From: Craig, Carrie D (CED)
To: Marijuana Licensing (CED sponsored)
Subject: RE: Standalone Butter and Oil Items for sale
Date: Wednesday, November 3, 2021 8:43:49 AM

Hi Nate,

I agree - should forward to the mj board email.

Thanks!

Carrie Craig
Records and Licensing Supervisor
Alcohol and Marijuana Control Office
550 West 7th Avenue, Suite 1600
Anchorage, AK 99501
907-269-0350

-----Original Message-----
From: Marijuana Licensing (CED sponsored)
Sent: Thursday, October 28, 2021 4:39 PM
To: Craig, Carrie D (CED) <carrie.craig@alaska.gov>
Cc: Marijuana Licensing (CED sponsored) <marijuana.licensing@alaska.gov>
Subject: FW: Standalone Butter and Oil Items for sale

Carrie - I interpreted this as being a part of the marijuana mailbox. Please let me know if you feel this requires any additional action on the part of licensing.

Thanks,

Nathan Hall
Occupational Licensing Examiner
Alcohol and Marijuana Control Office
550 West 7th Avenue, Suite 1600
Anchorage, AK 99501
907-334-0892
marijuana.licensing@alaska.gov

-----Original Message-----
From: Ryan Hallsten [mailto:ryan@getbakedak.com]
Sent: Wednesday, October 27, 2021 2:51 PM
To: Marijuana Licensing (CED sponsored) <marijuana.licensing@alaska.gov>

Subject: RE: Standalone Butter and Oil Items for sale

To Whom It May Concern,

May name is Ryan Hallsten. I am an employee at Baked Alaska in Fairbanks. I wanted to make a note regarding the questions received during the board meeting about selling butter and oil as a stand alone product. Other states have already legalized the sale of these lipids in their markets by requiring that the dosage of the stand alone butter, or oil, not exceed the legal limit for any one edible package. A great example of a manufacture already doing this is Sweet Grass Kitchen in Colorado; see below. They sell a 100 mg infused stick of butter as a stand alone edible item. This would be a simple update to the current regulation that would then allow manufacturers to sell these commonly used edible compounds as other stand alone items in their manufacturer menus and at retail facilities, without running the risk of selling an “edible” product with a potentially unlimited amount of THC or CBD.

I am interested in your discussion of this specific regulation, as these are items we would like to sell at Baked Alaska, but currently cannot.

Thank you for your time,

Ryan Hallsten

https://urldefense.com/v3/__https://livwell.com/order_ahead/sweet-grass-kitchen-cannabutter-100mg?sku=R1003017__;!!J2_8gdp6gZQ!-eS_nxVTtQfpzpfRxS84GG6yupaCIngD_LZOo4ewzHcVmKWixXJ12Sau_FlaaHjCRL_2dsQvsQ$

From: Lacy Wilcox
To: Marijuana, CED ABC (CED sponsored)
Subject: Referenced in AMIA"s 10.26.21 Verbal Testimony
Date: Tuesday, October 26, 2021 3:08:11 PM
Attachments: AMIA Full Logo_Black - Thumb copy.png

Hello MCB,

As mentioned in our testimony today, please visit the following link if interested in listening to the panelist discussion we hosted on federal legalization: https://us02web.zoom.us/rec/play/Hd65bUhXd0Ou-HtK19IlZVylP2N9XqAhbYY4ck6N9lRMjkkB7GfROatZRAZSY_r10MVrzyotxuou8EAG.e7rhQcdF2w724tZW

Thank you for all you do for our industry.

~ Lacy

Lacy Wilcox, President
Alaska Marijuana Industry Association
president@alaskamia.org
(907)419-0961

From: Klinkhart, Glen Edward (CED)
To: Marijuana, CED ABC (CED sponsored)
Subject: FW: Public comments regarding October 2021 meeting
Date: Monday, November 8, 2021 8:51:01 AM
Attachments: image002.png

For board mailbox.

Klink

Glen Klinkhart
Director
Alcohol Marijuana Control Office (AMCO)
550 West 7th Avenue, Suite 1600
Anchorage, Alaska 99501
Email: glen.klinkhart@alaska.gov
Phone: 907-269-0350

From: dollynda Phelps <jeffndol@yahoo.com>
Sent: Friday, November 5, 2021 3:16 PM
To: Klinkhart, Glen Edward (CED) <glen.klinkhart@alaska.gov>; CED AMCO REGS (CED sponsored) <amco.regs@alaska.gov>
Subject: Public comments regarding October 2021 meeting

11-5-21

To Glen Klinkhart and the MCB board,

I feel some progress was made during the last meeting, the issue of excise tax delinquency was finally addressed, among other things. One new concern that is rearing it's head is the fundamental lack of knowledge regarding cannabis for some members of the MCB.

The Marijuana Control Board is responsible for licensing, practical regulations to implement licensing, and public safety. The AMCO Mission Statement:

"Enforce alcohol and marijuana commerce laws and provide clear, consistent standards for licensure to protect the public from harm."

The members of the MCB must do their due diligence to be knowledgeable regarding the topic they are regulating, or they cannot do so reasonably or effectively. At the last meeting in October, one of our newer MCB members demonstrated a sheer lack of knowledge and understanding of cannabis and cannabis products, effectively slowing down the meeting for no apparent reason, and almost not approving a very commonly used product. Specifically, the approval of a marijuana product that contains CBD and THC.

I am not sure why this was even in question, CBD and THC exist naturally together in thousands of strains of cannabis, they are proven to have synergistic effects when used together, and have long been used together to treat many medical conditions. In fact, CBD is commonly used to negate the effects of the psychoactive properties of THC if someone were to over-indulge. This is fact. Please see a few of the easily found documented articles regarding these statements. We are not here to debate cannabis, we are far past that point. Now we need to understand it.

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165946/

“CBD may help reduce unwanted effects of THC:”

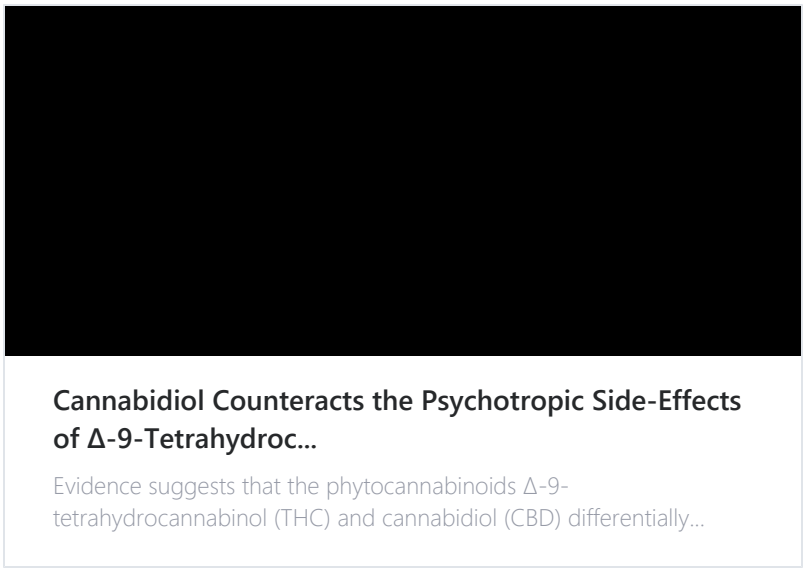
“Some people experience side effects like anxiety, hunger, and sedation after taking THC. Rat and human studies covered in the same 2011 review suggest that CBD may help reduce these side effects.”

https://www.healthline.com/health/the-entourage-effect

Cannabidiol Counteracts the Psychotropic Side-Effects of Δ-9-Tetrahydrocannabinol in the Ventral Hippocampus through Bidirectional Control of ERK1–2 Phosphorylation

Cannabidiol Counteracts the Psychotropic Side-Effects of Δ-9-Tetrahydrocannabinol

in the Ventral Hippocampus through Bidirectional Control of ERK1–2 Phosphorylation



Cannabidiol Counteracts the Psychotropic Side-Effects of Δ-9-Tetrahydroc...

Evidence suggests that the phytocannabinoids Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) differentially...

These scholarly articles also provide proof of the necessity to change our lab reporting requirements, as THC content does NOT indicate the potency of that product. The potency of a product is determined by so many other compounds, terpenes and other cannabinoids, not just THC. So how are we protecting the public when all we are giving them is one irrelevant number, and a false sense of security that this number represents how strong a product is?? This needs to be addressed.

My point here is not limited to understanding CBD, but more broadly, cannabis in general. I appreciate the time each board member donates to the regulation of marijuana, but with that seat comes responsibility. You must reasonably educate yourselves to have a fundamental understanding of marijuana if you are to regulate marijuana. I encourage each of you to reach out to the industry with questions if you are on unfamiliar grounds, we are here to help! I know many of us have an open door policy and are happy to spend that time with you upon request.

Thank you for your time and consideration,

Dollynda Phelps

Peace Frog Botanicals

Kenai

From: Kreative Konfections
To: Marijuana, CED ABC (CED sponsored)
Subject: For the Edification of the Marijuana Control Board - THC & CBD - evidence and studies
Date: Thursday, November 11, 2021 5:02:55 PM

I highly recommend that the Board read the following for more information on how THC and CBD used together, often in 1:1 ratios, are used for the alleviation of pain symptoms brought on by a number of different conditions. This report was produced in 2017.

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC): National Academies Press (US); 2017 Jan 12. 4, **Therapeutic Effects of Cannabis and Cannabinoids**. Available from: https://www.ncbi.nlm.nih.gov/books/NBK425767/ This link is copied in full below.

The full report can be found here:
https://www.ncbi.nlm.nih.gov/books/NBK423845/pdf/Bookshelf_NBK423845.pdf

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Jenny Koenig
Co-Owner / Manager
Kreative Konfections LLC

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 Δ9-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 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

Go to:

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 suggest 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, rheumatoid 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 example, 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

Go to:

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 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

Go to:

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 cannabisnaïve 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/m2 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

Go to:

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 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

Go to:

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 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

Go to:

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 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

Go to:

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 provided 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

Go to:

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

Go to:

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

Go to:

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

Go to:

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 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

Go to:

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

Go to:

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

Go to:

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

Go to:

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.

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

Go to:

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 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

Go to:

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

Go to:

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

Go to:

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

Go to:

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.

SCHIZOPHRENIA AND OTHER PSYCHOSES

Go to:

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

Go to:

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

Go to:

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.

Box Icon

BOX 4-1

Summary of Chapter 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.

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Footnotes

Go to:

1 ClinicalTrials.gov: NCT02447198, NCT02926859.

2 ClinicalTrials.gov: NCT01361607.

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.

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.

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

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

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

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).

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.

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

Bookshelf ID: NBK425767

From:	Robert D. Martin
To:	Marijuana, CED ABC (CED sponsored)
Subject:	Proposed Alice"s marijuana dispensary in Eagle River (business license #2126763.)
Date:	Wednesday, November 17, 2021 11:07:48 AM

Dear Sir/Madam:

My name is Bob Martin. I'm writing to offer my whole-hearted support for the issuance by the State of Alaska for a Marijuana Establishment License to “Alice’s” (business license #2126763.)

I base my recommendation on a variety of factors. These factors include my residence in Eagle River of almost 40 years, commensurate with almost four decades as an active commercial real estate agent. These experiences persuade me that this is a business that will not only thrive in my community, but it will also represent it well by: 1) adhering to all applicable rules and regulations; and 2) being a good for-profit business, thereby contributing to our city as a whole.

Since marijuana sales were legalized in Alaska, it has been my observation that marijuana dispensaries typically improve the value of the building they are in and help to increase the security of the surrounding area, through close attention to ID checking and cameras on or about the premises.

A marijuana dispensary will often move into an underutilized property and makes it better. Dispensaries place a premium on creating an attractive, inviting and secure destination for their customers and the state’s regulations help to insure their status as good neighbors. As a result, the value of the building often increases as do the values of the surrounding properties. I am very familiar with the proposed location for Alice’s and feel it is well-suited for this business type. There is no reason a marijuana customer should have to drive into Anchorage to purchase this product.

I also base my recommendation on the many years that I have known Chris Shill. As the owner and hard-working operator of Wintergreen Services, Chris has faithfully plowed our driveway snow storm after snow storm and I have come to know him as a friend and to trust him with my property. I think he is a serious person who will bring the right business acumen and careful professionalism that this particular business will demand. I look forward to watching him make a success of it.

I thank you for taking this letter of support into account as you deliberate on the approval of this application.

Sincerely,
Robert D. Martin
Eagle River, Alaska

From: Daniella Ambrosino May
To: Marijuana, CED ABC (CED sponsored)
Subject: Letter of Support for Alice"s
Date: Wednesday, November 17, 2021 9:16:40 PM
Attachments: Support letter for retail marijuana shop.pdf

To whom it may concern,

Attached is a letter of support for Alice's. A retail marijuana business looking to open in Eagle River, and as a community member I support their business.

Thank you,
Daniella

--
Regards,
Daniella N. Ambrosino May

As a resident of Eagle River, I whole heartedly support, and welcome a retail marijuana dispensary in our community. The state of Alaska legalized recreational use of marijuana in 2014. This legalization made Alaska only the 3rd state in the union to decriminalize and industrialize the recreational use of marijuana putting Alaska at in the forefront of the industry. It is now 2021, and the community of Eagle River-Chugiak still does not have a dispensary within its boundaries. Considering recreational dispensaries have been legal for almost 10 years the lack of a retail business in this area is a completely missed opportunity.

This is a legal industry that will provide our community with additional opportunities for growth as well as a new stream of revenue. Concerns about theft, and impaired driving that have previously been mentioned as a means to deter a retail shop from opening in Eagle River are an unfounded dog whistle as there are several businesses that sell alcohol within our community. Residents of this area who responsibly use marijuana should be able to spend their money purchasing these products in the community. Retail shops are a revenue generator, and this is something we need in Eagle River. Personally, I do not use marijuana, but it is not my place to restrict what other adults do with their free time as recreational marijuana is legal. There is no good reason to not support a retail marijuana business from opening in our community.

I welcome a retail marijuana shop to open in Eagle River, and am happy to support the owners of Alice's in their business venture. Hopefully this business will be able to revitalize one of our currently vacant storefronts, and become a wonderful part of the community.

Sincerely,
Daniella May
18921 Danny Dr
Eagle River, AK

From: Quaid Brinker
To: Marijuana, CED ABC (CED sponsored)
Subject: License Capping
Date: Tuesday, November 30, 2021 3:52:15 PM

Dear Members of the Alaska Marijuana Control Board,

My name is Quaid Brinker. I am the General Manager at Green Growcer, a marijuana retail in Anchorage. I am writing to you to express my support for license capping in Alaska, and more specifically Anchorage.

I started in this industry up in Fairbanks, where a license cap has already been established. I believe the cap is set somewhere between 15-20 retails, and what has resulted is a highly competitive market that benefited the consumer & businesses before the market had an opportunity to get oversaturated. The primary reason I believe a license cap is important is there are already almost (if not more than) 100 marijuana retails in the Anchorage area, with a lot more on the way and no plans for a cap anytime soon. What will result is an oversaturated market if a cap is not soon implemented.

On top of oversaturation, if federal legalization were to occur, without a cap there is little to nothing stopping big businesses in the lower 48 from coming up here, establishing businesses, and flooding the market with cheap out of state product and killing many of the local businesses and cultivations that have put in the work to get us this far already. This is an Alaskan market, and I'd love for it to stay that way. I am very proud to carry nothing but Alaskan flower/edibles/concentrates, and I'd hate to be forced to carry cheaper and/or inferior product from out of state just to keep our business afloat. If I have to talk to one more Californian with a business degree trying to sell me something, I think I may keel over.

What I'm hoping to avoid is seeing companies resorting to unsavory business tactics such as price wars, widespread use of exclusivity contracts with cultivations/manufacturing companies, lowballing, and an overall air of negativity within the industry. My favorite part about this industry is the community aspect. I have a long list of retails that I'm happy to send customers to if they are looking for a specific product we don't have available, with all of them happy to reciprocate. I don't want retails to feel like they must hoard customers & cultivations just to keep their business afloat. An oversaturated industry helps no one and is detrimental to the longevity of this market.

Thank you for your time and consideration,

Quaid Brinker

(907)341-7976