Journal of Primary Care & Community Health
Volume 10: 1–7
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2150132719884838
journals.sagepub.com/home/jpc
SAGE

Medical Cannabis for the Primary Care Physician

Deepika Slawek[1], Senthil Raj Meenrajan[2], Marika Rose Alois[2], Paige Comstock Barker[2], Irene Mison Estores[2], and Robert Cook[1]

Abstract

Medical cannabis use is common in the United States and increasingly more socially acceptable. As more patients seek out and acquire medical cannabis, primary care physicians will be faced with a growing number of patients seeking information on the indications, efficacy, and safety of medical cannabis. We present a case of a patient with several chronic health conditions who asks her primary care provider whether she should try medical cannabis. We provide a review of the pharmacology of medical cannabis, the state of evidence regarding the efficacy of medical cannabis, variations in the types of medical cannabis, and safety monitoring considerations for the primary care physician.

Keywords

medical cannabis, primary care, chronic pain, medical marijuana, adverse effects

Introduction

Cannabis use is common in the United States and increasing. Cannabis was the most commonly used illicit substance in the United States in 2016 in a national survey, with an estimated 24 million (9%) Americans who used cannabis in the past month.[1] This trend has coincided with a growing number of states that have legalized medical cannabis. Thirty-three states in the United States and the District of Columbia have laws allowing for use of medical cannabis.[2] Cannabis has been more widely accepted in other parts of the world, including the Netherlands and Canada more recently. Israel has been a leader in cannabis research over the years. With the growing prevalence and social acceptability of cannabis use,[3] primary care physicians (PCPs) are faced with more patients seeking information on medical cannabis. Even if the PCP is not prescribing medical cannabis, their patients may be using it and providers should be able to discuss the pros and cons of cannabis use and help to monitor for improvements and for potential adverse outcomes.

To illustrate these points, this article will describe a case of a patient engaged in primary care who is considering whether to try medical cannabis for chronic pain. The subsequent review gives a description of key information that is important for PCPs to know when caring for patients who choose to use medical cannabis, including a brief review of the pharmacology of medical cannabis, the state of evidence regarding its efficacy, variations in the types of medical cannabis, and safety monitoring considerations for the PCP.

Clinical Example

Ms J is a 54-year-old woman with a 15-year history of chronic back pain after a car accident. She has tried pharmacologic management for her pain with duloxetine as well as physical therapy and trigger point injections. The use of opioids for her pain has been discouraged due to the chronic nature of her symptoms and she had negative side effects from gabapentin and amitriptyline. In addition, Ms J complains of insomnia and irritability due to poor sleep. Ms J tells her PCP that given her continued pain, she visited a medical cannabis provider, acquired certification for cannabis to manage her pain, and visited a dispensary where

[1]Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA
[2]University of Florida, Gainesville, FL, USA

Corresponding Author:
Deepika Slawek, Division of General Internal Medicine, Department of Medicine, Montefiore Medical Center, 3300 Kossuth Avenue, Bronx, NY 10467, USA.
Email: dslawek@montefiore.org

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

she encountered many different options for modes of consumption and type of product. She would like an opinion from the primary care perspective on (1) whether she should start medical cannabis for management of her symptoms, (2) whether one type of medical cannabis is better than another, and (3) what side effects or complications she should be concerned about.

Basic Pharmacology of Cannabis

As cannabis is increasingly accepted, it is important for PCPs to understand its basic pharmacology, as well as the formulations their patients might be using. Cannabis describes a family of plants that include marijuana plants, derived mainly from *Cannabis sativa* and *Cannabis indica*, as well as hemp. The cannabis plant produces over 100 cannabinoids and terpenes, the most widely studied of which are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The remaining cannabinoids and terpenes contribute to the smell, taste, and possibly therapeutic effect of cannabis.[4] Cannabinoids can be endogenous (endocannabinoid), plant-derived (phytocannabanoid), or synthetic, and they act as neurotransmitters within the human endocannabinoid system.[4]

The human endocannabinoid system includes cannabinoids and cannabinoid receptors (CB_1 and CB_2). The 2 most well-known endocannabinoids are anandamide and 2-archidonoylglycerol (2-AG). Anandamide and 2-AG target CB_1 and CB_2 receptors, respectively. Similarly, THC acts primarily on CB_1 receptors, and CBD on CB_2.[5]

CB_1 receptors exist primarily in areas of the brain that regulate appetite, memory, fear, and motor responses. Stimulation of CB_1 receptors in the brain leads to psychotropic effects from cannabis. CB_1 receptors are also found outside of the brain in the gastrointestinal tract, adipocytes, liver, and skeletal muscle. CB_2 is primarily expressed in macrophages and other macrophage-derived cells that are part of the immune system.[6]

Medical cannabis can be either plant-derived or synthetic, contains different amounts and ratios of THC and CBD, and can be delivered by several routes of administration, including smoking, vaping, oromucosal, ingestion, and topical. Route of administration affects the rate of absorption of THC and CBD, and thus influences the onset, intensity, and duration of the clinical effect of cannabis. Peak THC blood levels are reached within 30 minutes and subside within 1 to 3.5 hours when cannabis is smoked.[7,8] In contrast, peak THC levels are reached within 30 minutes to 2 hours when ingested and can last 5 to 8 hours.[8] Sublingual and oromucosal THC and CBD avoid first-pass metabolism in the liver, but peak serum THC and CBD concentrations are reached 1 to 8 hours after administration.[4]

Some forms of medical cannabis have undergone clinical trials and are available in the United States and/or other international settings. Nabiximols, which contains plant-derived THC and CBD as an oromucosal spray, is available outside of the United States for use in treating spasticity, nausea, vomiting, and pain.[9] In the United States, the Food and Drug Administration (FDA) approved the first plant-derived cannabinoid for medical use, Epidiolex (CBD), for treatment of seizure disorder.[10] Synthetic therapeutic cannabinoids, including dronabinol (synthetic THC) and nabilone (synthetic THC), are FDA approved for nausea, vomiting, and cachexia.[6]

Products at the dispensary Ms J visited include a range of options that contain THC alone, CBD alone, and several different THC/CBD ratios, and that can be administered by several different modes of consumption. The potential medical effects and side effects could thus vary by the relative amounts of THC and CBD, and the timing and duration of the effects will vary according to the mode of consumption.

Indications and Efficacy of Medical Cannabis

When counseling Ms J on how medical cannabis may affect her symptoms, interpreting the cannabis literature can be challenging for several reasons. First, formulations vary by state due to the patchwork of state-based legislation. Products used in the literature may not be representative of what is available to medical cannabis patients at a local level. In practice, patients self-titrate to symptom relief and are encouraged to do so. Furthermore, medical cannabis has largely been sought for the management of symptoms, rather than conditions. Recent data from the Florida Department of Health show the top indications for currently registered persons in Florida are chronic pain and posttraumatic stress disorder.[11] In New York State, similarly, the most common condition for which patients are certified to receive medical cannabis is chronic pain.[12]

A detailed summary of all known evidence regarding the clinical efficacy of cannabis is beyond the scope of this review, and has been summarized elsewhere including a comprehensive review of the literature published by the National Academies of Sciences, Engineering and Medicine in 2017.[6] Here, we describe evidence for some of the more common indications that are relevant to Ms J.

Chronic Pain

Chronic pain, such as that seen in Ms J's case, is the most commonly cited reason for seeking out medical cannabis.[13] Medical cannabis is used to treat chronic pain related to neuropathy, cancer, multiple sclerosis, rheumatoid arthritis, musculoskeletal issues, drug toxicity, and HIV.[6]

A systematic review of over 28 randomized controlled trials found that cannabinoids have greater odds of ≥30% reduction in pain scores compared with placebo.[14] Cannabis

reduces neuropathic pain in a dose-dependent fashion in other analyses.[15] In these analyses, oral cannabinoids were found to have a smaller beneficial effect than inhaled cannabinoids.[14,15] Though these findings are promising, the sample sizes are very small, many of the studies focused on specific products, including synthetic cannabinoids, and confidence intervals span close to the level of significance.[14] Thus, we have very limited evidence regarding the efficacy of products available to patients in states with medical cannabis, including the relative benefits of THC, CBD, or various THC/CBD ratios for pain.

The mechanism of cannabis' analgesia is not completely understood. One potential mechanism is the interaction of cannabinoids with the human endocannabinoid system, thus leading to a reduction in pain stimuli or inflammation.[16] Cannabis may also reduce emotional stress related to chronic pain, or shift perceptions of pain.[17]

Patients report that medical cannabis helps them reduce or stop other pain medications such as opioids.[18,19] Among patients who use cannabis to manage their pain in California, an overwhelming percentage of those who were surveyed reported that cannabis was better at treating their pain than opioids and that they have subsequently reduced their chronic opioid use.[19] In another sample of patients in Colorado using nonmedical cannabis, the majority endorsed using cannabis to self-manage pain and reported a reduction in other analgesic use when using cannabis. These observations have been documented in other states that have legalized medical cannabis as well.[20,21]

Anxiety and Posttraumatic Stress Disorder

Anxiety and posttraumatic stress disorder (PTSD) are common reasons for seeking out medical cannabis.[22,23] Among individuals engaged in care there is a growing desire to reduce the use of prescription anxiolytics, such as benzodiazepines, due to medication safety concerns.[24] There is also evidence that cannabis is used to self-manage anxiety.[18] Patients who use cannabis report that they subsequently reduce their prescription anxiolytic use, including benzodiazepines.[18,25,26]

The mechanism by which cannabis addresses anxiety is not completely understood. Preclinical data show a relationship between anxiety and decreased endocannabinoids.[27] There are few studies testing the efficacy of cannabis for the treatment of anxiety. In small randomized controlled trials cannabis has been found to be effective for short-term treatment of anxiety symptoms.[6,14,28]

Self-management of PTSD with cannabis is common[29] and PTSD is a commonly listed indication for certification.[2] In surveys among combat veterans who use cannabis at least once per week, cannabis use is associated with improvement in some symptoms of PTSD, such as disturbing thoughts and dreams.[30] Preclinical studies suggest that THC can reduce signals of fear and threat as directed by the amygdala and that CBD can modulate emotional and social processes.[31] Several small studies have been performed in people with PTSD, primarily among veterans. Unfortunately, most of these studies were poor quality, due to short follow-up, small sample size, and lack of a comparison group. In the context of these limitations, cannabinoids have been found to improve PTSD symptoms.[32-35]

Insomnia

Insomnia is experienced by up to 35% of individuals in the United States.[36] Known therapies exist that are effective in the management of insomnia, such as behavioral therapy, benzodiazepines, and hypnotics.[36] However, available pharmacologic therapies come with risk of side effects and negative health outcomes.[24] Though insomnia is not a commonly listed indication for certification of medical cannabis, many patients self-manage insomnia with cannabis,[17] and seek medical cannabis for insomnia.[37,38] Early research on cannabis and sleep shows that cannabis improves sleep onset and reduces the occurrences of awakening during sleep. Other research has found a reduction in REM (rapid eye movement) sleep with cannabis use and has raised concern that cannabis used for sleep could lead to negative consequences. These include developing tolerance to cannabis and thus increasing the dose of THC required in order to achieve the desired effect, and sleep disturbance when stopping cannabis use, therefore encouraging continued use.[39]

Cannabis has been tested for the management of obstructive sleep apnea as well. One randomized controlled trial found improved self-reported and observed clinical measures in patients given synthetic THC versus placebo.[40] Despite this, though, the American Academy of Sleep Medicine has advised that further research is needed prior to recommending cannabis for the management of obstructive sleep apnea.[41]

Other specific indications for medical cannabis in which there is some evidence of benefit include intractable nausea and vomiting,[6,16,42-45] cachexia,[42,46] inflammatory bowel disease,[47-51] epilepsy,[52-56] and spasticity.[14,57] As these symptoms are seen less often in the primary care setting than the previously described indications, they are not within the scope of this article.

Follow-up and Monitoring

Ms J decides to start using medical cannabis, including 10-mg CBD tablets twice daily, and a vape pen that contains THC with 2-second inhalations as needed for pain. She experiences improvement in her chronic pain, but she also reports feeling somewhat dizzy and confused, particularly immediately after using vaped THC. Her family members

say that she is more active and sleeping better, but ask about the risk of cannabis addiction, whether she can drink any alcohol with cannabis, and whether she is at risk for lung disease related to vaping.

PCPs should monitor for health consequences of medical cannabis use, while also considering how medical cannabis could affect other prescription medications. The response to cannabis can vary based on route of administration[58] and adverse events or side effects can present as acute toxicity[58] or effects from long-term exposure. Since legalization of medical cannabis, observational data have emerged describing cannabis-related adverse events.[59]

Psychiatric Symptoms

Chronic cannabis use is associated with psychiatric symptoms, including anxiety,[60] depression,[60] and psychosis, and has been linked to worsening schizophrenia in those with a preexisting genetic vulnerability.[61,62] However, a direct causal relationship is difficult to establish as a multitude of confounding factors blur the relationship between cannabis use and psychiatric illness. For example, people with symptoms like anxiety or stress may be more likely to use cannabis.[63] New or worsening psychiatric symptoms should be monitored for in patients who are using medical cannabis, and termination of use encouraged if identified.

Cannabis Hyperemesis Syndrome

Gastrointestinal symptoms were the most common cause for emergency room visits related to cannabis use in a recent study in Colorado state.[59] The most common severe gastrointestinal side effect of cannabis use, cannabis hyperemesis syndrome,[64] presents as cyclical nausea and vomiting and abdominal pain in the setting of chronic cannabis use. Symptoms may improve with hot showers or baths and resolve after cessation of cannabis use.[65] Patients using cannabis should be screened for these symptoms during primary care visits and termination of cannabis use should be encouraged for those experiencing cannabis hyperemesis syndrome.

Motor-Vehicle Accidents

There is concern that cannabis use will lead to motor vehicle accidents associated with cannabis intoxication.[66] Cannabis use impairs driving in a dose-response manner.[67] However, population level studies have not shown a relationship between medical cannabis laws and an increase in motor vehicle accidents or traffic fatalities.[68,69] Patients should be cautioned regarding driving impairment while using cannabis, and advised to avoid driving if intoxicated.

Pulmonary Effects

Chronic cannabis use can lead to symptoms of chronic bronchitis, including cough, sputum production, and wheezing.[70,71] Cannabis use may result in some changes to pulmonary function tests, but unlike tobacco, it does not result in chronic obstructive pulmonary disease in observational studies.[70,71] The mode of consumption could be associated with specific types of respiratory syndromes. A new lung disease associated with heavy vaping use was emerging in late 2019.[72,73] To date, it remains unclear whether the risk is limited to specific types of vaping products or oils, or with specific use patterns. For patients who choose to vape, providers should recommend avoiding products purchased outside of registered facilities (eg, from a street dealer) and should monitor for changes in breathing.

Cannabis smoking may predispose individuals to pneumonia through damage of central airways and changes in local immune response.[74-76] Smoked cannabis contains carcinogens, raising concerns about lung cancer. Observational studies show increased risk of lung cancer in all users,[77] only among heavy users,[78] and not at all.[78] These studies included potential confounders that may have skewed results. Further research is needed to understand how people using cannabis should be monitored for cancer.

Drug-Drug Interactions

THC and CBD are metabolized in the cytochrome P450 (CYP450) system. Most drug interactions with medical cannabis are drugs that are also metabolized by this system.[79] Cannabis may inhibit the metabolism of strong CYP450 inhibitors, such as warfarin, rifampicin, and omeprazole.[80] Cannabis has additive sedative effects with other sedating agents.[81,82]

PCPs should be aware that they may need to taper other medications that their patients are taking for pain or anxiety, for example. Given the potential for drug interactions, it can be important to increase monitoring of medications that need to be within a specific therapeutic window, at least temporarily, if someone is starting medical cannabis for the first time, and to monitor patients much like they would if they were using herbal or dietary supplements. Some states have published tables with known drug interactions that can be accessed online.[83]

Risk of Cannabis Use Disorder

All patients using medical cannabis should be screened for cannabis use disorder (CUD). Based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, CUD is defined as use leading to negative social, occupational, psychological, and physical consequences.[84] In patients

receiving medical cannabis or using recreational cannabis, providers should monitor for symptoms and recommend tapering off of cannabis if they develop CUD.

Few valid, succinct, and reliable screening tools are available. The Cannabis Use Disorder Identification Test (CUDIT) is a 10-item screening tool that is 73% sensitive and 95% specific.[85] However, its length makes it difficult to use in a clinical setting. Modifications of the CUDIT, including the CUDIT-R[86] and the CUDIT-Short Form,[87] attempt to make more brief screening tools appropriate for busy clinical settings, but none of these measures have been studied in the primary care setting.

Conclusions

Ms J's PCP recommended that she avoid other sedating substances like alcohol while using her medical cannabis. Her medical cannabis provider also recommended that she reduce her THC consumption by using a vaped pen with a lower THC/CBD ratio. With these changes, her pain control and side effects improved. Her children report that she is more at ease and seems in less pain.

No matter the laws around medical cannabis, PCPs benefit from understanding what the potential uses, adverse events, and risks are of using medical cannabis. In order to make recommendations based on high-quality evidence, more randomized controlled trials and pragmatic trials are needed. Studies using cannabis are extremely restricted in the United States. Federal government's Schedule 1 classification of cannabis, which prohibits its use for research except for in limited settings. As providers and patient advocates, we should press for changes in these laws to allow for more substantive research that is applicable to our patients.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Cook receives funding from the National Institutes of Health, including research grant R01DA042069.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Deepika Slawek https://orcid.org/0000-0001-8403-8433

References

1. Substance Abuse and Mental Health Services Administration. *Key Substance Use and Mental Health Indicators in the United States: Results From the 2016 National Survey on Drug Use and Health*. Rockland, MD: Center for Behavioral Health Statistics and Quality; 2017.
2. National Conference of State Legislatures. State medical marijuana laws. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Published 2018. Accessed September 30, 2019.
3. Carliner H, Brown QL, Sarvet AL, Hasin DS. Cannabis use, attitudes, and legal status in the US: a review. *Prev Med*. 2017;104:13-23.
4. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4:1770-1804.
5. Mackie K. Cannabinoid receptors as therapeutic targets. *Annu Rev Pharmacol Toxicol*. 2006;46:101-122.
6. 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: National Academies Press; 2017. doi:10.17226/24625
7. Fabritius M, Chtioui H, Battistella G, et al. Comparison of cannabinoid concentrations in oral fluid and whole blood between occasional and regular cannabis smokers prior to and after smoking a cannabis joint. *Anal Bioanal Chem*. 2013;405:9791-9803.
8. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *J Anal Toxicol*. 1992;16:276-282.
9. Flachenecker P, Henze T, Zettl UK. Nabiximols (THC/CBD oromucosal spray, Sativex®) in clinical practice—results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity. *Eur Neurol*. 2014;71:271-279.
10. US Food and Drug Administration. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm611046.htm. Published 2018. Accessed April 11, 2019.
11. Physician Certification Pattern Review Panel. The Florida Board of Medicine and Board of Osteopathic Medicine. https://ww10.doh.state.fl.us/pub/osteo/Osteo/Public%20Book/PCPRP%20Data%20Review_2019.pdf. Published August 19, 2019. Accessed on October 1, 2019.
12. New York State Department of Health. Medical use of marijuana under the Compassionate Care Act. https://www.health.ny.gov/regulations/medical_marijuana/docs/two_year_report_2016-2018.pdf. Published November 14, 2018. Accessed September 27, 2019.
13. Ilgen MA, Bohnert K, Kleinberg F, et al. Characteristics of adults seeking medical marijuana certification. *Drug Alcohol Depend*. 2013;132:654-659.
14. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313:2456-2473.
15. Romero-Sandoval EA, Kolano AL, Alvarado-Vazquez PA. Cannabis and cannabinoids for chronic pain. *Curr Rheumatol Rep*. 2017;19:67.
16. Wilkie G, Sakr B, Rizack T. Medical marijuana use in oncology: a review. *JAMA Oncol*. 2016;2:670-675.
17. Bossong MG, van Hell HH, Jager G, Kahn RS, Ramsey NF, Jansma JM. The endocannabinoid system and emotional processing: a pharmacological fMRI study with 9-tetrahydrocannabinol. *Eur Neuropsychopharmacol*. 2013;23:1687-1697.

18. Bachhuber M, Arnsten JH, Wurm G. Use of cannabis to relieve pain and promote sleep by customers at an adult use dispensary [published online July 2, 2019]. *J Psychoactive Drugs*. doi:10.1080/02791072.2019
19. Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. *Cannabis Cannabinoid Res*. 2017;2:160-166.
20. Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *J Pain*. 2016;17:739-744.
21. Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare Part D. *Health Aff (Millwood)*. 2016;35:1230-1236.
22. Bonn-Miller MO, Babson KA, Vandrey R. Using cannabis to help you sleep: heightened frequency of medical cannabis use among those with PTSD. *Drug Alcohol Depend*. 2014;136:162-165.
23. Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. *Am J Drug Alcohol Abuse*. 2014;40:23-30.
24. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. *Am J Public Health*. 2016;106:686-688.
25. Piper BJ, DeKeuster RM, Beals ML, et al. Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. *J Psychopharmacol*. 2017;31:569-575.
26. Corroon JM Jr, Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs—a cross-sectional study. *J Pain Res*. 2017;10:989-998.
27. Korem N, Zer-Aviv TM, Ganon-Elazar E, Abush H, Akirav I. Targeting the endocannabinoid system to treat anxiety-related disorders. *J Basic Clin Physiol Pharmacol*. 2016;27:193-202.
28. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36:1219-1226.
29. Calhoun PS, Sampson WS, Bosworth HB, et al. Drug use and validity of substance use self-reports in veterans seeking help for posttraumatic stress disorder. *J Consult Clin Psychol*. 2000;68:923-927.
30. Earleywine M, Bolles JR. Marijuana, expectancies, and posttraumatic stress symptoms: a preliminary investigation. *J Psychoactive Drugs*. 2014;46:171-177.
31. Hindocha C, Cousijn J, Rall M, Bloomfield MAP. The effectiveness of cannabinoids in the treatment of posttraumatic stress disorder (PTSD): a systematic review [published online September 3, 2019]. *J Dual Diagn*. doi:10.1080/15504263.2019
32. Jetly R, Heber A, Fraser G, Boisvert D. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology*. 2015;51:585-588.
33. Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). *CNS Neurosci Ther*. 2009;15:84-88.
34. Roitman P, Mechoulam R, Cooper-Kazaz R, Shalev A. Preliminary, open-label, pilot study of add-on oral Δ9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clin Drug Investig*. 2014;34:587-591.
35. Elms L, Shannon S, Hughes S, Lewis N. Cannabidiol in the treatment of post-traumatic stress disorder: a case series. *J Altern Complement Med*. 2019;25:392-397.
36. Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB. Prevalence of healthy sleep duration among adults—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2016;65:137-141.
37. Metrik J, Bassett SS, Aston ER, Jackson KM, Borsari B. Medicinal versus recreational cannabis use among returning veterans. *Transl Issues Psychol Sci*. 2018;4:6-20.
38. Wilson MM, Masterson E, Broglio K. Cannabis use among patients in a rural academic palliative care clinic. *J Palliat Med*. 2019;22:1224-1226.
39. Babson KA, Sottile J, Morabito D. Cannabis, cannabinoids, and sleep: a review of the literature. *Curr Psychiatry Rep*. 2017;19:23.
40. Carley DW, Prasad B, Reid KJ, et al. Pharmacotherapy of apnea by cannabimimetic enhancement, the PACE clinical trial: effects of dronabinol in obstructive sleep apnea. *Sleep*. 2018;41:zsx184. doi:10.1093/sleep/zsx184
41. Ramar K, Rosen IM, Kirsch DB, et al. Medical cannabis and the treatment of obstructive sleep apnea: an American Academy of Sleep Medicine Position Statement. *J Clin Sleep Med*. 2018;14:679-681.
42. Abrams DI, Guzman M. Cannabis in cancer care. *Clin Pharmacol Ther*. 2015;97:575-586.
43. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage*. 1995;10:89-97.
44. de Jong BC, Prentiss D, McFarland W, Machekano R, Israelski DM. Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. *J Acquir Immune Defic Syndr*. 2005;38:43-46.
45. Mack A, Joy J. *Marijuana as Medicine? The Science Beyond the Controversy*. Washington, DC: National Academies Press; 2000.
46. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Ann Intern Med*. 2003;139:258-266.
47. Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. *Inflamm Bowel Dis*. 2014;20:472-480.
48. Ambrose T, Simmons A. Cannabis, cannabinoids, and the endocannabinoid system—is there therapeutic potential for inflammatory bowel disease? *J Crohns Colitis*. 2019;13:525-535.
49. Ravikoff Allegretti J, Courtwright A, Lucci M, Korzenik JR, Levine J. Marijuana use patterns among patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2013;19:2809-2814.
50. Naftali T, Schleider LBL, Dotan I, Lansky EP, Benjaminov FS, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol*. 2013;11:1276-1280.e1.

51. Naftali T, Mechulam R, Marii A, et al. Low-dose cannabidiol is safe but not effective in the treatment for Crohn's disease, a randomized controlled trial. *Dig Dis Sci*. 2017;62:1615-1620.
52. Cannabidiol (Epidiolex) for epilepsy. *Med Lett Drugs Ther*. 2018;60:182-184.
53. Devinsky O, Cross JH, Wright S. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med*. 2017;377:699-700.
54. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Engl J Med*. 2018;378:1888-1897.
55. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391:1085-1096.
56. Stockings E, Zagic D, Campbell G, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. *J Neurol Neurosurg Psychiatry*. 2018;89:741-753.
57. Koppel BS, Brust JC, Fife T, et al. 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*. 2014;82:1556-1563.
58. Noble MJ, Hedberg K, Hendrickson RG. Acute cannabis toxicity. *Clin Toxicol (Phila)*. 2019;57:735-742.
59. Monte AA, Shelton SK, Mills E, et al. Acute illness associated with cannabis use, by route of exposure: an observational study. *Ann Intern Med*. 2019;170:531-537.
60. Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W. Cannabis use and mental health in young people: cohort study. *BMJ*. 2002;325:1195-1198.
61. Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene × environment interaction. *Biol Psychiatry*. 2005;57:1117-1127.
62. Di Forti M, Sallis H, Allegri F, et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophr Bull*. 2014;40:1509-1517.
63. Volkow ND, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014;371:879.
64. Allen JH, de Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut*. 2004;53:1566-1570.
65. Schreck B, Wagneur N, Caillet P, et al. Cannabinoid hyperemesis syndrome: review of the literature and of cases reported to the French addictovigilance network. *Drug Alcohol Depend*. 2018;182:27-32.
66. Brady JE, Li G. Trends in alcohol and other drugs detected in fatally injured drivers in the United States, 1999-2010. *Am J Epidemiol*. 2014;179:692-699.
67. Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem*. 2013;59:478-492.
68. Santaella-Tenorio J, Mauro CM, Wall MM, et al. US Traffic Fatalities, 1985-2014, and their relationship to medical marijuana laws. *Am J Public Health*. 2017;107:336-342.
69. Rogeberg O. A meta-analysis of the crash risk of cannabis-positive drivers in culpability studies—avoiding interpretational bias. *Accid Anal Prev*. 2019;123:69-78.
70. Ribeiro L, Ind PW. Marijuana and the lung: hysteria or cause for concern? *Breathe (Sheff)*. 2018;14:196-205.
71. Tashkin DP. Marijuana and lung disease. *Chest*. 2018;154:653-663.
72. Schier JG, Meiman JG, Layden J, et al. Severe pulmonary disease associated with electronic-cigarette-product use—interim Guidance. *MMWR Morb Mortal Wkly Rep*. 2019;68:787-790.
73. Layden JE, Ghinai I, Pray I, et al. Pulmonary illness related to e-cigarette use in illinois and wisconsin—preliminary report [published online September 6, 2019]. *N Engl J Med*. doi:10.1056/NEJMoa1911614
74. Fligiel SE, Roth MD, Kleerup EC, Barsky SH, Simmons MS, Tashkin DP. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest*. 1997;112:319-326.
75. Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD. Marijuana and cocaine impair alveolar macrophage function and cytokine production. *Am J Respir Crit Care Med*. 1997;156:1606-1613.
76. Shay AH, Choi R, Whittaker K, et al. Impairment of antimicrobial activity and nitric oxide production in alveolar macrophages from smokers of marijuana and cocaine. *J Infect Dis*. 2003;187:700-704.
77. Zhang LR, Morgenstern H, Greenland S, et al. Cannabis smoking and lung cancer risk: pooled analysis in the International Lung Cancer Consortium. *Int J Cancer*. 2015;136:894-903.
78. Aldington S, Harwood M, Cox B, et al. Cannabis use and risk of lung cancer: a case-control study. *Eur Respir J*. 2008;31:280-286.
79. Alsherbiny MA, Li CG. Medicinal cannabis—potential drug interactions. *Medicines (Basel)*. 2018;6:E3.
80. Damkier P, Lassen D, Christensen MMH, Madsen KG, Hellfritzsch M, Pottegard A. Interaction between warfarin and cannabis. *Basic Clin Pharmacol Toxicol*. 2019;124:28-31.
81. Russo EB. Current therapeutic cannabis controversies and clinical trial design issues. *Front Pharmacol*. 2016;7:309.
82. Echeverria-Villalobos M, Todeschini AB, Stoicea N, Fiorda-Diaz J, Weaver T, Bergese SD. Perioperative care of cannabis users: a comprehensive review of pharmacological and anesthetic considerations. *J Clin Anesth*. 2019;57:41-49.
83. Colorado Department of Public Health & Environment. Potential drug interactions with marijuana. https://www.colorado.gov/pacific/marijuanahealthinfo/drug-interaction-table. Published 2019. Accessed September 26, 2019.
84. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
85. Adamson SJ, Sellman JD. A prototype screening instrument for cannabis use disorder: the Cannabis Use Disorders Identification Test (CUDIT) in an alcohol-dependent clinical sample. *Drug Alcohol Rev*. 2003;22:309-315.
86. Adamson SJ, Kay-Lambkin FJ, Baker AL, et al. An improved brief measure of cannabis misuse: the Cannabis Use Disorders Identification Test-Revised (CUDIT-R). *Drug Alcohol Depend*. 2010;110:137-143.
87. Bonn-Miller MO, Heinz AJ, Smith EV, Bruno R, Adamson S. Preliminary development of a brief cannabis use disorder screening tool: the Cannabis Use Disorder Identification Test Short-Form. *Cannabis Cannabinoid Res*. 2016;1:252-261.