 70 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
72	limit 71 to (journal and article)
73	limit 70 to (meta analysis or "systematic review")
74	limit 73 to (journal and (article or review))
75	suicide/
76	18 and 75
77	76 not 17
78	77
79	limit 78 to (human and English language and yr="1999–Current")
80	limit 78 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
81	limit 80 to (journal and article)
82	limit 79 to (meta analysis or "systematic review")
83	limit 82 to (journal and (article or review))
84	anxiety/
85	18 and 84
86	85 not 17
87	86
88	limit 87 to (human and English language and yr="1999–Current")
89	limit 88 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
90	limit 89 to (journal and article)
91	limit 88 to (meta analysis or "systematic review")
92	limit 91 to (journal and (article or review))

Search No.	Search Syntax
	Pregnancy
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	pregnancy outcomes.mp. or pregnancy outcome/
20	low birthweight.mp. or low birth weight/
21	premature labor/ or pre term delivery.mp.
22	birth defects.mp.
23	stillbirth/
24	miscarriage.mp. or spontaneous abortion/
25	neonatal mortality.mp. or newborn mortality/
26	physical growth.mp. or growth/
27	18 and 19
28	27 not 17
29	28
30	limit 29 to (human and english language)
31	18 and 20
32	31 not 17
33	32
34	limit 33 to (human and English language and yr="1999–Current")
35	18 and 21
36	35 not 17
37	36
38	limit 37 to (human and English language and yr="1999–Current")
39	18 and 22
40	39 not 17

Search No.	Search Syntax
41	40
42	limit 41 to (human and English language and yr="1999–Current")
43	or/23–25
44	18 and 43
45	18 and 43
46	45 not 17
47	46
48	46
49	limit 48 to (human and English language and yr="1999–Current")
50	18 and 26
51	50 not 17
52	51
53	limit 52 to (human and English language and yr="1999–Current")
54	limit 30 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
55	limit 30 to (meta analysis or systematic reviews)
56	limit 34 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
57	limit 34 to (meta analysis or systematic reviews)
58	limit 38 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
59	limit 38 to (meta analysis or systematic reviews)
60	limit 42 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
61	limit 42 to (meta analysis or systematic reviews)
62	limit 49 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
63	limit 49 to (meta analysis or systematic reviews)
64	limit 53 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
65	limit 53 to (meta analysis or systematic reviews)
66	breast feeding.mp. or Breast Feeding/

Search No.	Search Syntax
67	18 and 66
68	67 not 17
69	68
70	limit 69 to (English language and humans and yr="1999–Current")
71	Pregnancy/
72	71 and 18
73	72 not 17
74	73
75	limit 74 to (English language and humans and yr="1999–Current")
76	limit 70 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
78	limit 70 to (meta analysis or systematic reviews)
80	limit 75 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
82	limit 75 to (meta analysis or systematic reviews)

Search No.	Search Syntax
	Psychosocial
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	psychosocial.mp. or Social Adjustment/
20	psychosocial effects.mp.
21	or/19–20

Search No.	Search Syntax
22	21 and 18
23	22 not 17
24	limit 23 to (English language and humans and yr="1999–Current")
25	cognitive development.mp.
26	Cognition/
27	Achievement/ or academic achievement.mp.
28	or/25–27
29	28 and 18
30	29 not 17
31	30
32	limit 31 to (English language and humans and yr="1999–Current")
33	cognitive impairment.mp. or Cognition Disorders/
34	33 and 18
35	34 not 17
36	limit 35 to (English language and humans and yr="1999–Current")
37	Employment/
38	Income/
39	or/37–38
40	39 and 18
41	40 not 17
42	limit 41 to (English language and humans and yr="1999–Current")
43	Interpersonal Relations/ or social relationships.mp.
44	43 and 18
45	44 not 17
46	45
47	limit 46 to (English language and humans and yr="1999–Current")
48	Social Behavior/ or social roles.mp.
49	48 and 18
50	49 not 17
51	limit 50 to (English language and humans and yr="1999–Current")
52	24 or 32 or 36 or 42 or 47 or 51
53	limit 52 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
54	24 or 32 or 36 or 42 or 47 or 51
55	limit 54 to (meta analysis or systematic reviews)

Search No.	Search Syntax
	Respiratory
1	marijuana.mp. or cannabis/
2	cannabis.mp.

Search No.	Search Syntax
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	10 not 13
15	Rats/ or rats.ti,ab.
16	Mice/ or mice.ti,ab.
17	animals/ or animals.ti,ab.
18	or/15–17
19	pulmonary.mp. or Pulmonary Disease, Chronic Obstructive/
20	lung disease.mp. or Lung Diseases/ or Respiratory Tract Diseases/ or respiratory disease.mp. or COPD.mp.
21	or/19–20
22	21 and 14
23	22 not 18
24	23
25	limit 24 to (human and English language and yr="1999–Current")
26	limit 25 to (meta analysis or systematic reviews)
27	limit 25 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)

Search 3
Date: July 6, 2016

Total citations:
Systematic Reviews: 912
Primary Literature: 6,286
Total: 7,198

Databases (search engine): Medline (Ovid); Embase (Ovid); Cochrane (Ovid)

Note: Ovid command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MESH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The fields searched by a .mp in Embase and Medline include title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, and unique identifier. The fields searched by a .mp in Cochrane include title, short title, abstract, full text, keywords, caption text.

Search No.	Search Syntax
1	Cannabis/
2	Marijuana Smoking/
3	Marijuana Abuse/
4	Medical Marijuana/
5	Cannabinoids/
6	Dronabinol/
7	(cannabis or marijuana or cannabinoid or dronabinol or marinol).ti,ab.
8	THC.ti,ab
9	or/1–8
10	k2.ti,ab.
11	spice.ti,ab.
12	or/10–11
13	9 not 12
14	Mice/ or mice.ti,ab.
15	Rats/ or rats.ti,ab.
16	or/14–15
17	13 not 16
18	17
19	limit 18 to (English language and humans)
20	limit 19 to (classical article or clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or journal article or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or validation studies)

Search No.	Search Syntax
21	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or systematic reviews or technical report or video-audio media or webcasts)
22	20 not 21
23	limit 22 to yr=1999-current
24	limit 19 to (meta analysis or "review" or systematic reviews)
25	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "scientific integrity review" or technical report or video-audio media or webcasts)
26	24 not 25
27	limit 26 to yr=1999-current

Search 4
Date: July 8, 2016

Total citations:
Systematic Reviews: 20
Primary Literature: 1,376
Total: 1,396

Database (search engine): PsycINFO (ProQuest)

Note: Terms with SU in front of them are Subject Headings taken from the Thesaurus of Psychological Index Terms.

Search	Search Syntax
Systematic Reviews + Meta Analysis	((SU("Cannabinoids" OR "Cannabis" OR "Marijuana Usage" OR "Marijuana") OR TI,AB(cannabis OR marijuana OR cannabinoid OR dronabinol) NOT TI,AB("K-2" OR spice)) AND peer(yes) AND (la.exact("ENG"))) AND (me.exact(("Systematic Review" OR "Meta Analysis") NOT ("Empirical Study" OR "Quantitative Study" OR "Interview" OR "Longitudinal Study" OR "Followup Study" OR "Prospective Study" OR "Literature Review" OR "Treatment Outcome/Clinical Trial" OR "Qualitative Study" OR "Brain Imaging" OR "Clinical Case Study" OR "Retrospective Study" OR "Mathematical Model" OR "Twin Study" OR "Focus Group" OR "Field Study" OR "Experimental Replication" OR "Scientific Simulation" OR "Nonclinical Case Study")) AND rtype.exact(("Journal" OR "Peer-reviewed Journal" OR "Journal Article") NOT ("Comment/reply" OR "Editorial" OR "Letter" OR "Erratum/correction" OR "Review-book" OR "Column/opinion" OR "Abstract Collection" OR "Reprint" OR "Review-media" OR "Obituary")) AND po.exact(("Male" OR "Human" OR "Female" OR "Outpatient" OR "Inpatient") NOT "Animal") AND pd(19990101-20161231) AND PEER(yes))
Peer-reviewed Literature	(SU("Cannabinoids" OR "Cannabis" OR "Marijuana Usage" OR "Marijuana") OR TI(cannabis OR marijuana OR cannabinoid OR dronabinol) NOT TI,AB("K-2" OR spice)) AND peer(yes) AND (la.exact("ENG") AND me.exact(("Empirical Study" OR "Quantitative Study" OR "Longitudinal Study" OR "Followup Study" OR "Prospective Study" OR "Treatment Outcome/Clinical Trial" OR "Clinical Case Study" OR "Twin Study") NOT ("Interview" OR "Literature Review" OR "Qualitative Study" OR "Brain Imaging" OR "Mathematical Model" OR "Systematic Review" OR "Meta Analysis" OR "Field Study" OR "Focus Group")) AND rtype.exact(("Journal" OR "Peer-reviewed Journal" OR "Journal Article") NOT ("Comment/reply" OR "Editorial" OR "Letter" OR "Erratum/correction" OR "Review-book" OR "Column/opinion" OR "Abstract Collection" OR "Reprint" OR "Review-media" OR "Obituary"))) AND pd(19990101-20160601)

Search 5
Date: July 15, 2016

Total citations:
Systematic Reviews: 10
Primary Literature: 23
Total: 33

Database (search engine): Medline (Ovid); Embase (Ovid); Cochrane (Ovid)

Note: Ovid command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MESH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The fields searched by a .mp in Embase and Medline include title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, and unique identifier. The fields searched by a .mp in Cochrane include title, short title, abstract, full text, keywords, caption text.

Search No.	Search Syntax
1	nabilone.mp
2	spice.ti,ab.
3	K2.ti,ab.
4	or/2–3
5	1 not 4
6	Rats/ or rats.ti,ab.
7	Mice/ or mice.ti,ab.
8	animals/ or animals.ti,ab.
9	or/6–8
10	5 not 9
11	limit 10 to (English language and yr="1999-Current")
12	limit 11 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
13	limit 11 to (meta-analysis or systematic reviews)

Search 6
Date: August 2, 2016

Search Parameters: Published June 30, 2016–August 2, 2016

Total citations:
Systematic Reviews: 32
Primary Literature: 357
Total: 389

Database (search engine): Embase (Ovid)

Note: The Medline search was duplicated in PubMed to ensure that all e-pub and non-indexed / in-process citations were captured.

Epub Ahead of Print, In-Process, and Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, and Ovid MEDLINE(R), 1946 to Present

Search No.	Search Syntax
1	Cannabis/
2	Marijuana Smoking/
3	Marijuana Abuse/
4	Medical Marijuana/
5	Cannabinoids/
6	Dronabinol/
7	(cannabis or marijuana or cannabinoid or dronabinol or marinol).ti,ab.
8	nabilone.ti,ab.
9	or/1–8
10	k2.ti,ab.
11	spice.ti,ab.
12	or/10–11
13	9 not 12
14	Mice/ or mice.ti,ab.
15	Rats/ or rats.ti,ab.
16	or/14–15
17	13 not 16
18	17
19	limit 18 to (English language and humans)
20	limit 19 to (classical article or clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or journal article or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or validation studies)
21	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or Dnglish abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or systematic reviews or technical report or video-audio media or webcasts)
22	20 not 21
23	limit 22 to ed=20160630-20160901

Search No.	Search Syntax
24	limit 19 to (meta-analysis or "review" or systematic reviews)
25	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or English abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "scientific integrity review" or technical report or video-audio media or webcasts)
26	24 not 25
27	limit 26 to ed=20160630-20160901

Embase (Ovid)

Search No.	Search Syntax
1	major clinical study/
2	clinical article/
3	case report/
4	clinical trial/
5	controlled clinical trial/
6	phase 1 clinical trial/
7	phase 2 clinical trial/
8	phase 3 clinical trial/
9	phase 4 clinical trial/
10	randomized controlled trial/
11	double blind procedure/
12	single blind procedure/
13	crossover procedure/
14	multicenter study/
15	controlled study/
16	"clinical trial (topic)"/
17	"controlled clinical trial (topic)"/
18	"phase 1 clinical trial (topic)"/
19	"phase 2 clinical trial (topic)"/
20	"phase 3 clinical trial (topic)"/
21	"phase 4 clinical trial (topic)"/
22	"randomized controlled trial (topic)"/
23	"multicenter study (topic)"/
24	cannabis/

Search No.	Search Syntax
25	cannabis addiction/ or medical cannabis/ or "cannabis use"/ or cannabis smoking/ or cannabis derivative/
26	cannabinoid/
27	dronabinol/
28	nabilone/
29	(Cannabis or marijuana or cannabinoid or dronabinol or nabilone or marinol).ti,ab.
30	or/24–29
31	k2.ti,ab.
32	spice.ti,ab.
33	or/31–32
34	30 not 33
35	Mice/ or mice.ti,ab.
36	Rats/ or rats.ti,ab.
37	or/35–36
38	34 not 37
39	or/1–23
40	38 and 39
41	limit 40 to (journal and article)
42	limit 40 to (book or book series or chapter or conference abstract or conference paper or conference proceeding or "conference review" or editorial or erratum or letter or note or "review" or short survey or trade journal)
43	41 not 42
44	case report/
45	43 not 44
46	45
47	limit 46 to (human and English language)
48	limit 47 to yr="2016–Current"
49	limit 48 to dd=20160630-20161231
50	meta analysis/
51	"meta analysis (topic)"/
52	"meta analysis (topic)"/
53	"systematic review (topic)"/
54	or/50–53
55	38 and 54
56	limit 55 to (journal and (article or review))
57	56
58	limit 57 to (human and English language)
59	58
60	limit 59 to yr="2016–Current"
61	limit 60 to dd=20160630-20161231

REFERENCES

Higgins, J. P. T., D. G. Altman, P. C. Gøtzsche, P. Jüni, D. Moher, A. D. Oxman, J. Savovic, K. F. Schulz, L. Weeks, J. A. Sterne, the Cochrane Bias Methods Group, and the Cochrane Statistical Methods Group. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928. doi:10.1136/bmj.d5928.

Wells, G. A., B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell. 2011. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http:// www. ohri.ca/programs/clinical_ epidemiology/oxford.asp (accessed November 28, 2016).

Appendix C

Systematic Reviews

THERAPEUTIC EFFECTS OF CANNABIS AND CANNABINOIDS

Chronic Pain

Andreae, M. H., G. M. Carter, N. Shaparin, K. Suslov, R. J. Ellis, M. A. Ware, D. I. Abrams, H. Prasad, B. Wilsey, D. Indyk, M. Johnson, and H. S. Sacks. 2015. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *Journal of Pain* 16(12):1121–1232.

Fitzcharles, M. A., P. A. Ste-Marie, W. Hauser, D. J. Clauw, S. Jamal, J. Karsh, T. Landry, S. LeClercq, J. J. McDougall, Y. Shir, K. Shojania, and Z. Walsh. 2016. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: A systematic review of randomized controlled trials. *Arthritis Care and Research* 68(5):681–688.

Richards, B. L., S. L. Whittle, D. M. Van Der Heijde, and R. Buchbinder. 2012. Efficacy and safety of neuromodulators in inflammatory arthritis: A Cochrane systematic review. *Journal of Rheumatology* 39(Suppl 90):28–33.

Snedecor, S. J., L. Sudharshan, J. C. Cappelleri, A. Sadosky, P. Desai, Y. J. Jalundhwala, and M. Botteman. 2013. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. *Journal of Pain Research* 6:539–547.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Cancer

Rocha, F., J. dos Santos Junior, S. Stefano, and D. da Silveira. 2014. Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. *Journal of Neuro-Oncology* 116(1):11–24.

Chemotherapy-Induced Nausea and Vomiting

Phillips, R. S., A. J. Friend, F. Gibson, E. Houghton, S. Gopaul, J. V. Craig, and B. Pizer. 2016. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. *Cochrane Database of Systematic Reviews* 2:CD007786.

Smith, L. A., F. Azariah, T. C. V. Lavender, N. S. Stoner, and S. Bettiol. 2015. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database of Systematic Reviews* 11:CD009464.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Anorexia and Weight Loss

Lutge, E. E., A. Gray, and N. Siegfried. 2013. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database of Systematic Reviews* 4:CD005175.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Irritable Bowel Syndrome (IBS)

The committee did not identify any good- or fair-quality systematic reviews that reported on IBS.

Epilepsy

Gloss, D., and B. Vickrey. 2014. Cannabinoids for epilepsy. *Cochrane Database of Systematic Reviews* 3:CD009270.

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Spasticity Associated with Multiple Sclerosis and Paraplegia Caused by Spinal Cord Injury

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Tourette Syndrome

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Amyotrophic Lateral Sclerosis (ALS)

The committee did not identify any good- or fair-quality systematic reviews that reported on ALS.

Huntington's Disease

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Parkinson's Disease

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Dystonia

Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Dementia

Krishnan, S., R. Cairns, and R. Howard. 2009. Cannabinoids for the treatment of dementia. *Cochrane Database of Systematic Reviews* 2:CD007204.

van den Elsen, G. A. H., A. I. A. Ahmed, M. Lammers, C. Kramers, R. J. Verkes, M. A. van der Marck, and M. G. M. O. Rikkert. 2014. Efficacy and safety of medical cannabinoids in older subjects: A systematic review. *Ageing Research Reviews* 14(1):56–64.

Glaucoma

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Traumatic Brain Injury/Intracranial Hemorrhage

The committee did not identify any good- or fair-quality systematic reviews that reported on traumatic brain injury/intracranial hemorrhage.

Addiction

Marshall, K., L. Gowing, R. Ali, and B. Le Foll. 2014. Pharmacotherapies for cannabis dependence. *Cochrane Database of Systematic Reviews* 12:CD008940.

Prud'Homme, M., R. Cata, and D. Jutras-Aswad. 2015. Cannabidiol as an intervention for addictive behaviors: A systematic review of the evidence. *Substance Abuse: Research and Treatment* 9:33–38.

Anxiety

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Depression

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Sleep Disorders

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Posttraumatic Stress Disorder (PTSD)

The committee did not identify any good- or fair-quality systematic reviews that reported on PTSD.

Schizophrenia and Other Psychoses

McLoughlin, B. C., J. A. Pushpa-Rajah, D. Gillies, J. Rathbone, H. Variend, E. Kalakouti, and K. Kyprianou. 2014. Cannabis and schizophrenia. *Cochrane Database of Systematic Reviews* 10:CD004837.

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

CANCER INCIDENCE

Lung Cancer

Zhang, L. R., H. Morgenstern, S. Greenland, S.-C. Chang, P. Lazarus, M. D. Teare, P. J. Woll, I. Orlow, and B. Cox, on behalf of the Cannabis and Respiratory Disease Group of New Zealand, Y. Brhane, G. Liu, and R. J. Hung. 2015. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. *International Journal of Cancer* 136(4):894–903.

Head and Neck Cancers

de Carvalho, M. F., M. R. Dourado, I. B. Fernandes, C. T. Araujo, A. T. Mesquita, and M. L. Ramos-Jorge. 2015. Head and neck cancer among marijuana users: A meta-analysis of matched case-control studies. *Archives of Oral Biology* 60(12):1750–1755.

Testicular Cancer

Gurney, J., C. Shaw, J. Stanley, V. Signal, and D. Sarfati. 2015. Cannabis exposure and risk of testicular cancer: A systematic review and meta-analysis. *BMC Cancer* 15:897.

Esophageal Cancer

The committee did not identify any good- or fair-quality systematic reviews that reported on esophageal cancer.

Other Cancers in Adults

The committee did not identify any good- or fair-quality systematic reviews that reported on other cancers in adults.

Childhood Cancers

The committee did not identify any good- or fair-quality systematic reviews that reported on childhood cancers.

CARDIOMETABOLIC RISK

The committee did not identify any good- or fair-quality systematic reviews that reported on the health endpoints addressed in this chapter.

RESPIRATORY DISEASE

Pulmonary Function

Tetrault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

Chronic Obstructive Pulmonary Disease

The committee did not identify any good- or fair-quality systematic reviews that reported on chronic obstructive pulmonary disease.

Respiratory Symptoms, Including Chronic Bronchitis

Tetrault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

Asthma

Tetrault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

IMMUNITY

The committee did not identify any good- or fair-quality systematic reviews that reported on the health endpoints addressed in this chapter.

INJURY AND DEATH

All-Cause Mortality

Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review* 29(3):318–330.

Occupational Injury

The committee did not identify any good- or fair-quality systematic reviews that reported on occupational injury.

Motor Vehicle Crashes

Asbridge, M., J. A. Hayden, and J. L. Cartwright. 2012. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. *BMJ* 344:e536.

Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review* 29(3):318–330.

Elvik, R. 2013. Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. *Accident Analysis & Prevention* 60:254–267.

Hartman, R. L., and M. A. Huestis. 2013. Cannabis effects on driving skills. *Clinical Chemistry* 59(3):478-492.

Li, M. C., J. E. Brady, C. J. DiMaggio, A. R. Lusardi, K. Y. Tzong, and G. Li. 2012. Marijuana use and motor vehicle crashes. *Epidemiologic Reviews* 34:65–72.

Rogeberg, O., and R. Elvik. 2016. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction* 111:1348–1359.

Overdose Injuries and Death

The committee did not identify any good- or fair-quality systematic reviews that reported on overdose injuries and death.

PRENATAL, PERINATAL, AND NEONATAL EXPOSURE TO CANNABIS

Pregnancy Complications for the Mother

Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.

Fetal Growth and Development

Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.

Neonatal Conditions

Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.

Later Outcomes

The committee did not identify any good- or fair-quality systematic reviews that reported on later outcomes.

PSYCHOSOCIAL

Cognition

Batalla, A., S. Bhattacharyya, M. Yucel, P. Fusar-Poli, J. A. Crippa, S. Nogue, M. Torrens, J. Pujol, M. Farre, and R. Martin-Santos. 2013. Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. *PLOS ONE* 8(2):e55821.

Broyd, S. J., H. H. Van Hell, C. Beale, M. Yucel, and N. Solowij. 2016. Acute and chronic effects of cannabinoids on human cognition—A systematic review. *Biological Psychiatry* 79(7):557–567.

Grant, I., R. Gonzalez, C. L. Carey, L. Natarajan, and T. Wolfson. 2003. Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. *Journal of the International Neuropsychological Society* 9:679–689.

Martin-Santos, R., A. B. Fagundo, J. A. Crippa, Z. Atakan, S. Bhattacharyya, P. Allen, P. Fusar-Poli, S. Borgwardt, M. Seal, G. F. Busatto, and P. McGuire. 2010. Neuroimaging in Cannabis Use: A Systematic Review of the Literature. *Psychological Medicine* 40(3):383–398.

Schreiner, A. M., and M. E. Dunn. 2012. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: A meta-analysis. *Experimental and Clinical Psychopharmacology* 20(5):420–429.

Academic Achievement

Macleod, J., R. Oakes,A. Copello, I. Crome, M. Egger, M. Hickman, T. Oppenkowski, H. Stokes-Lampard, and G. Davey Smith. 2004. Psychological and social sequelae of cannabis and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* 363(9421):1579–1588.

Employment and Income

The committee did not identify any good- or fair-quality systematic reviews that reported on employment and income.

Social Relationships and Other Social Roles

Macleod, J., R. Oakes, A. Copello, I. Crome, M. Egger, M. Hickman, T. Oppenkowski, H. Stokes-Lampard, and G. Davey Smith. 2004. Psychological and social sequelae of cannabis and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* 363(9421):1579–1588.

MENTAL HEALTH

Schizophrenia and Other Psychoses

Donoghue, K., and G. A. Doody. 2012. Effect of illegal substance use on cognitive function in individuals with a psychotic disorder: A review and meta-analysis. *Neuropsychology* 26(6):785–801.

Large, M., S. Sharma, M. T. Compton, T. Slade, and O. Nielssen. 2011. Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Archives of General Psychiatry* 68(6):555–561.

Marconi, A., M. Di Forti, C. M. Lewis, R. M. Murray, and E. Vassos. 2016. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin* 42(5):1262–1269.

Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.

Myles, N., H. Newall, O. Nielssen, and M. Large. 2012. The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: Meta-analysis of possible confounding factors. *Current Pharmaceutical Design* 18(32):5055–5069.

Rabin, R. A., K. K. Zakzanis, and T. P. George. 2011. The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis. *Schizophrenia Research* 128(1–3):111–116.

Szoke, A., A. M. Galliot, J. R. Richard, A. Ferchiou, G. Baudin, M. Leboyer, and F. Schurhoff. 2014. Association between cannabis use and schizotypal dimensions—A meta-analysis of cross-sectional studies. *Psychiatry Research* 219(1):58–66.

van der Meer, F. J., E. Velthorst, C. J. Meijer, M. W. Machielsen, and L. de Haan. 2012. Cannabis use in patients at clinical high risk of psychosis: Impact on prodromal symptoms and transition to psychosis. *Current Pharmaceutical Design* 18(32):5036–5044.

Yucel, M., E. Bora, D. I. Lubman, N. Solowij, W. J. Brewer, S. M. Cotton, P. Conus, M. J. Takagi, A. Fornito, S. J. Wood, P. D. McGorry, and C. Pantelis. 2012. The impact of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophrenia Bulletin* 38(2):316–330.

Zammit, S., T. H. Moore, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M., Burke, and G. Lewis. 2008. Effects of cannabis use on outcomes of psychotic disorders: Systematic review. *British Journal of Psychiatry* 193(5):357–363.

Bipolar Disorder

Gibbs, M., C. Winsper, S. Marwaha, E. Gilbert, M. Broome, and S. P. Singh. 2015. Cannabis use and mania symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders* 171:39–47.

Depression

Lev-Ran, S., B. Le Foll, K. McKenzie, T. P. George, and J. Rehm. 2013. Bipolar disorder and co-occurring cannabis use disorders: Characteristics, co-morbidities and clinical correlates. *Psychiatry Research* 209(3):459–465.

Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.

Suicide

Borges, G., C. L. Bagge, and R. Orozco. 2016. A literature review and meta-analyses of cannabis use and suicidality. *Journal of Affective Disorders* 195:63–74.

Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.

Anxiety

Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.

Posttraumatic Stress Disorder (PTSD)

The committee did not identify any good- or fair-quality systematic reviews that reported on PTSD.

PROBLEM CANNABIS USE

Development of Problem Cannabis Use

The committee did not identify any good- or fair-quality systematic reviews that reported on the development of problem cannabis use.

Risk and Protective Factors for Developing Problem Cannabis Use

Humphreys, K. L., T. Eng, and S. S. Lee. 2013. Stimulant medication and substance use outcomes: A meta-analysis. *JAMA Psychiatry* 70(7):740–749.

Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.

Risk and Protective Factors for Severity and Persistence of Problem Cannabis Use

The committee did not identify any good- or fair-quality systematic reviews that reported on the risk and protective factors for severity and persistence of problem cannabis use.

ABUSE OF OTHER SUBSTANCES

The committee did not identify any good- or fair-quality systematic reviews that reported on abuse of other substances.

Appendix D

Public Session Agendas

COMMITTEE MEETING
June 23–24, 2016

Meeting Location
The National Academies' Keck Center
Room 106
500 Fifth Street, NW
Washington, DC 20001

OPEN SESSION AGENDA

The National Academies of Sciences, Engineering, and Medicine has been charged to appoint an ad hoc committee of experts to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents, as well as to identify both a short- and long-term research agenda focused on improving our understanding of the association of marijuana uses relevant to health outcomes.

Thank you for joining us at this meeting. If you have a continued interest in the progress of this study, please feel free to subscribe to our listserv, which can be accessed through our study's website: http://nationalacademies.org/hmd/activities/publichealth/marijuanahealtheffects.aspx.

1:15 p.m. Welcome, Introductions, and Opening Remarks
Marie McCormick, Committee Chair

1:30 p.m. Sponsor Briefing on the Statement of Task
- Remarks from Sponsor Organizations
  - Steve Gust, Ph.D.
    National Institute on Drug Abuse
  - Debbie Winn, Ph.D.
    National Cancer Institute

- Amy Cohn, Ph.D. (via WebEx)
  Truth Initiative
- Question and Answer Session with Committee and Sponsors

2:30 p.m. Adjourn Open Session

COMMITTEE MEETING
August 18, 2016
1:00–4:00pm (EDT)

Meeting Location
The National Academies' Keck Center
Room 106
500 Fifth Street, NW
Washington, DC
20001

Registration for in-person or webcast attendance:
http://www.surveygizmo.com/s3/2943914/
Open-Session-Health-Effects-of-Marijuana
Please note that in-person seating is limited

OPEN SESSION AGENDA

The National Academies of Sciences, Engineering, and Medicine has been charged to appoint an ad hoc committee of experts to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents, as well as to identify both a short- and long-term research agenda focused on improving our understanding of the association of marijuana uses relevant to health outcomes.

Thank you for joining us at this meeting. If you have a continued interest in the progress of this study, please feel free to subscribe to our listserv, which can be accessed through our study's website: http://nationalacademies.org/hmd/activities/publichealth/marijuanahealtheffects.aspx.

1:00 p.m. Welcome, Introductions, and Opening Remarks
Marie McCormick, Committee Chair

1:15 p.m. Panel Discussions:

Health Effects of Cannabis

Speakers:

- Dr. Leslie R. Walker-Harding (Chair, Department of Pediatrics, Penn State Health Milton S. Hershey Medical Center; Medical Director, Penn State Children's Hospital)
- Dr. Sheryl Ryan (Professor of Pediatrics, Yale School of Medicine; Chief, Section of Adolescent Medicine, Yale School of Medicine)
- Dr. Michael Van Dyke (Section Chief, Environmental Epidemiology and Occupational Health, Colorado Department of Public Health and Environment)
- Dr. Peggy van der Pol (Senior Researcher, The Trimbos Institute, Netherlands Institute for Mental Health and Addiction)

Health Impact of Interest: The Role of Cannabis Use in Motor Vehicle Accidents

Speaker:

- Dr. Richard Compton (Director, National Highway Traffic Safety Administration, Office of Behavioral Safety Research)

Therapeutic Effects of Cannabis

Speakers:

- Dr. Igor Grant (Professor and Chair of the Department of Psychiatry at the University of California, San Diego School of Medicine; Director, HIV Neurobehavioral Research Program)
- Dr. Sheryl Ryan (Professor of Pediatrics, Yale School of Medicine; Chief, Section of Adolescent Medicine, Yale School of Medicine)

3:45 p.m. Question and Answer Session

4:00 p.m. Adjourn Open Session

Appendix E

Biographical Sketches for Committee Members, Staff, Fellow, and Advisor

COMMITTEE MEMBERS

Marie C. McCormick, M.D., Sc.D. (Chair), is currently the Sumner and Esther Feldberg Professor of Maternal and Child Health in the Department of Social and Behavioral Sciences at the Harvard T.H. Chan School of Public Health and a professor of pediatrics at the Harvard Medical School, and she is also a senior associate for academic affairs in the Department of Neonatology at the Beth Israel Deaconess Medical Center. Dr. McCormick is a pediatrician with a second doctorate in health services research, with all of her postgraduate training done at Johns Hopkins. In 1987 she joined the faculty of the Department of Pediatrics at Harvard Medical School, and in 1991 she became a professor and the chair of the Department of Maternal and Child Health at the Harvard School of Public Health and a professor of pediatrics. Her research has focused on the effectiveness of perinatal and neonatal health services on the health of women and children with a particular concern in the outcomes of very premature infants. She has been a senior investigator on the evaluations of two national demonstration programs (the Robert Wood Johnson Foundation National Perinatal Regionalization Program and, currently, the federal Healthy Start Program). In addition, she has provided significant scientific input, in a variety of roles, to the design and conduct of Infant Health and Development Project, the largest multisite, randomized trial of early childhood educational intervention, in particular, serving as the principal investigator of the follow-up done at 18 years of age. She is a member of the National Academy of Medicine, among other organizations. Her work

on several committees, most notably the Immunization Safety Review Committee, has earned her the David Rall Medal for exceptional service.

Donald I. Abrams, M.D., is chief of the Hematology-Oncology Division at Zuckerberg San Francisco General Hospital and a professor of clinical medicine at the University of California, San Francisco (UCSF). He was one the original clinician/investigators to recognize and define many early AIDS-related conditions. He has long been interested in clinical trials of complementary medicine interventions for human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) and cancer, including evaluations of medicinal cannabis. In 1997 he received funding from the National Institute on Drug Abuse to conduct a clinical trial of the short-term safety of cannabinoids in HIV infection. Subsequently he was granted funds by the University of California Center for Medicinal Cannabis Research to conduct studies of the effectiveness of cannabis in a number of clinical conditions. He completed a placebo-controlled study of smoked cannabis in patients with painful HIV-related peripheral neuropathy as well as a study evaluating vaporization as a smokeless delivery system for medicinal cannabis. His last National Institute on Drug Abuse–funded trial investigated the safety and pharmacokinetic interaction between vaporized cannabis and sustained-release opioid analgesics in patients with chronic pain. He is currently conducting a translational National Heart, Lung, and Blood Institute–funded trial investigating vaporized cannabis in patients with sickle cell disease. He received an A.B. in molecular biology from Brown University in 1972 and graduated from the Stanford University School of Medicine in 1977. After completing an internal medicine residency at the Kaiser Foundation Hospital in San Francisco, he became a fellow in hematology-oncology at UCSF, before joining the faculty. In 2004, he completed a distance learning fellowship in integrative medicine from the University of Arizona and has since been providing integrative oncology consultations at the UCSF Osher Center for Integrative Medicine.

Margarita Alegría, Ph.D., is the chief of the Disparities Research Unit at Massachusetts General Hospital and a professor in the Departments of Medicine and Psychiatry at Harvard Medical School. Dr. Alegría is currently the principal investigator (PI) of four National Institutes of Health (NIH)-funded research studies: International Latino Research Partnership; Effects of Social Context, Culture and Minority Status on Depression and Anxiety; Building Community Capacity for Disability Prevention for Minority Elders; and Mechanisms Underlying Racial/Ethnic Disparities in Mental Disorders. She is also the co-PI of a William T. Grant Foundation project titled Understanding the Experience of Majority and Minority Sta-

tus through Photovoice. Dr. Alegría has published more than 200 papers, editorials, intervention training manuals, and several book chapters on topics such as improvement of health care services delivery for diverse racial and ethnic populations, conceptual and methodological issues with multicultural populations, and ways to bring the community's perspective into the design and implementation of health services. In 2011, she was elected as a member of the National Academy of Medicine. The recipient of several awards, Dr. Alegría was recently selected as *El Planeta*'s (Massachusetts's largest circulating Spanish-language newspaper) 2013's Powermeter 100 most influential people for the Hispanic community in Massachusetts. Dr. Alegría also received the 2016 Cynthia Lucero Latino Mental Health Award by William James College.

William Checkley, M.D., Ph.D., is an associate professor of medicine at the Johns Hopkins University School of Medicine and has a joint appointment in the Department of International Health at the Bloomberg School of Public Health. His areas of clinical expertise include epidemiology, pulmonary disease, and critical care medicine. Dr. Checkley also serves as the medical director for Johns Hopkins International. Dr. Checkley earned his M.D. from Northwestern University and received his Ph.D. from Johns Hopkins University. He completed his internal medicine residency training at Emory University and his fellowship training in pulmonary and critical care medicine at Johns Hopkins School of Medicine. His research interests include international lung health, epidemiology, mechanical ventilation, and acute lung injury. Dr. Checkley has been recognized by the National Institutes of Health with the 2007 Postdoctoral National Research Service Award and the 2009 Pathway to Independence Career Award. He is certified in pulmonary disease and internal medicine by the American Board of Internal Medicine.

R. Lorraine Collins, Ph.D., is a psychologist and professor of community health and health behavior and the associate dean for research at the State University of New York at Buffalo (UB) School of Public Health and Health Professions (SPHHP). For two decades she conducted research as a senior scientist at UB's Research Institute on Addictions before joining the SPHHP as associate dean for research in 2008. Dr. Collins's research interests include cognitive and behavioral approaches to the conceptualization, prevention, and treatment of addictive behaviors, particularly among emerging and young adults. Examples of her projects funded by the National Institutes of Health include a study to examine the combined use of alcohol and marijuana and a study of the use of technology in interventions to reduce marijuana use.

Ziva D. Cooper, Ph.D., is an associate professor of clinical neurobiology in the Department of Psychiatry at Columbia University Medical Center. Dr. Cooper's primary research focus is translational studies investigating the effects of abused drugs and how these effects differ between males and females. For nearly a decade, she has been building on her training in preclinical models of drug dependence and developing an expertise in human laboratory studies on cannabis, cannabinoids, opioids, and cocaine while maintaining research projects in animal models of substance use. Her current research investigates the direct neurobiological effects of emerging drugs of abuse, including synthetic cannabinoids (i.e., K2, Spice) in laboratory animals and the direct physiological and behavioral effects of cannabis and cannabinoids as they pertain to both their abuse potential and potential therapeutic effects in double-blind, placebo-controlled human laboratory studies.

Adre J. du Plessis, M.B.Ch.B., M.P.H., is the director of the Fetal Medicine Institute, the division chief of fetal and transitional medicine, and director of the Fetal Brain Program at Children's National Health System. In addition, Dr. Du Plessis is a professor of pediatrics and neurology at the George Washington University School of Medicine. Dr. Du Plessis is a leading international expert in the normal and abnormal development of the brain as well as the mechanisms of injury to the immature brain. His career-long research focus has been on the nervous system of the fetus and newborn, the hazards and mechanisms of injury, and the potential prevention of insult to the brain. Under his leadership, the Fetal Medicine Institute provides individualized and specialized care to patients during and after the baby's birth. Dr. Du Plessis received his M.B.Ch.B. from the University of Cape Town, South Africa. He trained in pediatrics at the University of Cape Town, South Africa, and at Penn State University. In addition, he trained in child neurology at the St. Louis and Boston Children's Hospitals.

Sarah Feldstein Ewing, Ph.D., is a professor at the Oregon Health and Science University. Dr. Feldstein Ewing is a licensed clinical child psychologist with more than a decade of experience using a variety of evidence-based approaches to prevent and intervene with adolescent health risk behavior, including alcohol use, cannabis use, and human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) risk behavior. At this time, her lab has enrolled more than 1,000 youth within large-scale clinical trials to evaluate the developmental fit and treatment outcomes for motivational interviewing, behavioral skills training, cognitive behavioral approaches, mindfulness, and contingency management. She has published widely regarding the developmental fit, neurocognitive

mechanisms, gender differences, and cross-cultural adaptation of these prevention and intervention approaches for this developmental stage. She has also developed a highly innovative National Institutes of Health–funded line of translational research, evaluating the connection between basic biological mechanisms (e.g., functional brain activation, brain structure, genetic factors) and youth health risk behavior (e.g., clinical symptoms, HIV risk behaviors, treatment outcomes). She has conducted this work with alcohol-abusing adolescents, cannabis-abusing adolescents, adolescents engaged in risky sex, and youths with a high body mass index. Ultimately, the goal of her laboratory is to employ translational studies to (1) determine the driving factors underlying successful treatment outcomes, (2) develop more efficacious interventions, and (3) evaluate the efficacy of interventions in order to improve health outcomes and reduce the current disparities for high-risk adolescents of all backgrounds.

Sean Hennessy, Pharm.D., Ph.D., is a professor of epidemiology and a professor of systems pharmacology and translational therapeutics at the University of Pennsylvania Perelman School of Medicine. His primary field of interest is pharmacoepidemiology, which is the study of the health effects of medications in populations.

Kent Hutchison, Ph.D., is a professor of psychology and neuroscience and the director of clinical training at the University of Colorado Boulder. He completed his Ph.D. in clinical psychology at Oklahoma State University and then subsequently completed an internship at Brown University, where he stayed as a postdoctoral fellow specializing in research on addiction from 1995 to 1998. After leaving Brown University, Dr. Hutchison accepted a faculty position at the University of Colorado Boulder. He was promoted to associate professor in 2002 and full professor in 2007. Dr. Hutchison moved to the Mind Research Network (MRN) in Albuquerque, New Mexico, to pursue a program of research combining neuroimaging, clinical outcomes, and genetics in 2007, where he served as the chief science officer for 2 years. In 2011 he returned to the University of Colorado to help set up the Intermountain Neuroimaging Consortium, which involves the operation of two identical magnetic resonance scanners, one in Albuquerque at MRN and one in Boulder at the University of Colorado. He continues to serve as a liaison between the two organizations. Dr. Hutchison has a long track record of funding from the National Institutes of Health and publications. His research combines neuroimaging, epigenetic, pharmacological, and clinical perspectives. Recently he has focused on how inflammatory processes that result from alcohol abuse may damage important executive control circuits in the brain, ultimately contributing to loss of control over alcohol use. In large

part because of the change in Colorado law legalizing cannabis, he has also become very interested in cannabinoids and has launched several studies to gather data about the effects of cannabis with different ratios of tetrahydrocannabinol to cannabidiol on a variety of measures, including measures related to cognitive function and immune system inflammation.

Norbert E. Kaminski, Ph.D., is the director of the Institute for Integrative Toxicology and a professor of pharmacology and toxicology in the Cell and Molecular Biology Program at Michigan State University. Research being conducted in his laboratory is in the general areas of immunopharmacology and immunotoxicology and encompasses a number of extramurally funded projects. A major emphasis of all of these projects is the elucidation of the molecular mechanisms for the impairment of signal transduction cascades and gene expression during lymphocyte activation by drugs and chemicals. One major research focus is to characterize the mechanism for immune modulation by cannabinoid compounds. This effort has led to the first characterization of cannabinoid receptors within the immune system. Current goals include elucidation of signal transduction events initiated through—as well as independently of—cannabinoid receptors, including the peroxisome proliferator activated receptor (PPARy), leading to aberrant cytokine gene expression by T lymphocytes. A second major research focus is the characterization of the molecular mechanism responsible for altered B cell function produced by halogenated aromatic hydrocarbons, including dioxins and polychlorinated biphenols. This research, which resulted in the first characterization of the aryl hydrocarbon (AH) receptor and aryl hydrocarbon receptor nuclear translocator in B cells, has led to testing of the hypothesis that dioxin and dioxin-like compounds suppress antibody responses by impairing B cell differentiation in an AH receptor-dependent manner. A third area of his research concerns studies aimed at characterizing the role of cytokine expression patterns in airway remodeling induced by chemical and protein respiratory allergens as well as by respiratory pathogens.

Sachin Patel, M.D., Ph.D., is an associate professor of psychiatry and behavioral sciences and of molecular physiology and biophysics and director of the Division of Addiction Psychiatry at Vanderbilt University Medical Center. Dr. Patel's overall research goal is to understand the role of neuronal cannabinoid signaling in brain function relevant to psychiatric disorders. His lab has recently focused specifically on the role of the cannabinoid system in the regulation of stress response physiology and the subsequent development of anxiety and depressive phenotypes relevant to affective disorders. The lab is using animal models to examine the effects of adolescent stress exposure on the cannabinoid system and

cannabinoid-mediated synaptic plasticity in the amygdala, a key brain region implicated in affective disorders and developmental disorders, including autism. His lab is also interested in the role of cannabinoid signaling in modulating behavioral and synaptic alterations induced by very early life stress. Given that stress, especially early life stress, is associated with significantly higher rates of psychiatric disorders, including depression and posttraumatic stress disorder, understanding the cellular and molecular adaptations induced by stress exposure could provide opportunities for the development of novel therapeutic interventions for stress-related psychiatric disorders in children and adults. Another major focus of Dr. Patel's research is understanding the fundamental mechanisms of cannabinoid-mediated synaptic plasticity in the amygdala and how these forms of plasticity change during development. Understanding how the cannabinoid system modulates synaptic efficacy within emotional centers of the brain could provide mechanistic insight into developmental alterations induced by cannabis use during adolescence, which has been shown to be a risk factor for the development of psychiatric disorders, including schizophrenia. His lab is interested in understanding the mechanisms by which cannabis exposure early in life leads to an increased risk for the development of psychiatric disorders during adulthood.

Daniele Piomelli, Ph.D., is a professor of anatomy and neurobiology, has joint appointments in biological chemistry and pharmacology, and holds the Louise Turner Arnold Chair in Neurosciences at the University of California, Irvine (UCI), School of Medicine. Dr. Piomelli was trained in neuroscience and pharmacology. Research in his lab is focused on the function of lipid-derived messengers, with particular emphasis on the endogenous cannabinoids anandamide and 2-arachidonoylglycerol. Current research efforts converge on three areas: the formation and deactivation of anandamide and 2-arachidonoylglycerol; physiological roles of the endogenous cannabinoid system; and development of therapeutic agents that target anandamide and 2-arachidonoylglycerol metabolism. Primary neural cell cultures and state-of-the-art analytical techniques such as liquid chromatography/mass-spectrometry are used to investigate the formation and deactivation of anandamide and 2-arachidonoylglycerol in brain cells. Protein purification and cloning approaches are employed to characterize the molecular mechanisms underlying these processes. Cellular pharmacology and medicinal chemistry, in collaboration with leading international labs, are used to identify pharmacological agents that interfere with various aspects of endogenous cannabinoid function, and their therapeutic potential is explored in vitro and in vivo.

Stephen Sidney, M.D., M.P.H., is the director of research clinics at the Division of Research, Kaiser Permanente Northern California, where he has been conducting epidemiological studies since 1982. He is certified by the American Board of Internal Medicine and is a fellow of the American Heart Association Council on Epidemiology and Prevention. Dr. Sidney's research interests include cardiovascular diseases, including stroke, physical activity and fitness, cognitive function, and obesity, with an emphasis on health disparities. He conducted a National Institute on Drug Abuse–funded study from 1991 to 1994 on health outcomes associated with marijuana use utilizing survey and health outcome data from Kaiser Permanente Northern California, a large integrated health care system. He is the principal investigator of the Oakland field center of National Heart, Lung, and Blood Institute–funded Cardiovascular Risk Development in Young Adults (CARDIA) study, an ongoing 30-year longitudinal study of cardiovascular risk and disease development in individuals who were 18–30 years old at baseline, which includes marijuana use data collected throughout the study period. Dr. Sidney has authored or co-authored more than 360 peer-reviewed scientific publications covering a diverse range of topics, primarily in the area of cardiovascular epidemiology and also including more than 20 articles regarding epidemiological aspects of cannabis use and health outcomes. He received a B.A. in mathematics from Yale University, an M.D. from the Stanford University School of Medicine, and an M.P.H. in epidemiology from the University of California, Berkeley, School of Public Health.

Robert B. Wallace, M.D., M.Sc., is the Irene Ensminger Stecher professor of epidemiology and internal medicine at the University of Iowa Colleges of Public Health and Medicine. He has a variety of public health experiences. He was an Epidemic Intelligence Service Officer with the Centers for Disease Control and Prevention. He has conducted many population health studies as well as clinical trials, focusing on the prevention and control of chronic illnesses and other disabling conditions of older persons. These have included neurological conditions, fracture, cancers, coronary disease, mental illnesses, and the health of older women. He has continuing experience with community interventions related to the prevention of falls and motor vehicle injuries in older persons. He was a member of the U.S. Preventive Services Task Force and the National Advisory Council on Aging of the National Institute on Aging (National Institutes of Health [NIH]). He is an elected member of the National Academy of Medicine and has been a past chair of National Academies of Sciences, Engineering, and Medicine's Board on Population Health and Public Health Practice and Board on the Health of Select Populations and he has had substantial experience with National Academies studies

and panels. He is currently involved in several actively funded research projects by NIH, including several related to nutritional issues.

John Wiley Williams, M.D., M.H.S., is a professor of medicine at Duke University Medical Center and a past recipient of the Veterans Affairs (VA) Health Services Career Development Award and a Robert Wood Johnson Foundation Generalist Faculty Scholar Award. He received his bachelor and M.D. degrees from the University of North Carolina. Dr. Williams completed residency training at the University of Iowa and a research fellowship at Duke University. He is a primary care internist who is trained in epidemiology, biostatistics, and literature synthesis. Dr. Williams's topical interests include depression, mental health services, dementia, and the implementation of best practices. He is scientific editor for the *NC Medical Journal* and a medical editor for the Foundation for Informed Medical Decision Making. Dr. Williams directs the Durham VA Evidence Synthesis Program and has led numerous systematic reviews, many focusing on mental health services. Dr. Williams is board certified in internal medicine and active in clinical practice and resident physician education at the Durham VA Medical Center.

STUDY STAFF, FELLOW, AND ADVISOR

Jennifer A. Cohen, M.P.H., is a program officer in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine on the Board on Population Health and Public Health Practice. She received her undergraduate degree and her M.P.H. from the University of Maryland. Ms. Cohen has been involved with the National Academies committees that produced *Organ Procurement and Transplantation*; *Clearing the Air: Asthma and Indoor Air Exposures*; *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes*; *Veterans and Agent Orange: Update 2000*; *Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans*; *Veterans and Agent Orange: Update 2004*; *Veterans and Agent Orange: Update 2006*; *Veterans and Agent Orange: Update 2008*; *Veterans and Agent Orange: Update 2010*; *Veterans and Agent Orange: Update 2012*; *Post-Vietnam Dioxin Exposure in Agent Orange-Contaminated C-123 Aircraft*; and *Veterans and Agent Orange: Update 2014.* She was also rapporteur for *Challenges and Successes in Reducing Health Disparities*.

Brownsyne Tucker Edmonds, M.D., M.S., M.P.H. (*Norman F. Grant/American Board of Obstetrics and Gynecology Fellow*) is an assistant professor in the Department of Obstetrics and Gynecology at the Indiana University School of Medicine. Originally from Atlanta, Georgia, she received

her undergraduate degree in Community Health and African American Studies at Brown University. She went on to receive her medical degree from Brown Medical School, and, concurrently, completed a master's in public health at the Harvard School of Public Health with a concentration in quantitative methods. Dr. Tucker Edmonds trained in obstetrics and gynecology at Duke University Medical Center, where she served as an administrative chief resident in her final year. She then entered the Robert Wood Johnson Foundation Clinical Scholars Program fellowship at the University of Pennsylvania, where she received health services research training and a master's in health policy research. Most recently, she completed a clinical ethics fellowship through the Indiana University Health Fairbanks Center for Medical Ethics. Her work currently focuses on communication and decision making in the management of periviable deliveries—when end-of-life decisions are made at the very beginning of life.

Kelsey Geiser, M.A., is a research associate with the Health and Medicine Division's Board on Population Health and Public Health Practice. Previously, she worked in the Division of Behavioral and Social Sciences and Education with the Board on Children, Youth, and Families on two consensus studies: *Parenting Matters: Supporting Parents of Children Ages 0–8* and *Preventing Bullying Through Science, Policy, and Practice*. Prior to her work at the National Academies, Ms. Geiser wrote for the Stanford News Service and worked in the Palo Alto district office of Congresswoman Anna Eshoo. She has a B.A. and an M.A. in history from Stanford University with a focus on the historical treatment of women's and family health issues.

Hope R. Hare, M.F.A., is the administrative assistant for the Board on Population Health and Public Health Practice. She keeps the board information updated, administers the twice-yearly board meeting, and provides support for the board director and staff. Ms. Hare has worked for the National Academies of Sciences, Engineering, and Medicine since 2001. She holds an M.F.A. from Cornell University.

Leigh Miles Jackson, Ph.D. (*Study Director*), is a senior program officer in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine's Board on Population Health and Public Health Practice. Previously, she worked in the Division of Behavioral and Social Sciences and Education with the Board on Children, Youth, and Families. She has served as the study director for the Committee on the Use of Economic Evidence to Inform Investments in Children, Youth, and Families and as the program officer for the Roundtable on the

Communication and Use of Social and Behavioral Sciences. Prior to joining the National Academies, she was a developmental psychopathology and neurogenomics research fellow at Vanderbilt University, where she investigated the role of chronic sleep disturbance and specific epigenetic modifications on the health outcomes of adolescents. She has a bachelor's degree in chemistry from Wake Forest University and a Ph.D. in molecular and systems pharmacology from Emory University.

Rose Marie Martinez, Sc.D. (*Senior Board Director*), has been the director of the Health and Medicine Division's Board on Population Health and Public Health Practice since 1999. Prior to joining the National Academies of Sciences, Engineering, and Medicine, Dr. Martinez was a senior health researcher at Mathematica Policy Research (1995–1999), where she conducted research on the impact of health system change on the public health infrastructure, access to care for vulnerable populations, managed care, and the health care workforce. She is a former assistant director for health financing and policy with the U.S. General Accounting Office and served for 6 years directing research studies for the Regional Health Ministry of Madrid, Spain.

Matthew Masiello, is a research assistant for the Health and Medicine Division's Board on Population Health and Public Health Practice. He recently graduated from American University with a B.A. in international studies and a minor in public health. Prior to the working at the National Academies of Sciences, Engineering, and Medicine, he worked within several health-focused organizations, including the American Cancer Society and the Windber Research Institute.

Marjorie Pichon, is a senior program assistant for the Health and Medicine Division's Board on Population Health and Public Health Practice. While at the National Academies of Sciences, Engineering, and Medicine she has contributed to projects such as a National Strategy for the Elimination of Hepatitis B and C, Public Health Approaches to Reduce Vision Impairment and Promote Eye Health, and a workshop on Strategies to Improve Cardiac Arrest Survival. Prior to joining the National Academies, Ms. Pinchon served as a Community Health Corps volunteer for MedStar PromptCare, assisting underserved members of the community gain access to medical care. She graduated from Lewis & Clark College in May 2014 with a B.A. in psychology and a minor in rhetoric and media studies. During this time she collaborated on research in the college's Human Computer Interaction Lab studying how the structure of play influences creativity in children.

Kathleen Stratton, Ph.D. (*Advisor*), began her career at the National Academies of Sciences, Engineering and Medicine in 1990 in what was known at the time as the Institute of Medicine (IOM). She has spent most of her time with the Board on Population Health and Public Health Practice. She has staffed committees addressing vaccine safety and development, pandemic preparedness, environmental and occupational health, drug safety, Medicare payment programs, and tobacco control. She was given the IOM Cecil Research Award in 2002 for sustained contributions to vaccine safety and was made a staff scholar in 2005. After 2 years at The Pew Charitable Trusts working on U.S. Food and Drug Administration reform, she returned to the National Academies in Fall 2013. She received a B.A. in natural sciences from Johns Hopkins University and a Ph.D. in pharmacology and toxicology at the University of Maryland at Baltimore. She conducted postdoctoral research in the Department of Neuroscience at the Johns Hopkins School of Medicine.

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