Clearing the Smoke on Cannabis

Medical Use of Cannabis and Cannabinoids

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This is the fifth in a series of reports that reviews the effects of cannabis use on various aspects of human functioning and development. Other reports in this series address the link between regular cannabis use and mental health, regular cannabis use and cognitive functioning, cannabis use during pregnancy and breastfeeding/chestfeeding, cannabis use and driving, respiratory effects of cannabis use, and edible cannabis, cannabis extracts and cannabis topicals. This report is intended for researchers and healthcare professionals.

Key Points

- About 13% of people living in Canada report using cannabis for medical purposes, the majority (74%) of which do not have a document authorizing use from a healthcare professional.

- Most people who use cannabis for medical purposes self-report beneficial effects across a wide range of health conditions.

- The available clinical evidence does not support the use of cannabis and cannabinoids for most health conditions, at least not as a first-line treatment option.

- A significant amount of research is currently examining the efficacy of cannabinoids in treating symptoms of many health conditions, including pain, cancer, psychiatric disorders, neurodegenerative disorders and substance use disorders. Some of this research is generating promising data.

- Healthcare providers are an important point of contact for individuals seeking information about cannabis use for medical purposes. Yet, research shows that they may not have the training that they would like in order to discuss cannabis for medical purposes with their patients or to authorize cannabis products for this purpose.

- More focus should be put on equipping healthcare professionals with the information they need to increase their knowledge and communicate with patients on the use of cannabis for medical purposes.

Canadian Centre on Substance Use and Addiction

Evidence. Engagement. Impact.

Background

Cannabis use for medical purposes is fairly common in Canada. As indicated by the 2022 Canadian Cannabis Survey, about 13% of people living in Canada said they used cannabis for a medical reason in the past year. The majority (74%) of them did not have a document from a healthcare professional supporting or authorizing use for medical purposes (Health Canada, 2022). Cannabis use for medical purposes seems to be more common in people in older age segments, although medical use has also been occurring in emerging adults (ages 18–25 years) (Smith et al., 2019). Recent research suggests that women may be more likely to use cannabis products for managing mental or physical health problems than men (Wadsworth et al., 2023). Cannabis and cannabinoids are being used to manage various health conditions, with pain, sleep, anxiety and depression being the most common (Corroon & Phillips, 2018; Kalaba & Ware, 2022; Kosiba et al., 2019; Sexton et al., 2016; Tumati et al., 2021; Turna et al., 2019a; Wadsworth et al., 2023).

Most people who use cannabis for medical purposes self-report beneficial effects for a broad range of health conditions (Boehnke et al., 2019; Cuttler et al., 2018; Sexton et al., 2016; Tumati et al., 2021). The 2022 Canadian Cannabis Survey found that 68% of people who used cannabis for medical purposes in the past year reported beneficial effects on physical health and 66% reported beneficial effects on mental health (Health Canada, 2022). At the same time, there appears to be growing interest in cannabis health products that do not require practitioner oversight, particularly those containing cannabidiol (CBD) (Health Canada, 2020). Growing interest in CBD products has brought increased attention to this market; however, there is limited evidence establishing its safety and efficacy for most health conditions. In research examining product descriptions of CBD products, over half of product descriptions made a therapeutic claim for medical conditions (Zenone et al., 2021). Certainly, informing cannabis consumers of the latest evidence on cannabis for medical purposes is needed now more than ever.

A large body of preclinical research demonstrates the significance of the endocannabinoid system in mental and physical health (Fisher et al., 2021; Meccariello, 2020; Walker et al., 1999). Targeting various aspects of the endocannabinoid system has been shown to improve outcomes in many animal models of disease (Mayo et al., 2022). Yet, preclinical data have not always translated well to clinical trials, where available clinical evidence that supports the use of cannabis and cannabinoids to treat most health conditions remains controversial, at least as

a first-line treatment option. However, some evidence has demonstrated that, when conventional medications do not help, cannabinoids may be useful in managing symptoms associated with specific conditions. For instance, in Canada, nabiximols (sold under the brand name Sativex),nabilone (Cesamet) and cannabidiol (Epidiolex) are the only approved cannabinoid products used for some specific health conditions. Nabilone is indicated for the management of severe nausea and vomiting associated with cancer therapy. Nabiximols is indicated as adjunctive or add-on treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis who have not responded adequately to other therapies and who show meaningful improvement during an initial trial of nabiximols therapy. Epidiolex has been recently approved in Canada for treating two types of treatment-resistant childhood seizure disorders (Dravet syndrome and Lennox-Gastaut syndrome).

Table 1 displays the most common cannabinoid drugs used therapeutically and in clinical trials. A significant amount of research is currently examining the efficacy of cannabinoids in treating symptoms of many health conditions, including pain, cancer, epilepsy, psychiatric disorders, neurodegenerative disorders and substance use disorders. Some of this research is generating promising data.

In 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) published a report titled *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* ("the 2017 NASEM report"). The report presented an extensive overview on the health effects of cannabis and cannabinoids, as well as recommendations to promote cannabis research and inform public health decisions (National Academies of Sciences, Engineering, and Medicine [NASEM], 2017). This current report provides an overview of recent research (i.e., since the release of the NASEM report) on the medical use of cannabis and cannabinoids, with a focus on systematic reviews and meta-analyses of clinical trials. This report is not an exhaustive review of the literature and is not meant to provide medical guidance or guarantee the safety and efficacy of any cannabis products.

Pain

Pain seems to be the most common medical reason for cannabis use. Most individuals using cannabis for this reason report that it is effective in alleviating their pain (Boehnke et al., 2019; Kalaba et al., 2021; Sexton et al., 2016; Tumati et al., 2021). Clinical research has suggested that cannabinoids can reduce pain; however, conclusions about the magnitude of this effect vary across studies and specific pain subtypes.

Cannabinoids

Cannabis plants contains hundreds of known chemicals, called phytocannabinoids or natural cannabinoids, among which Δ9-tetrahydrocannabinol (THC) is the primary psychoactive component of the cannabis plant responsible for the "high" from ingesting or inhaling cannabis. Cannabidiol (CBD), another natural cannabinoid, contributes to many of the pharmacological actions of cannabis, but it does not produce the high of THC. Other natural cannabinoids present in cannabis in much lower concentrations than THC and CBD include cannabigerol (CBG), cannabivarin (CBV) and cannabichromene (CBC). Cannabinoids can also be produced synthetically (i.e., made in a laboratory), but are functionally similar to THC or other natural cannabinoids. Some of them, including nabiximols (Sativex) and nabilone (Cesamet), are used therapeutically. However, other synthetic cannabinoids (e.g., Spice, K2) are substances that are controlled under the *Controlled Drugs and Substances Act* and have only been used recreationally, not medically.

Endocannabinoid System

The human body produces substances called endocannabinoids, among which anandamide (AEA) and 2-arachidonoylglycerol (2-AG), similarly to THC, produce their effects by binding to and activating cannabinoid receptors that are named CB1 and CB2 receptors. The highest concentrations of the CB1 receptor are in the central nervous system (brain and spinal cord) where they regulate the level of activity of neurons. The CB1 receptor is also located widely throughout the body at lower concentrations on various cells primarily responsible for inflammation and immunity. Unlike CB1 receptors, CB2 receptors can be primarily found outside the brain and spinal cord (i.e., peripheral system) mostly on immune cells and inflammatory cells. They are also present in relatively smaller quantities within the brain, primarily located on glial cells. They can also be found in smaller quantities than elsewhere in the body, in the brain, mostly on glial cells. The endocannabinoid system, which comprises the endocannabinoids, the CB1 and CB2 receptors and the enzymes that form endocannabinoids and break them down, regulate many functions in the brain and the body, including learning and memory, sleep, emotions, pain, immunity, temperature and inflammation.

Table 1. Name and method of administration of cannabinoid drugs most often used therapeutically and in clinical trials

Common Name	Trade Name	Cannabinoid	Method of Administration
Cannabidiol[1] (pharmaceutical-grade cannabidiol oil)	Epidiolex	CBD	Oral (liquid)
Nabiximols[1]	Sativex	Botanically derived THC and CBD at a ratio of 1:1	Sublingual (spray)
Nabilone[1]	Cesamet Canemes	Synthetic analog of THC	Oral (pill)
Dronabinol	Marinol Syndros	Synthetically produced THC	Oral (pill)

[1] Nabilone, nabiximols and cannabidiol are approved in Canada for adjunctive treatment of specific conditions. Among these are severe nausea and vomiting associated with chemotherapy (nabilone), spasticity associated with multiple sclerosis (nabiximols) and two types of treatment-resistant childhood seizure disorders (Dravet syndrome and Lennox-Gastaut syndrome) (cannabidiol).

Neuropathic Pain

The 2017 NASEM report concluded that there was substantial evidence suggesting that cannabis-based products, namely oral cannabis extracts and synthetic cannabinoids, were effective in treating neuropathic pain (NASEM, 2017).

A more recent systematic review of systematic reviews examined 15 randomized controlled trials (RCTs).

Thirteen of the 15 trials assessed neuropathic pain (the remaining two analyzed cancer pain). It was reported that approximately 39% of patients taking medical cannabinoids (versus 30% of placebo patients) reported at least 30% reduction in pain intensity. However, it was concluded that there was still some uncertainty about whether cannabinoids could improve neuropathic pain (Allan et al., 2018). Similarly, a meta-analysis found that cannabinoid treatment (nabiximols, nabilone, cannabis)

among individuals with chronic pain associated with various medical conditions resulted in pain reduction, although safety considerations were noted (Yanes et al., 2019). A systematic review and meta-analysis of 36 RCTs found moderate evidence to support cannabinoids in the two-week treatment of chronic noncancer–related pain, noting nonserious adverse events. There was less reliable evidence for treating chronic pain over periods longer than two weeks (Johal et al., 2020).

Several later systematic reviews and meta-analyses concluded that inhaled, oral and oromucosal administration of cannabinoids may provide small reductions in pain for individuals with chronic noncancer pain (Dykukha et al., 2021; Wong et al., 2020). The most recent systematic review of 32 RCTs found that noninhaled cannabis resulted in a very small to small improvement in a variety of different outcomes related to chronic pain, including pain alleviation, physical functioning and sleep quality (Wang et al., 2021). For more information, see Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline.

Fibromyalgia

The 2017 NASEM report concluded that there is moderate evidence suggesting that cannabinoids, in particular nabiximols, may alleviate some symptoms related to fibromyalgia, such as sleep problems (NASEM, 2017).

Recent clinical studies are interested in the utility of cannabinoids as an effective analgesic treatment for fibromyalgia and fibromyalgia-associated symptoms, such as sleep disorders, anxiety and depression (Habib & Artul, 2018; Habib & Avisar, 2018; Sagy et al., 2019; Yassin, et al., 2019). More recently, a critical review analyzing the available clinical evidence for the therapeutic effects of cannabinoids for fibromyalgia highlighted a lack of methodological rigour and serious methodological limitations. This, in turn, prevented definitive conclusions about the effects of cannabinoids for fibromyalgia (Cameron & Hemingway, 2020). Similar conclusions have been generated by several other systematic reviews, indicating that more high-quality research is needed to determine dosage, length of treatment, adverse effects and concerns surrounding dependence (Khurshid et al., 2021; Kurlyandchik et al., 2021; Berger et al., 2020).

Cancer

Cancer Pain

The 2017 NASEM report concluded that there is substantial evidence to support that cannabis and cannabinoids are effective in the treatment of chronic pain, including cancer pain (NASEM, 2017).

Other recent meta-analyses and systematic reviews of clinical trials concluded that there was insufficient evidence to suggest that cannabinoids (i.e., nabiximols or THC) provide notable pain relief in patients with refractory cancer pain, either as an adjunct or replacement to opioid treatment (Boland et al., 2020; Fallon et al., 2017; Urbina & Duran, 2016; Hauser et al., 2019; Tateo, 2017; Tallant et al., 2020). However, some evidence suggests that cannabinoids may improve quality of life (Lichtman et al., 2018). Presently, the scientific evidence supporting (or refuting) the use of cannabis and cannabinoids for cancer pain remains limited.

Nausea and Vomiting

The 2017 NASEM report indicated that there was conclusive evidence that oral cannabinoids were effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting (NASEM, 2017). Around the same time, a systematic review found that THC was more effective than antiemetics, including prochlorperazine, metoclopramide and domperidone, in reducing chemotherapy-induced nausea and vomiting among children and adolescents. However, the likelihood of moderate adverse effects such as drowsiness and dizziness was noted (Wong et al., 2017). In an umbrella review of systematic reviews, it was concluded that there is reasonable evidence to suggest that cannabinoids can improve nausea and vomiting associated with chemotherapy. However, adverse effects such as dizziness, sedation, confusion and dissociation were very common and were suggested to potentially interfere with the benefits of using cannabinoids for nausea and vomiting (Allan et al., 2018). Consistent with previous literature reviews, a multicentre RCT found that adding THC, CBD, or both to antinausea treatment resulted in less nausea and vomiting, but moderate side effects such as sedation, dizziness or disorientation were reported (Grimison et al., 2020).

In Canada, nabilone (Cesamet) is indicated for the treatment of severe nausea and vomiting associated with chemotherapy.

Cancer Cachexia

The 2017 NASEM report concluded that there is insufficient evidence suggesting that cannabis and cannabinoids can alleviate symptoms associated with cancer cachexia (NASEM, 2017). A meta-analysis of three clinical trials found that cannabinoids increased appetite in patients with cancer cachexia but did not improve the overall quality of life of patients and induced mild adverse events (Wang et al., 2019). By contrast, two more recent systematic reviews of clinical trials found a lack of evidence on the efficacy of cannabinoids in the treatment of cachexia, suggesting more research is needed on its clinical efficacy (Hammond et al., 2021; Razmovski-Naumovski et al., 2022).

Neurological and Neurodegenerative Disorders

Multiple Sclerosis (MS)

The 2017 NASEM report concluded that there was substantial evidence that oral cannabinoids were effective in improving patient-reported MS spasticity symptoms, although limited evidence for an effect on clinician-measured spasticity was available (NASEM, 2017). More recently, a narrative review stated that nabiximols had positive effects on spasticity in individuals with MS (Conte et al., 2021), and an RCT on spasticity in MS found that cannabinoid treatment resulted in positive effects in balance and walking (De Blasiis et al., 2021).

An RCT comparing CBD oromucosal spray with first-line antispastics medication found that the CBD spray was more effective in improving resistant MS spasticity than first-line antispasticity medication (Markova et al., 2019). Another RCT found that a CBD oromucosal spray reduced spasticity duration and severity in individuals with resistant MS. Specifically, those with severely resistant MS achieved therapeutic benefits (displaying a numerical reduction in their scores) while those with moderately resistant MS did not have statistically significant results (Meuth et al., 2020).

In Canada, nabiximols (Sativex) is indicated as adjunctive treatment for symptomatic relief of spasticity in adult patients with MS who have not responded adequately to other therapies and who demonstrate meaningful improvement during an initial trial of therapy.

Alzheimer Disease

The 2017 NASEM report concluded that there is limited evidence to suggest that cannabinoids may be helpful in treating the symptoms of Alzheimer disease (NASEM, 2017). The evidence was not strong or consistent enough to establish definitive conclusions.

Since then, one recent systematic review and meta-analysis of RCTs found preliminary evidence that oral cannabinoids (dronabinol, nabilone, oral THC) improved neuropsychiatric symptoms in individuals with dementia (Bahji et al., 2020). By contrast, a more recent meta-analysis of four RCTs with Alzheimer disease, vascular dementia or mixed dementia found inconclusive evidence for the effects of cannabinoids (dronabinol, nabilone, oral THC) on dementia and emphasized further investigation (Kuharic et al., 2021). Several other systematic reviews found no conclusive evidence to support the use of cannabinoids for aggression and agitation in patients with dementia and Alzheimer disease (Charernboon et al., 2021; Paunescu et al., 2020; Ruthirakuhan et al., 2019).

Parkinson Disease

The 2017 NASEM report concluded that there is insufficient evidence suggesting that cannabinoids, compounds found in cannabis, might be helpful in managing symptoms related to Parkinson disease (NASEM, 2017).

Most of the available clinical evidence indicates that cannabinoids (e.g., nabilone, CBD) have minimal effects on motor function, but may be beneficial for managing nonmotor symptoms, such as anxiety and sleep disturbances (Carroll et al., 2004; de Faria et al., 2020; Chagas et al., 2014; Peball et al., 2020). More recently, a systematic review of trials and uncontrolled studies found insufficient evidence for cannabinoid treatment of Parkinson disease symptomatology such as levodopa-induced dyskinesias, anxiety and tremors (Bougea et al., 2020). A systematic review of randomized and nonrandomized studies found insufficient evidence for recommendation of cannabis treatment for Parkinson disease but benefits such as reductions in anxiety and pain were noted, emphasizing the need for further investigation (Urbi et al., 2022).

Seizures

The 2017 NASEM report concluded that there is insufficient evidence on the relationship between cannabinoids and its efficacy in treating seizures and that no conclusion can be drawn (NASEM, 2017). However, since then, CBD has received a lot of attention for its therapeutic effects in certain forms of epilepsy. Indeed, several recent RCTs conducted in children and young adults with Dravet syndrome and Lennox-Gastaut syndrome showed that highly purified, plant-derived CBD (Epidiolex), taken together with antiepileptic medications, significantly reduced the frequency of seizures. Mild to moderate adverse effects such as sedation, diarrhea, vomiting, decreased appetite and elevated liver enzymes were noted (Devinsky et al., 2017; Devinsky et al., 2018; Thiele et al., 2018). Two subsequent RCTs found that long-term CBD (Epidiolex) treatment was

safe and effective in reducing seizure frequency in patients with Dravet syndrome and Lennox-Gastaut syndrome (Devinsky et al., 2019; Laux et al., 2019). Some research has also suggested that CBD (Epidiolex) treatment could increase quality of life and mood in adult patients with treatment-resistant epilepsy, independent of the positive effects of CBD on seizure control (Gaston et al., 2019).

A meta-analysis of four RCTs found that CBD treatment, with or without clobazam, was effective in reducing seizure frequency in Dravet syndrome and Lennox-Gastaut syndrome. CBD-only treatment was associated with fewer adverse effects than the combination of CBD and clobazam (Devinsky et al., 2020). Another analysis of RCTs with patients with Dravet syndrome or Lennox-Gastaut syndrome found that CBD in combination with clobazam reduced seizure frequency and resulted in increased sedation and somnolence compared to those receiving clobazam-only treatment (Gunning et al., 2021). Together, these findings suggest that while the combination of CBD and clobazam is effective in reducing seizure frequency, it produces more adverse effects than either compound alone.

Several systematic reviews and meta-analyses concluded that CBD, in combination with traditional antiepileptics, was effective in reducing seizure frequency in Dravet syndrome and Lennox-Gastaut syndrome but did note higher rates of adverse events compared to placebo (Lattanzi et al., 2020a, Lattanzi et al., 2021). A lack of randomization for concomitant clobazam and a small sample size were noted as limitations of current RCTs (Lattanzi et al., 2020b). More recent clinical trials and systematic reviews of clinical trials reported similar findings to those presented in this section (Patel et al., 2021; Scheffer et al., 2021; Treves et al., 2021).

Epidiolex (a highly purified, plant-derived CBD) has been recently approved in Canada for treating seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients aged two years and older.

Mental Health and Psychiatric Disorders

Psychosis and Schizophrenia

The 2017 NASEM report concluded that there is insufficient evidence to support that cannabis use is associated with better mental health outcomes for those with schizophrenia and other psychoses (NASEM, 2017).

A growing body of research indicates that frequent use of cannabis can increase the risk of psychosis, especially among individuals with a family history of psychotic disorders, adolescents and those who use high THC products (Konefal et al., 2019; Petrilli et al., 2022; Robinson et al., 2022).

In a study conducted in 88 patients with schizophrenia, patients receiving adjunctive CBD showed improvements in their psychotic symptoms as well as their cognitive performance compared to the placebo group (McGuire et al., 2018). Conversely, another study showed that adjunctive CBD did not improve cognitive or psychotic symptoms of patients with schizophrenia. In addition, with the exception of more sedation in CBD-treated patients, the reported side effects (diarrhea, nausea and headache) were similar between both treatment and placebo groups (Boggs et al., 2018).

To exert its potential antipsychotic effects, it is believed that CBD interacts with various cellular signalling pathway mechanisms in brain areas involved in schizophrenia, such as the ventral hippocampus and striatum (Hudson et al., 2019; Renard et al., 2016). In line with this hypothesis, a recent trial conducted in 33 antipsychotic-medication-naïve participants at high risk of psychosis showed that CBD normalized neuronal activation in the hippocampus, midbrain and striatum, brain regions strongly involved in psychosis onset and psychotic symptoms (Bhattacharyya et al., 2018). More studies are needed to understand the mechanisms underlying CBD's potential antipsychotic effects.

Anxiety Disorders

Anxiety relief is among the most common medical reasons for why people use cannabis (Cuttler et al., 2018; Kosiba et al., 2019; Sexton et al., 2016). Most people (~90%) who use cannabis for anxiety (or depression) report that cannabis is effective in managing their symptoms. The NASEM report concluded in 2017, that evidence showing the effectiveness of CBD in reducing anxiety symptoms for individuals with social anxiety disorders (evaluated through a public speaking test) is limited (NASEM, 2017).

A large body of preclinical evidence indicates that the endocannabinoid system plays an important role in fear and anxiety responses (Petrie et al., 2021). However, evidence for the utility of cannabis and cannabinoids in treating symptoms of anxiety in humans is much more limited — and controversial. For instance, studies in humans showed a dose-dependent effect of THC on anxiety with low doses reducing anxiety and, conversely, high doses producing anxiety (Sharpe et al., 2020). A meta-analysis concluded that pharmaceutical THC (with or without CBD) might reduce anxiety in individuals with certain medical conditions (primarily chronic noncancer pain and multiple sclerosis), although the evidence grade was very low (Black et al., 2019).

A review of case studies and clinical trials showed potential efficacy of cannabis and cannabinoids in psychiatric disorders, including anxiety disorders (Sarris et al., 2020). A systematic review and meta-analysis of 14 clinical trials found that cannabinoid treatment reduced anxiety symptoms, most effectively in younger patients with anxiety disorders who were undergoing long-term treatment. However, these anxiolytic effects were no longer apparent after correction for publication bias in the included trials (Bahji et al., 2020b). Another systematic review found limited high-quality evidence supporting the use of cannabis and cannabinoids in managing mood and anxiety disorders (Botsford et al., 2020). Similarly, a systematic review of RCTs with limited sample sizes found insufficient evidence for CBD and THC treatment for anxiety disorders and stated that further research is needed (Stanciu et al., 2021).

There is some promising evidence for the use of CBD in anxiety disorders. A systematic review of RCTs reported potential efficacy of CBD treatment in anxiety but noted the need for larger-scale RCTs (Bonaccorso et al., 2019). Similarly, a systematic review of randomized and uncontrolled studies found evidence for CBD treatment for anxiety disorders, but again suggested the need for further investigation using study designs that focus on dosing strategy and clinical outcome measurements (Skelley et al., 2020). A scoping review of RCTs and within-subject studies found that CBD was tolerated in substance use and insomnia disorders, with potential efficacy in anxiety and psychotic symptoms (Kirkland et al., 2022).

Presently, there is limited high-quality published evidence (based on clinical trials) supporting the usefulness of THC, CBD or other cannabinoids in treating anxiety or anxiety disorders. Further research studies are also needed to evaluate the effectiveness, optimal dosages, methods of use and safety profiles of THC, CBD, or both for the treatment or relief of anxiety symptoms.

Depressive Disorders

Cannabis is often used to self-manage symptoms of depression with individuals reporting that cannabis is effective in alleviating their depressive symptoms (Kosiba et al., 2019; Sexton et al., 2016). The 2017 NASEM report found limited evidence suggesting that nabiximols, dronabinol and nabilone do not effectively reduce depressive symptoms in individuals with chronic pain or multiple sclerosis (NASEM, 2017). Since then, there have been multiple reviews of case studies and clinical trials and they all arrived at a similar conclusion: the available evidence to date does not support the efficacy and safety of cannabinoids (THC, CBD) to treat mood disorders, including depression (Botsford et al., 2020; Lowe et al., 2019; Sarris et al., 2020; Stanciu et al., 2021).

Posttraumatic Stress Disorder (PTSD)

Altered functioning of the endocannabinoid system is believed to underpin certain stress-related features of PTSD (Hill et al., 2018), and the use of cannabinoids is thought to provide some value in the treatment of PTSD (Loflin et al., 2017). Individuals living with PTSD use cannabis to manage PTSD-associated flashbacks, hyperarousal, stress, anxiety, depression and insomnia symptoms (Bonn-Miller et al., 2014a; Bonn-Miller et al., 2014b). Formation of fear memory, during and following exposure to a traumatic event, coupled with impaired extinction of this fear memory are core features in the development of PTSD (Kida, 2019). Modulating different aspects of fear memory (e.g., consolidation, reconsolidation), through behavioural or pharmacological interventions or a combination of both, might therefore be a potential treatment for PTSD (Astill Wright et al., 2021).

The 2017 NASEM report indicated there is limited evidence, derived from a single small trial of fair quality, indicating that nabilone may be effective in alleviating symptoms associated with posttraumatic stress disorder (NASEM, 2017).

More recently, a systematic review of trials concluded that cannabinoids may decrease PTSD symptomatology, such as sleep disturbances and nightmares, but also noted the low quality of studies with small sample sizes (Hindocha et al., 2020). Nevertheless, another systematic review found cannabinoid treatment to be effective and well tolerated for patients with PTSD, with reported adverse events such as lightheadedness, dizziness and headaches (Forsythe et al., 2021). While this evidence is promising, it should be noted that several other systematic reviews do not seem to support the use of cannabinoids in PTSD, largely due to low quality of evidence (Orsolini et al., 2019; Sarris et al., 2020; Stanciu et al., 2021). A small case series study found that the use of CBD as an adjunctive therapy was associated with a 28% reduction in PTSD symptom severity in 91% of individuals with PTSD (Elms et al., 2019).

Sleep Disturbances

Sleep disturbances, namely insomnia, are another common medical reason for cannabis use (Kalaba & Ware, 2022; Tumati et al., 2021; Wadsworth et al., 2023). The 2017 NASEM report concluded that regarding cannabis use and sleep, there is moderate evidence suggesting that cannabinoids, such as nabiximols, may improve sleep outcomes in individuals with certain disorders, including sleep apnea, multiple sclerosis and chronic pain (NASEM, 2017).

A review of open-label trials and RCTs found that cannabinoids can improve sleep quality, but the studies were limited by small sample sizes and the use of measures

that were not validated. Thus, this review identified gaps that needed further investigation, such as differences between THC and CBD, and identification of adverse events in cannabinoid use (Kuhathasan et al., 2019). Similarly, a review of two RCTs and three nonrandomized studies looking at cannabinoid treatment for insomnia found there to be a lack of diagnostic clarity, poorly defined participant groups and limited power to detect important outcomes in the studies, which presents the need to further investigate the use of cannabinoids for insomnia disorder using high-quality RCTs (Bhagavan et al., 2020). Around the same time, similar conclusions were made by two additional reviews (Sarris et al., 2020; Suraev et al., 2020a). A comprehensive review looking at the efficacy of cannabis in treating sleep disorders found that cannabis has little to no effect on sleep disorders, with some studies showing adverse effects (Kolla et al., 2022). This said, there is some evidence suggesting that CBD or cannabis with high content of CBD may promote subjective feelings of sleepiness as compared to placebo (Spindle et al., 2020).

It should be noted that while short-term use of THC might help with sleep, it appears that frequent cannabis use has the opposite effects (Kuhathasan et al., 2019; Vaughn et al., 2010). Indeed, the association between regular cannabis use and symptoms of insomnia, including poor sleep quality, decreased sleep duration and increased latency to sleep have frequently been reported in clinical studies (Bolla et al., 2008; Conroy et al., 2016; Johnson & Breslau, 2001; Ogeil et al., 2015; Sznitman et al., 2020). For some individuals, cannabis use, especially when initiated during adolescence, can increase the risk of developing insomnia later in life (Ogeil et al., 2019; Winiger et al., 2020). For others, poor sleep quality, insomnia symptoms and sleep disorders beginning during adolescence might encourage the use of cannabis, especially for individuals with certain genes involved in regulating the endocannabinoid system, circadian rhythms and sleep behaviours (Fakier & Wild, 2011; Hasler et al., 2017; Maple, et al., 2016; Roane & Taylor, 2008; Winiger et al., 2020).

Substance Use Disorders

The 2017 NASEM report concluded that there is no evidence to either support or deny the effectiveness of cannabis in the treatment of substance use disorders (NASEM, 2017).

Alcohol Use Disorder

A systematic review conducted in rodents, humans and cell cultures found that CBD weakens alcohol use withdrawal in rodents among other benefits, which is further supported by the well-tolerated CBD treatment in human subjects (Turna et al., 2019b). Presently, there does not appear to be published data from RCTs assessing potential therapeutic effects of cannabinoids for alcohol use disorder.

Opioid Use Disorder

Over the last decade, growing evidence from animal studies has shown that endocannabinoid and opioid systems share functional interactions in brain regions that control tolerance, dependence and addiction (Lopez-Moreno et al., 2010; Scavone et al., 2013). A large body of evidence coming from animal models of opioid addiction have shown interesting effects of various cannabinoids (THC, CBD, 2-arachidonoylglycerol [2-AG], anandamide) in reducing the severity of addiction behaviours (Hurd et al., 2015; Lopez-Moreno et al., 2010; Scavone et al., 2013). As such, a strong interest for targeting the endocannabinoid system for treating symptoms associated with opioid use disorders has emerged. Some recent observational studies in humans have demonstrated that cannabis use reduces the use of opioids in patients with chronic pain (Boehnke et al., 2019; Lucas et al., 2019; Lucas et al., 2021; Safakish et al., 2020; Sagy et al., 2019). Another study showed that daily cannabis use increased the rate of opioid injection cessation among three prospective cohorts of people who inject drugs in Vancouver, Canada (Reddon et al., 2020).

Although cannabinoids have demonstrated interesting findings in animal models of addiction, the available data in humans from robust RCTs remains limited and is still urgently required.

Cannabis Use Disorder

Clinical data evaluating the efficacy of cannabinoids in cannabis use disorder is limited. Some RCTs have shown that relatively high doses of nabiximols combined with psychosocial interventions could reduce the severity of cannabis withdrawal symptoms and cannabis craving during cannabis abstinence. However, only a small reduction in cannabis use was observed, and it was not clear whether this was attributed to the nabiximols, the psychosocial intervention, or both (Allsop et al., 2014; Trigo et al., 2016; Trigo et al., 2018). Additionally, a more recent RCT found that nabiximols treatment with psychosocial interventions for those with cannabis dependence was found to be beneficial and to last up to three months (Lintzeris et al., 2020).

Some research suggests that CBD may be useful in reducing cannabis use in people with cannabis use disorder. An open-label trial showed that CBD improved psychological symptoms and cognitive deficits associated with the use of regular cannabis in individuals with cannabis use disorder who were not engaged to quit cannabis use (Solowij et al., 2018). Finally, another clinical study comprising

82 individuals with cannabis use disorder who desired to quit cannabis use, showed that CBD, at the doses of 400 mg and 800 mg, was more effective than CBD 200 mg or placebo in reducing cannabis use and increasing cannabis abstinence. Moreover, CBD was well tolerated with no severe adverse effects (Freeman et al., 2020).

Conclusions and Implications

Overall, the available evidence from clinical studies does not support the use of cannabis and cannabinoids for most health conditions, at least not as a first-line treatment option. However, this evidence has not deterred people from using cannabis (and cannabinoids) for various mental and physical health conditions. As mentioned earlier, survey data indicate that about 13% of people living in Canada report using cannabis for medical purposes, many of whom find benefits of their use (Health Canada, 2022).

There is clearly a disconnect between self-reported evidence and clinical evidence. Most people who use cannabis for medical reasons find it beneficial. However, people who use cannabis for medical purposes and those considering use for this reason should be informed of (or at least have access to) the latest high-quality evidence, whether it supports their personal experiences or not. The challenge now is to determine how to best disseminate the available clinical evidence on cannabis use for medical purposes without discounting often self-reported benefits of cannabis for various health conditions.

Healthcare providers are an important point of contact for individuals seeking information about cannabis use for medical purposes. Yet a recent survey found that Canadian physicians-in-training reported receiving significantly less instruction on cannabis for medical purposes than they desired (Pierre et al., 2020). In another study, family physicians practising in Ontario raised concerns about the limited evidence for the therapeutic use of cannabis and their lack of education regarding it, harms associated with cannabis use, and drug interactions in older adults (Ng et al., 2021). In a study comprising the 12 nursing regulatory bodies in Canada, only seven had policies and statements related to cannabis, and discrepancies were noted in the role of nurses in the administration of medical cannabis. Several barriers were also identified regarding nursing engagement in care related to medical cannabis, including lack of knowledge and clinical guidelines (Balneaves & Alraja, 2019). Similar views were expressed in a recent qualitative study on perceptions of cannabis among older adults. Most participants who were using cannabis for a medical reason or who were considering use for this reason said they had not consulted with their family doctor. A lack of perceived physician knowledge about cannabis as well as stigma were the most common reasons for why they had not consulted with their family doctor (Renard et al., 2023).

Cannabis use may be associated with cognitive impairment (Broyd et al., 2016), increased risk for stroke, cardiovascular and respiratory dysfunction (Latif et al., 2020; Ribeiro & Ind, 2016), psychiatric diseases and other mental health problems (Hindley et al., 2020). Frequent cannabis use might also be associated with symptoms of a cannabis use disorder, even among people who use for medical reasons (Turna et al., 2020). Similar to what was outlined in the HSO standards on *Cannabis Use for Medical Purposes: Inpatient Care Settings* (Health Standards Organization, 2022), evaluating the beneficial and potentially negative health effects of cannabis will need to be considered with the person who uses or is considering using cannabis. Continued monitoring for adverse effects may also be needed. To this end, CCSA recommends future efforts to equip healthcare professionals with the information and resources they need to increase their own knowledge and their ability to clearly communicate evidence to their patients.

The conversation around cannabis use for medical use may be especially important now as Canada evaluates its current medical cannabis regulatory framework. As indicated in our response to the federal government's public consultation on cannabis legalization and regulation, A Public Health Perspective on Cannabis Legalization and Regulation in Canada, CCSA believes that the decision to use cannabis for medical purposes should be informed by a healthcare professional and require some level of monitoring or follow-up, as would be expected for any other medical product. For this reason, CCSA suggested that cannabis for medical purposes continue to exist as a separate program overseen by Health Canada. In addition, people who use cannabis for medical purposes, despite where they get the cannabis products or whether they have authorization through the medical program, should have access to guidance from a healthcare professional.

References

Allan, G. M., Finley, C. R., Ton, J., Perry, D., Ramji, J., Crawford, K., …Kolber, M. R. (2018). Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. *Canadian Family Physician, 64*(2), e78–e94. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5964405/

Allsop, D. J., Copeland, J., Lintzeris, N., Dunlop, A. J., Montebello, M., Sadler, C., …Norberg, M. M. (2014). Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA Psychiatry*, *71*(3), 281–291. https://doi:10.1001/jamapsychiatry.2013.3947

Astill Wright, L., Horstmann, L., Holmes, E. A., & Bisson, J. I. (2021). Consolidation/reconsolidation therapies for the prevention and treatment of PTSD and re-experiencing: A systematic review and meta-analysis. *Translational Psychiatry*, *11*(1), 453. https://doi.org/10.1038/s41398-021-01570-w

Bahji, A., Meyyappan, A. C., & Hawken, E. R. (2020b). Efficacy and acceptability of cannabinoids for anxiety disorders in adults: A systematic review & meta-analysis. *Journal of Psychiatric Research*, *129,* 257–264. https://doi.org/10.1016/j.jpsychires.2020.07.030

Balneaves, L. G. & Alraja, A. A. (2019). "Guarding their practice": A descriptive study of Canadian nursing policies and education related to medical cannabis. *BMC Nursing*. *18*, 66. https://doi.org/10.1186/s12912-019-0390-7

Berger, A. A., Keefe, J., Winnick, A., Gilbert, E., Eskander, J. P., Yazdi, C., Kaye, A. D., Viswanath, O., & Urits, I. (2020). Cannabis and cannabidiol (CBD) for the treatment of fibromyalgia. *Best Practice & Research Clinical Anaesthesiology*, *34*(3), 617–631. https://doi.org/10.1016/j.bpa.2020.08.010

Bhagavan, C., Kung, S., Doppen, M., John, M., Vakalalabure, I., Oldfield, K., Braithwaite, I., & Newton-Howes, G. (2020). Cannabinoids in the treatment of insomnia disorder: A aystematic review and meta-analysis. *CNS Drugs*, *34(*12), 1217–1228. https://doi.org/10.1007/s40263-020-00773-x

Bhattacharyya, S., Wilson, R., Appiah-Kusi, E., O'Neill, A., Brammer, M., Perez, J., …McGuire, P. (2018). Effect of cannabidiol on medial temporal, midbrain, and striatal dysfunction in people at clinical high risk of psychosis: A randomized clinical trial. *JAMA Psychiatry*, *75*(11), 1107–1117. https://doi.org/10.1001/jamapsychiatry.2018.2309

Black, N., Stockings, E., Campbell, G., Tran, L. T., Zagic, D., Hall, W. D., …Degenhardt, L. (2019). Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: A systematic review and meta-analysis. *The Lancet Psychiatry*, *6*(12), 995–1010. https://doi.org/10.1016/S2215-0366(19)30401-8

Boehnke, K. F., Scott, J. R., Litinas, E., Sisley, S., Williams, D. A., & Clauw, D. J. (2019). Pills to pot: observational analyses of cannabis substitution among medical cannabis users with chronic pain. *The Journal of Pain*, *20*(7), 830–841. https://doi.org/10.1016/j.jpain.2019.01.010

Boggs, D. L., Surti, T., Gupta, A., Gupta, S., Niciu, M., Pittman, B., …Ranganathan, M. (2018). The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. *Psychopharmacology* (Berl.), *235*(7), 1923–1932. https://doi.org/10.1007/s00213-018-4885-9

Boland, E. G., Bennett, M. I., Allgar, V., & Boland, J. W. (2020). Cannabinoids for adult cancer-related pain: Systematic review and meta-analysis. *BMJ Supportive & Palliative Care*, *10*(1), 14–24. https://doi.org/10.1136/bmjspcare-2019-002032

Bolla, K. I., Lesage, S. R., Gamaldo, C. E., Neubauer, D. N., Funderburk, F. R., Cadet, J. L., …Benbrook, A. R. (2008). Sleep disturbance in heavy marijuana users. *Sleep*, *31*(6), 901–908. https://doi.org/10.1093/sleep/31.6.901

Bonaccorso, S., Ricciardi, A., Zangani, C., Chiappini, S., & Schifano, F. (2019). Cannabidiol (CBD) use in psychiatric disorders: A systematic review. *Neurotoxicology, 74*, 282–298. https://doi.org/10.1016/j.neuro.2019.08.002

Bonn-Miller, M. O., Babson, K. A., & Vandrey, R. (2014). Using cannabis to help you sleep: Heightened frequency of medical cannabis use among those with PTSD. *Drug and Alcohol Dependence, 136*, 162–165. https://doi.org/10.1016/j.drugalcdep.2013.12.008

Bonn-Miller, M. O., Boden, M. T., Bucossi, M. M., & Babson, K. A. (2014). Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. *American Journal of Drug and Alcohol Abuse*, *40*(1), 23–30. https://doi.org/10.3109/00952990.2013.821477

Botsford, S. L., Yang, S., & George, T. P. (2020). Cannabis and cannabinoids in mood and anxiety disorders: Impact on illness onset and course, and assessment of therapeutic potential. *The American Journal on Addictions*, *29*(1), 9–26. https://doi.org/10.1111/ajad.12963

Bougea, A., Koros, C., Simitsi, A.-M., Chrysovitsanou, C., Leonardos, A., & Stefanis, L. (2020). Medical cannabis as an alternative therapeutics for Parkinsons' disease: Systematic review. *Complementary Therapies in Clinical Practice*, *39*, Article 101154. https://doi.org/10.1016/j.ctcp.2020.101154

Broyd, S. J., van Hell, H. H., Beale, C., Yücel, M., & Solowij, N. (2016). Acute and chronic effects of cannabinoids on human cognition–A systematic review. *Biological Psychiatry*, *79*(7), 557–567. https://doi.org/10.1016/j.biopsych.2015.12.002

Cameron, E. C., & Hemingway, S. L. (2020). Cannabinoids for fibromyalgia pain: A critical review of recent studies (2015–2019). *Journal of Cannabis Research*, *2*, 1–11. https://doi.org/10.1186/s42238-020-00024-2

Charernboon, T., Lerthattasilp, T., & Supasitthumrong, T. (2021). Effectiveness of cannabinoids for treatment of dementia: A systematic review of randomized controlled trials. *Clinical Gerontologist*, *44*(1), 16–24. https://doi.org/10.1080/07317115.2020.1742832

Conroy, D. A., Kurth, M. E., Strong, D. R., Brower, K. J., & Stein, M. D. (2016). Marijuana use patterns and sleep among community-based young adults. *Journal of Addictive Diseases*, *35(*2), 135–143. https://doi.org/10.1080/10550887.2015.1132986

Conte, A., & Vila Silván, C. (2021). Review of available data for the efficacy and effectiveness of nabiximols oromucosal spray (Sativex®) in multiple sclerosis patients with moderate to severe spasticity. *Neuro-Degenerative Diseases*, *21*(3–4), 55–62. https://doi.org/10.1159/000520560

Corroon, J., & Phillips, J. A. (2018). A cross-sectional study of cannabidiol users. *Cannabis and Cannabinoid Research*, *3*(1), 152–161. http://doi.org/10.1089/can.2018.0006

Cuttler, C., Spradlin, A., & McLaughlin, R. J. (2018). A naturalistic examination of the perceived effects of cannabis on negative affect. *Journal of Affective Disorders*, *235*, 198–205. https://doi.org/10.1016/j.jad.2018.04.054

De Blasiis, P., Siani, M. F., Fullin, A., Sansone, M., Melone, M. A. B., Sampaolo, S., Signoriello, E., & Lus, G. (2021). Short and long term effects of nabiximols on balance and walking assessed by 3d-gait analysis in people with multiple sclerosis and spasticity. *Multiple Sclerosis and Related Disorders*, *51*, Article 102805. https://doi.org/10.1016/j.msard.2021.102805

Devinsky, O., Cross, J. H., Laux, L., Marsh, E., Miller, I., Nabbout, R., . . . Wright, S. (2017). Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *New England Journal of Medicine*, *376*(21), 2011–2020. https://doi.org/10.1056/NEJMoa1611618

Devinsky, O., Patel, A. D., Cross, J. H., Villanueva, V., Wirrell, E. C., Privitera, M., … VanLandingham, K. E. (2018). Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. *New England Journal of Medicine*, *378*(20), 1888–1897. https://doi.org/10.1056/NEJMoa1714631

Devinsky, O., Nabbout, R., Miller, I., Laux, L., Zolnowska, M., Wright, S., & Roberts, C. (2019). Long-term cannabidiol treatment in patients with Dravet syndrome: An open-label extension trial. *Epilepsia*, *60*(2), 294–302. https://doi.org/10.1111/epi.14628

Devinsky, O., Thiele, E. A., Wright, S., Checketts, D., Morrison, G., Dunayevich, E., & Knappertz, V. (2020). Cannabidiol efficacy independent of clobazam: Meta-analysis of four randomized controlled trials. *Acta Neurologica Scandinavica, 142*(6), 531–540. https://doi.org/10.1111/ane.13305

Dykukha, I., Malessa, R., Essner, U., & Überall, M. A. (2021). Nabiximols in chronic neuropathic pain: A meta-analysis of randomized placebo-controlled trials. *Pain Medicine, 22*(4), 861–874. https://doi.org/10.1093/pm/pnab050

Fakier, N., & Wild, L. G. (2011). Associations among sleep problems, learning difficulties and substance use in adolescence. *Journal of Adolescence, 34*(4), 717–726. https://doi.org/10.1016/j.adolescence.2010.09.010

Fallon, M. T., Albert Lux, E., McQuade, R., Rossetti, S., Sanchez, R., Sun, W., … Kornyeyeva, E. (2017). Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: Two double-blind, randomized, placebo-controlled phase 3 studies. *British Journal of Pain*, 11(3), 119–133. https://doi.org/10.1177/2049463717710042

Fisher, E., Moore, R. A., Fogarty, A. E., Finn, D. P., Finnerup, N. B., Gilron, I., … Eccleston, C. (2021). Cannabinoids, cannabis, and cannabis-based medicine for pain management: A systematic review of randomised controlled trials. *Pain, 162*(Suppl 1), S45–S66. https://doi.org/10.1097/j.pain.0000000000001929

Forsythe, M. L., & Boileau, A. J. (2021). Use of cannabinoids for the treatment of patients with post-traumatic stress disorder. *Journal of Basic and Clinical Physiology and Pharmacology*, *33*(2), 121–132. https://doi.org/10.1515/jbcpp-2020-0279

Freeman, T. P., Hindocha, C., Baio, G., Shaban, N. D., Thomas, E. M., Astbury, D., ... Curran, H. V. (2020). Cannabidiol for the treatment of cannabis use disorder: A phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *The Lancet Psychiatry*, *7*(10), 865–874. https://doi.org/10.1016/S2215-0366(20)30290-X

Gaston, T. E., Szaflarski, M., Hansen, B., Bebin, E. M., & Szaflarski, J. P. (2019). Quality of life in adults enrolled in an open-label study of cannabidiol (CBD) for treatment-resistant epilepsy. *Epilepsy & Behavior*, *95*, 10–17. https://doi.org/10.1016/j.yebeh.2019.03.035

Grimison, P., Mersiades, A., Kirby, A., Lintzeris, N., Morton, R., Haber, P., …Stockler, M. (2020). Oral THC:CBD cannabis extract for refractory chemotherapy-induced nausea and vomiting: A randomised, placebo-controlled, phase II crossover trial. *Annals of Oncology*, *31*(11), 1553–1560. https://doi.org/10.1016/j.annonc.2020.07.020

Gunning, B., Mazurkiewicz-Bełdzińska, M., Chin, R. F. M., Bhathal, H., Nortvedt, C., Dunayevich, E., & Checketts, D. (2021). Cannabidiol in conjunction with clobazam: Analysis of four randomized controlled trials. *Acta Neurologica Scandinavica*, *143*(2), 154–163. https://doi.org/10.1111/ane.13351

Habib, G., & Artul, S. (2018). Medical cannabis for the treatment of fibromyalgia. *Journal of Clinical Rheumatology*, *24*(5), 255–258. https://doi.org/10.1097/RHU.0000000000000702

Habib, G., & Avisar, I. (2018). The consumption of cannabis by fibromyalgia patients in Israel. *Pain Research and Treatment*, 2018, Article 7829427. https://doi.org/10.1155/2018/7829427

Hammond, S., Erridge, S., Mangal, N., Pacchetti, B., & Sodergren, M. H. (2021). The effect of cannabis-based medicine in the treatment of cachexia: A systematic review and meta-analysis. *Cannabis & Cannabinoid Research*, *6*(6), 474–487. https://doi.org/10.1089/can.2021.0048

Hasler, B. P., Franzen, P. L., de Zambotti, M., Prouty, D., Brown, S. A., Tapert, S. F., …De Bellis, M. D. (2017). Eveningness and later sleep timing are associated with greater risk for alcohol and marijuana use in adolescence: Initial findings from the national consortium on alcohol and neurodevelopment in adolescence study. *Alcoholism: Clinical and Experimental Research*, *41*(6), 1154–1165. https://doi.org/10.1111/acer.13401

Häuser, W., Welsch, P., Klose, P., Radbruch, L., & Fitzcharles, M. A. (2019). Efficacy, tolerability and safety of cannabis-based medicines for cancer pain: A systematic review with meta-analysis of randomised controlled trials. *Schmerz* (Berlin, Germany), *33*(5), 424–436. https://doi.org/10.1007/s00482-019-0373-3

Health Canada. (2020). *Summary report: Consultation on potential market for health products containing cannabis that would not require practitioner oversight.* Ottawa, Ont.; Author. https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/summary-report-consultation-potential-market-health-products-cannabis.html

Health Canada (2022). *Canadian cannabis survey 2022: Summary.* Ottawa, Ont.; Author. https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/canadian-cannabis-survey-2022-summary.html

Health Standards Organization. (2022). *Cannabis use for medical purposes: Inpatient care settings*. Ottawa, Ont.: Health Standards Organization. https://store.healthstandards.org/products/cannabis-use-for-medical-purposes-inpatient-care-settings-can-hso-11013-2012-e

Hill, M. N., Campolongo, P., Yehuda, R., & Patel, S. (2018). Integrating endocannabinoid signaling and cannabinoids into the biology and treatment of posttraumatic stress disorder. *Neuropsychopharmacology, 43*(1), 80–102. https://doi.org/10.1038/npp.2017.162

Hindocha, C., Cousijn, J., Rall, M., & Bloomfield, M. A. P. (2020). The effectiveness of cannabinoids in the treatment of posttraumatic stress disorder (PTSD): A systematic review. *Journal of Dual Diagnosis*, *16*(1), 120–139. https://doi.org/10.1080/15504263.2019.1652380

Hindley, G., Beck, K., Borgan, F., Ginestet, C. E., McCutcheon, R., Kleinloog, D., …Howes, O. D. (2020). Psychiatric symptoms caused by cannabis constituents: A systematic review and meta-analysis. *The Lancet Psychiatry*, *7*(4), 344–353. https://doi.org/10.1016/S2215-0366(20)30074-2

Hudson, R., Renard, J., Norris, C., Rushlow, W. J., & Laviolette, S. R. (2019). Cannabidiol counteracts the psychotropic side-effects of Δ-9-tetrahydrocannabinol in the ventral hippocampus through bidirectional control of erk1-2 phosphorylation. *The Journal of Neuroscience*, *39*(44), 8762–8777. https://doi.org/10.1523/JNEUROSCI.0708-19.2019

Johal, H., Devji, T., Chang, Y., Simone, J., Vannabouathong, C., & Bhandari, M. (2020). Cannabinoids in chronic non-cancer pain: A systematic review and meta-analysis. *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*, *13*. https://doi.org/10.1177/1179544120906461

Johnson, E. O., & Breslau, N. (2001). Sleep problems and substance use in adolescence. *Drug and Alcohol Dependence*, *64*(1), 1–7. https://doi.org/10.1016/S0376-8716(00)00222-2

Kalaba, M., & Ware, M. A. (2022). Cannabinoid profiles in medical cannabis users: Effects of age, gender, symptoms, and duration of use. *Cannabis and Cannabinoid Research*, *7*(6), 840–851. https://doi.org/10.1089/can.2020.0120

Khurshid, H., Qureshi, I. A., Jahan, N., Went, T. R., Sultan, W., Sapkota, A., & Alfonso, M. (2021). A systematic review of fibromyalgia and recent advancements in treatment: Is medicinal cannabis a new hope? *Cureus*, *13*(8), Article e17332. https://doi.org/10.7759/cureus.17332

Kida, S. (2019). Reconsolidation/destabilization, extinction and forgetting of fear memory as therapeutic targets for PTSD. *Psychopharmacology*, *236*(1), 49–57. https://doi.org/10.1007/s00213-018-5086-2

Kirkland, A. E., Fadus, M. C., Gruber, S. A., Gray, K. M., Wilens, T. E., & Squeglia, L. M. (2022). A scoping review of the use of cannabidiol in psychiatric disorders. *Psychiatry Research*, *308*, Article 114347. https://doi.org/10.1016/j.psychres.2021.114347

Kolla, B. P., Hayes, L., Cox, C., Eatwell, L., Deyo-Svendsen, M., & Mansukhani, M. P. (2022). The effects of cannabinoids on sleep. *Journal of Primary Care & Community Health*, *13*. https://doi.org/10.1177/21501319221081277

Konefal, S., Gabrys, R., & Porath, A. (2019). *Clearing the smoke on cannabis: Regular use and mental health*. Ottawa, Ont.: Canadian Centre on Substance Use and Addiction. https://www.ccsa.ca/sites/default/files/2019-08/CCSA-Cannabis-Use-Mental-Health-Report-2019-en_0.pdf

Kosiba, J. D., Maisto, S. A., & Ditre, J. W. (2019). Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis. *Social Science & Medicine, 233*, 181–192. https://doi.org/10.1016/j.socscimed.2019.06.005

Kuharic, D. B., Markovic, D., Brkovic, T., Kegalj, M. J., Rubic, Z., Vukasovic, A. V., …Puljak, L. (2021). Cannabinoids for the treatment of dementia. *Cochrane Database of Systematic Reviews*, *9*(9), Article CD012820. https://doi.org/10.1002/14651858.CD012820.pub2

Kuhathasan, N., Dufort, A., MacKillop, J., Gottschalk, R., Minuzzi, L., & Frey, B. N. (2019). The use of cannabinoids for sleep: A critical review on clinical trials. *Experimental and Clinical Psychopharmacology*, *27*(4), 383–401. https://doi.org/10.1037/pha0000285

Kurlyandchik, I., Tiralongo, E., & Schloss, J. (2021). Safety and efficacy of medicinal cannabis in the treatment of fibromyalgia: A systematic review. *The Journal of Alternative and Complementary Medicine*, *27*(3), 198–213. https://doi.org/10.1089/acm.2020.0331

Latif, Z., & Garg, N. (2020). The impact of marijuana on the cardiovascular system: A review of the most common cardiovascular events associated with marijuana use. *Journal of Clinical Medicine*, *9*(6), 1925. https://doi.org/10.3390/jcm9061925

Lattanzi, S., Trinka, E., Striano, P., Rocchi, C., Salvemini, S., Silvestrini, M., & Brigo, F. (2021). Highly purified cannabidiol for epilepsy treatment: A systematic review of epileptic conditions beyond Dravet Syndrome and Lennox–Gastaut Syndrome. *CNS Drugs*, *35*(3), 265–281. https://doi.org/10.1007/s40263-021-00807-y

Laux, L. C., Bebin, E. M., Checketts, D., Chez, M., Flamini, R., Marsh, E. D., …Weinstock, A. (2019). Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox–Gastaut syndrome or Dravet syndrome: Expanded access program results. *Epilepsy Research*, *154*, 13–20. https://doi.org/10.1016/j.eplepsyres.2019.03.015

Lichtman, A. H., Lux, E. A., McQuade, R., Rossetti, S., Sanchez, R., Sun, W., …Fallon, M. T. (2018). Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. *Journal of Pain and Symptom Management, 55*(2), Article e171, 179–188. https://doi.org/10.1016/j.jpainsymman.2017.09.001

Lintzeris, N., Mills, L., Dunlop, A., Copeland, J., Mcgregor, I., Bruno, R., …Bhardwaj, A. (2020). Cannabis use in patients 3 months after ceasing nabiximols for the treatment of cannabis dependence: Results from a placebo-controlled randomised trial. *Drug and Alcohol Dependence*, *215*, Article 108220. https://doi.org/10.1016/j.drugalcdep.2020.108220

Lobos Urbina, D. & Peña Durán, J. (2016). Are cannabinoids effective for treatment of pain in patients with active cancer? *Medwave, 16 Suppl 3,* e6539. https://doi.org/10.5867/medwave.2016.6539

Loflin, M. J., Babson, K. A., & Bonn-Miller, M. O. (2017). Cannabinoids as therapeutic for PTSD. *Current Opinion in Psychology, 14*, 78–83. https://doi.org/10.1016/j.copsyc.2016.12.001

Lopez-Moreno, J., Lopez-Jimenez, A., Gorriti, M., & de Fonseca, F. R. (2010). Functional interactions between endogenous cannabinoid and opioid systems: Focus on alcohol, genetics and drug-addicted behaviors. *Current Drug Targets*, *11*(4), 406–428. https://doi.org/10.2174/138945010790980312

Lowe, D. J., Sasiadek, J. D., Coles, A. S., & George, T. P. (2019). Cannabis and mental illness: A review. *European Archives of Psychiatry and Clinical Neuroscience*, *269*(1), 107–120. https://doi.org/10.1007/s00406-018-0970-7

Lucas, P., Baron, E. P., & Jikomes, N. (2019). Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduction Journal, 16*(1), 9. https://doi.org/10.1186/s12954-019-0278-6

Lucas, P., Boyd, S., Milloy, M. J., & Walsh, Z. (2021). Cannabis significantly reduces the use of prescription opioids and improves quality of life in authorized patients: Results of a large prospective study. *Pain Medicine*, 22(3), 727–739. https://doi.org/10.1093/pm/pnaa396

Ma, H., Zhang, G., Mou, C., Fu, X., & Chen, Y. (2018). Peripheral CB1 receptor neutral antagonist, AM6545, ameliorates hypometabolic obesity and improves adipokine secretion in monosodium glutamate induced obese mice. *Frontiers in Pharmacology*, *9*, 156. https://doi.org/10.3389/fphar.2018.00156

Maple, K. E., McDaniel, K. A., Shollenbarger, S. G., & Lisdahl, K. M. (2016). Dose-dependent cannabis use, depressive symptoms, and *FAAH* genotype predict sleep quality in emerging adults: A pilot study. *The American Journal of Drug and Alcohol Abuse*, *42*(4), 431–440. https://doi.org/10.3109/00952990.2016.1141913

Markovà, J., Essner, U., Akmaz, B., Marinelli, M., Trompke, C., Lentschat, A., & Vila, C. (2019). Sativex® as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: A double-blind, placebo-controlled randomised clinical trial. *International Journal of Neuroscience*, *129*(2), 119–128. https://doi.org/10.1080/00207454.2018.1481066

Mayo, L. M., Rabinak, C. A., Hill, M. N., & Heilig, M. (2022). Targeting the endocannabinoid system in the treatment of posttraumatic stress disorder: A promising case of preclinical-clinical translation? *Biological Psychiatry, 91*(3), 262–272. https://doi.org/10.1016/j.biopsych.2021.07.019

McGuire, P., Robson, P., Cubala, W. J., Vasile, D., Morrison, P. D., Barron, R., …Wright, S. (2018). Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. *American Journal of Psychiatry*, *175*(3), 225–231. https://doi.org/10.1176/appi.ajp.2017.17030325

Meccariello, R. (2020). Endocannabinoid system in health and disease: Current situation and future perspectives. *International Journal of Molecular Sciences*, *21*(10), 3549. https://doi.org/10.3390/ijms21103549

Meuth, S. G., Henze, T., Essner, U., Trompke, C., & Vila Silván, C. (2020). Tetrahydrocannabinol and cannabidiol oromucosal spray in resistant multiple sclerosis spasticity: Consistency of response across subgroups from the SAVANT randomized clinical trial. *International Journal of Neuroscience*, *130*(12), 1199–1205. https://doi.org/10.1080/00207454.2020.1730832

National Academies of Sciences, Engineering, and Medicine. (2017). *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, D.C.: Author. https://doi.org/10.17226/24625

Ng, J. Y., Gilotra, K., Usman, S., Chang, Y., & Busse, J. W. (2021). Attitudes toward medical cannabis among family physicians practising in Ontario, Canada: A qualitative research study. *Canadian Medical Association Open Access Journal*, 9(2), E342–E348. https://doi.org/10.9778/cmajo.20200187

Ogeil, R. P., Cheetham, A., Mooney, A., Allen, N. B., Schwartz, O., Byrne, M. L., …Lubman, D. I. (2019). Early adolescent drinking and cannabis use predicts later sleep-quality problems. *Psychology of Addictive Behaviors*, *33*(3), 266–273. https://doi.org/10.1037/adb0000453

Ogeil, R. P., Phillips, J. G., Rajaratnam, S. M., & Broadbear, J. H. (2015). Risky drug use and effects on sleep quality and daytime sleepiness. *Human Psychopharmacology: Clinical and Experimental*, *30*(5), 356–363. https://doi.org/10.1002/hup.2483

Orsolini, L., Chiappini, S., Volpe, U., Berardis, D. D., Latini, R., Papanti, G. D., & Corkery, A. J. M. (2019). Use of medicinal cannabis and synthetic cannabinoids in post-traumatic stress disorder (PTSD): A systematic review. *Medicina*, *55*(9). https://doi.org/10.3390/medicina55090525

Patel, A. D., Mazurkiewicz-Bełdzińska, M., Chin, R. F., Gil-Nagel, A., Gunning, B., Halford, J. J., …Devinsky, O. (2021). Long-term safety and efficacy of add-on cannabidiol in patients with Lennox–Gastaut syndrome: Results of a long-term open-label extension trial. *Epilepsia, 62*(9), 2228–2239. https://doi.org/10.1111/epi.17000

Petrie, G. N., Nastase, A. S., Aukema, R. J., & Hill, M. N. (2021). Endocannabinoids, cannabinoids and the regulation of anxiety. *Neuropharmacology, 195*, Article 108626. https://doi.org/10.1016/j.neuropharm.2021.108626

Petrilli, K., Ofori, S., Hines, L., Taylor, G., Adams, S., & Freeman, T. P. (2022). Association of cannabis potency with mental ill health and addiction: A systematic review. *The Lancet Psychiatry, 9*(9), 736–750. https://doi.org/10.1016/S2215-0366(22)00161-4

Pierre, M. S., Matthews, L., & Walsh, Z. (2020). Cannabis education needs assessment among Canadian physicians-in-training. *Complementary Therapies in Medicine, 49*, 102328. https://doi.org/10.1016/j.ctim.2020.102328

Razmovski-Naumovski, V., Luckett, T., Amgarth-Duff, I., & Agar, M. R. (2022). Efficacy of medicinal cannabis for appetite-related symptoms in people with cancer: A systematic review. *Palliative Medicine*, *36*(6), 912–927. https://doi.org/10.1177/02692163221083437

Reddon, H., DeBeck, K., Socias, M. E., Lake, S., Dong, H., Karamouzian, M., …Milloy, M. (2020). Frequent cannabis use and cessation of injection of opioids, Vancouver, Canada, 2005–2018. *American Journal of Public Health*, *110*, 1553–1560. https://doi.org/10.2105/AJPH.2020.305825

Renard, J., Wadsworth, E., Cristiano, N., & Gabrys, R. (2023). *Perceptions of cannabis among older adults in Canada* [Poster presentation], Canadian Centre on Substance Use and Addiction Issues of Substance conference, Vancouver, B.C.

Renard, J., Loureiro, M., Rosen, L. G., Zunder, J., de Oliveira, C., Schmid, S., …Laviolette, S. R. (2016). Cannabidiol counteracts amphetamine-induced neuronal and behavioral sensitization of the mesolimbic dopamine pathway through a novel mTOR/p70S6 kinase signaling pathway. *Journal of Neuroscience, 36*(18), 5160–5169. https://doi.org/10.1523/JNEUROSCI.3387-15.2016

Ribeiro, L. I., & Ind, P. W. (2016). Effect of cannabis smoking on lung function and respiratory symptoms: A structured literature review. *NPJ Primary Care Respiratory Medicine*, *26*, Article 16071. https://doi.org/10.1038/npjpcrm.2016.71

Roane, B. M., & Taylor, D. J. (2008). Adolescent insomnia as a risk factor for early adult depression and substance abuse. *Sleep*, *31*(10), 1351–1356. https://pubmed.ncbi.nlm.nih.gov/18853932

Robinson, T., Ali, M. U., Easterbrook, B., Hall, W., Jutras-Aswad, D., & Fischer, B. (2022). Risk-thresholds for the association between frequency of cannabis use and the development of psychosis: A systematic review and meta-analysis. *Psychological Medicine*, 1–11. https://doi.org/10.1017/S0033291722000502

Ruthirakuhan, M., Lanctôt, K. L., Vieira, D., & Herrmann, N. (2019). Natural and synthetic cannabinoids for agitation and aggression in Alzheimer's disease: A meta-analysis. *The Journal of Clinical Psychiatry, 80*(2), Article 18r12617. https://doi.org/10.4088/JCP.18r12617

Safakish, R., Ko, G., Salimpour, V., Hendin, B., Sohanpal, I., Loheswaran, G., & Yoon, S. Y. R. (2020). Medical cannabis for the management of pain and quality of life in chronic pain patients: A prospective observational study. *Pain Medicine*, *21*(11), 3073–3086. https://doi.org/10.1093/pm/pnaa163

Sagy, I., Bar-Lev Schleider, L., Abu-Shakra, M., & Novack, V. (2019). Safety and efficacy of medical cannabis in fibromyalgia. *Journal of Clinical Medicine*, 8(6), 807. https://doi.org/10.3390/jcm8060807

Sarris, J., Sinclair, J., Karamacoska, D., Davidson, M., & Firth, J. (2020). Medicinal cannabis for psychiatric disorders: A clinically-focused systematic review. *BMC Psychiatry*, *20*(1), Article 24. https://doi.org/10.1186/s12888-019-2409-8

Scavone, J., Sterling, R., & Van Bockstaele, E. (2013). Cannabinoid and opioid interactions: Implications for opiate dependence and withdrawal. *Neuroscience, 248*, 637–654. https://doi.org/10.1016/j.neuroscience.2013.04.034

Scheen, A. J., Finer, N., Hollander, P., Jensen, M. D., Van Gaal, L. F., & Group, R.-D. S. (2006). Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: A randomised controlled study. *The Lancet, 368*(9548), 1660–1672. https://doi.org/10.1016/S0140-6736(06)69571-8

Scheffer, I. E., Halford, J. J., Miller, I., Nabbout, R., Sanchez-Carpintero, R., Shiloh-Malawsky, Y., …Devinsky, O. (2021). Add-on cannabidiol in patients with Dravet syndrome: Results of a long-term open-label extension trial. *Epilepsia*, *62*(10), 2505–2517. https://doi.org/10.1111/epi.17036

Sexton, M., Cuttler, C., Finnell, J. S., & Mischley, L. K. (2016). A cross-sectional survey of medical cannabis users: Patterns of use and perceived efficacy. *Cannabis and Cannabinoid Research*, *1*(1), 131–138. https://doi.org/10.1089/can.2016.0007

Sharpe, L., Sinclair, J., Kramer, A., de Manincor, M., & Sarris, J. (2020). Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. *Journal of Translational Medicine*, *18*, Article 374. https://doi.org/10.1186/s12967-020-02518-2

Skelley, J. W., Deas, C. M., Curren, Z., & Ennis, J. (2020). Use of cannabidiol in anxiety and anxiety-related disorders. *Journal of the American Pharmacists Association*, *60*(1), 253–261. https://www.sciencedirect.com/science/article/pii/S154431911930514X

Smith, J. M., Mader, J., Szeto, A. C., Arria, A. M., Winters, K. C., & Wilkes, T. C. R. (2019). Cannabis use for medicinal purposes among Canadian university students. *The Canadian Journal of Psychiatry*, 64(5), 351–355. https://doi.org/10.1177/0706743718818420

Solowij, N., Broyd, S. J., Beale, C., Prick, J. A., Greenwood, L. M., van Hell, H., ...Yücel, M. (2018). Therapeutic effects of prolonged cannabidiol treatment on psychological symptoms and cognitive function in regular cannabis users: A pragmatic open-label clinical trial. *Cannabis and Cannabinoid Research, 3(*1), 21–34. https://doi.org/10.1089/can.2017.0043

Spindle, T. R., Cone, E. J., Goffi, E., Weerts, E. M., Mitchell, J. M., Winecker, R. E., ...Vandrey, R. (2020). Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. *Drug and Alcohol Dependence, 211*, Article 107937. https://doi.org/10.1016/j.drugalcdep.2020.107937

Stanciu, C. N., Brunette, M. F., Teja, N., & Budney, A. J. (2021). Evidence for use of cannabinoids in mood disorders, anxiety disorders, and PTSD: A systematic review. *Psychiatric Services*, *72*(4), 429–436. https://doi.org/10.1176/appi.ps.202000189

Suraev, A., Grunstein, R. R., Marshall, N. S., D'Rozario, A. L., Gordon, C. J., Bartlett, D. J., ...Hoyos, C. M. (2020a). Cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) for chronic insomnia disorder ('CANSLEEP' trial): Protocol for a randomised, placebo-controlled, double-blinded, proof-of-concept trial. *BMJ Open, 10*(5), Article e034421. https://doi.org/10.1136/bmjopen-2019-034421

Tallant, J. (2020). Cannabinoids for the treatment of cancer-related pain: A systematic review. *Cancer Nursing Practice, 19*(2), 37–42. https://doi.org/10.7748/cnp.2020.e1669

Tateo, S. (2017). State of the evidence: Cannabinoids and cancer pain—a systematic review. *Journal of the American Association of Nurse Practitioners, 29*(2), 94–103. https://doi.org/10.1002/2327-6924.12422

Treves, N., Mor, N., Allegaert, K., Bassalov, H., Berkovitch, M., Stolar, O. E., & Matok, I. (2021). Efficacy and safety of medical cannabinoids in children: A systematic review and meta-analysis. *Scientific Reports, 11*(1), Article 23462. https://doi.org/10.1038/s41598-021-02770-6

Trigo, J. M., Lagzdins, D., Rehm, J., Selby, P., Gamaleddin, I., Fischer, B., ...Le Foll, B. (2016). Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings*. Drug and Alcohol Dependence, 161*, 298–306. https://doi.org/10.1016/j.drugalcdep.2016.02.020

Trigo, J. M., Soliman, A., Quilty, L. C., Fischer, B., Rehm, J., Selby, P., ...Streiner, D. L. (2018). Nabiximols combined with motivational enhancement/cognitive behavioral therapy for the treatment of cannabis dependence: A pilot randomized clinical trial. *PLOS One*, *13*(1), Article e0190768. https://doi.org/10.1371/journal.pone.0190768

Tumati, S., Lanctôt, K. L., Wang, R., Li, A., Davis, A., & Herrmann, N. (2021). Medical cannabis use among older adults in Canada: Self-reported data on types and amount used, and perceived effects. *Drugs & Aging*, *39*, 153–163. https://doi.org/10.1007/s40266-021-00913-y

Turna, J., Simpson, W., Patterson, B., Lucas, P., & Van Ameringen, M. (2019a). Cannabis use behaviors and prevalence of anxiety and depressive symptoms in a cohort of Canadian medicinal cannabis users. *Journal of Psychiatric Research, 111*, 134–139. https://doi.org/10.1016/j.jpsychires.2019.01.024

Turna, J., Syan, S. K., Frey, B. N., Rush, B., Costello, M. J., Weiss, M., & MacKillop, J. (2019b). Cannabidiol as a novel candidate alcohol use disorder pharmacotherapy: A systematic review. *Alcoholism Clinical and Experimental Research*, *43*(4), 550–563. https://doi.org/10.1111/acer.13964

Urbi, B., Corbett, J., Hughes, I., Owusu, M. A., Thorning, S., Broadley, S. A., Sabet, A., & Heshmat, S. (2022). Effects of cannabis in Parkinson's disease: A systematic review and meta-analysis. *Journal of Parkinson's Disease*, *12*(2), 495–508. https://doi.org/10.3233/JPD-212923

Valverde, O., Noble, F., Beslot, F., Daugé, V., Fournié-Zaluski, M. C., & Roques, B. P. (2001). Δ⁹-tetrahydrocannabinol releases and facilitates the effects of endogenous enkephalins: Reduction in morphine withdrawal syndrome without change in rewarding effect. *European Journal of Neuroscience, 13*(9), 1816–1824. https://doi.org/10.1046/j.0953-816x.2001.01558.x

Vaughn, L. K., Denning, G., Stuhr, K. L., De Wit, H., Hill, M. N., & Hillard, C. J. (2010). Endocannabinoid signalling: Has it got rhythm? *British Journal of Pharmacology*, *160*(3), 530–543. https://doi.org/10.1111/j.1476-5381.2010.00790.x

Wadsworth, E., Cristiano, N., Gabrys, R., Renard, J., & Hammond, D. (2023). Cannabis consumption among adults aged 55–65 in Canada, 2018–2021. *Journal of Drug Issues*. *0*(0), 1–17. https://doi.org/10.1177/00220426231190022

Wang, J., Wang, Y., Tong, M., Pan, H., & Li, D. (2019). Medical cannabinoids for cancer cachexia: A systematic review and meta-analysis. *BioMed Research International,* Article 2864384. https://doi.org/10.1155/2019/2864384

Wang, L., Hong, P. J., May, C., Rehman, Y., Oparin, Y., Hong, C. J., Hong, B. Y., ...Busse, J. W. (2021). Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: A systematic review and meta-analysis of randomised clinical trials. *BMJ*. *374*, Article n1034. https://doi.org/10.1136/bmj.n1034

Winiger, E. A., Huggett, S. B., Hatoum, A. S., Friedman, N. P., Drake, C. L., Wright Jr, K. P., & Hewitt, J. K. (2020). Onset of regular cannabis use and young adult insomnia: An analysis of shared genetic liability. *Sleep*, *43*(5), zsz293. https://doi.org/10.1093/sleep/zsz293

Wong, S. S. C., Chan, W. S., & Cheung, C. W. (2020) Analgesic effects of cannabinoids for chronic non-cancer pain: A systematic review and meta-analysis with meta-regression. *Journal of Neuroimmune Pharmacology*. *15*(4), 801–829. https://doi.org/10.1007/s11481-020-09905-y

Wong, S. S., & Wilens, T. E. (2017). Medical cannabinoids in children and adolescents: A systematic review. *Pediatrics*, *140*(5). https://doi.org/10.1542/peds.2017-1818

Yanes, J. A., McKinnell, Z. E., Reid, M. A., Busler, J. N., Michel, J. S., Pangelinan., ...M. M., Sutherland. (2019). Effects of cannabinoid administration for pain: A meta-analysis and meta-regression. *Experimental and Clinical Psychopharmacology*, *27*(4), 370–382. https://doi.org/10.1037/pha0000281

Yassin, M., Oron, A., & Robinson, D. (2019). Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: An observational cross-over single centre study. *Clinical and Experimental Rheumatology, 37 Suppl 116*(1), 13–20. https://pubmed.ncbi.nlm.nih.gov/30418116

Zenone, M. A., Snyder, J., & Crooks, V. (2021). Selling cannabidiol products in Canada: A framing analysis of advertising claims by online retailers. *BMC Public Health, 21*, 1–10. https://doi.org/10.1186/s12889-021-11282-x