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Community series - purple haze: Issues on cannabis legalization, volume II

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Community series - purple haze: Issues on cannabis legalization, volume II

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Editorial: Community series - Purple Haze: issues on cannabis legalization, volume II

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Editorial on the Research Topic
Community series - Purple Haze: issues on cannabis legalization, volume II

Considering the progressive legalization of cannabis across jurisdictions, we prepared a Research Topic that addresses significant issues relevant for future legalization initiatives. This Research Topic follows a first Research Topic on the same theme (https://www.frontiersin.org/research-topics/11986/purple-haze-issues-on-cannabis-legalization). The current Research Topic seeks to: (i) document the psychiatric and cognitive consequences of cannabis products, used either for recreational or medical purposes; (ii) document the impacts of cannabis legalization in North America, with special attention to youth, emergency department visits and sex/gender differences; (iii) provide a framework for medical cannabis administration; and (iv) define priority areas deserving more research.

Among the potential harms of cannabis, the association with psychosis is one of the issues that has received the most attention in the context of recreational cannabis legalization. As Hall points out, the nature of this association is too often judged by the authors' preconceptions about the merits of recreational marijuana legalization (RML), with opponents of RML being prone to assert the causal nature of the association, and supporters being inclined to deny it. In his article, Hall shows that the literature is sufficiently robust to support a causal interpretation of the association between cannabis and psychosis. With nuance, he argues that one can nonetheless be in favor of RML, as taking a stance on such a policy requires considering all its advantages and disadvantages, and that presumed advantages (example: reducing the share of the illegal market, increasing potential access to prevention) may outweigh its disadvantages.

In addition to psychosis, the impact of cannabis on youth is another major concern. In their scoping review, Kaur et al. analyzed 140 studies to determine whether cannabis produces more harm in young people. The available literature shows that initiating cannabis use at a younger age is clearly associated with worse outcomes for psychosis and cannabis use disorder. Regarding depression and suicidality, the evidence is mixed, and there is a relative lack of data in the case of anxiety. Despite the methodological limitations of the studies (e.g., uncontrolled confounding factors), the authors argue that there is sufficient evidence to recommend to delay as much as possible the age of initiation of cannabis use.

The actual impact of legalizing cannabis for recreational use remains a controversial topic. To shed some light on the subject, Athanassiou et al. performed a systematic review of studies published to date. As quality criteria, the authors selected only longitudinal studies that compared key public health outcomes between regions (e.g., States) that had or had not legalized the substance. Thirty-two studies were identified showing that RML in the United States is associated with increases in the prevalence of cannabis use in adults, increases in healthcare-related service use, increases in traffic fatalities, increases in alcohol use, no change in cigarette use and an unexplained decrease in opioid prescriptions. The potential impact on RML on crime and suicide were insufficiently studied.

In the Canadian context, Rubin-Kahana et al. examined the impact of RML on youth. To date, the data do not suggest a marked increase in consumption among young people. On the other hand, preliminary results suggest a potential increase in hospitalizations and emergency department (ED) visits among young people, but these trends remain to be confirmed. In the future, research will need to pay close attention to high-potency cannabis use among young people. In a complementary manuscript, Matheson and Le Foll discussed the effects of RML as a function of sex and gender. Cannabis has traditionally been more prevalent in men than women. However, the gap between men and women is narrowing. It is not known whether RML may have played a role in this trend. It is important to bear in mind, however, that in general, men have a more favorable opinion of RML, and perceive less harm associated with the substance. Matheson and Le Foll highlight the lack of data on sex and gender differences in car accidents and hospitalizations, and the need to study the impact of RML on trans-gender and gender-diverse populations.

In an article devoted to cannabis-related ED visits, Crocker et al. observed an increase in ED visits following the legalization of recreational cannabis use. Although these events are not frequent, cannabis-related ED presentations are complex; hence, it would be relevant to make brief interventions available to those affected. Furthermore, with the increase in delta-9-tetrahydrocannabinol (Δ^9-THC) content in cannabis, the authors mention that it is reasonable to anticipate that the prevalence of cannabis-related ED visits could increase in the future.

The understanding of the impacts of RML extend beyond legal changes. The unfolding of changes in policy also critically matter. In Canada, the province of Ontario had the highest number of in-person retail stores 3 years after RML in October 2018. Using data from the *Ontario Cannabis Store*, Tassone et al. draw a detailed portrait of the products sold in this province. Beyond the diversity of products, what is particularly striking is that most inhaled products have concentrations of Δ9-THC higher than 20%. There is growing evidence that high-potency cannabis produces more harm (1). However, this literature is based on a cut-off of 10% to classify cannabis as having high-potency. These data illustrate the urgent need to update our knowledge on cannabis with a potency higher than 20%.

Regarding the legalization of cannabis for medical purposes, there are no clinical guidelines to follow. In order to fill this gap, Maccallum et al. propose a practical framework providing general recommendations relating to modes of administration, compounds contained in cannabis, dosage, frequency of administration, characteristics of treated individuals and drug-drug interactions. In an article on the hepatic metabolism of ingested cannabinoids, Smith and Gruber review drug-drug interactions. They discuss interactions between cannabidiol and certain drugs including anti-epileptics and antidepressants. Among the areas to be investigated in the future, the authors highlight the need to better understand interactions involving minor cannabinoids such as cannabinol.

Finally, in an article on the addictive potential of medical cannabis, Cooke et al. documented the number of people who developed a cannabis use disorder (CUD) during a clinical trial lasting 12 months ($n = 163$). Worryingly, they observed that 11.7% of participants and 17.1% of people with (nearly-) daily use developed a CUD during the intervention. The addictive potential of medical cannabis will require close monitoring in the future.

With increasing legalization in different jurisdictions, it is vital to allocate resources for research, prevention, treatment, and policy initiatives. In light of the findings discussed in this topic, it is important to establish ongoing monitoring and seize this opportunity to develop new prevention and harm reduction strategies.

Author contributions

SP wrote the manuscript. YK, AB, and MP provided critical comments. All authors approved the final version of the manuscript.

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Conflict of interest

MP was employed by Connecticut Council on Problem Gambling. MP has consulted for Opiant Pharmaceuticals, Idorsia Pharmaceuticals, AXA, Game Day Data, Baria-Tek, and the Addiction Policy Forum; has been involved in a patent application with Yale University and Novartis; has received research support (to Yale) from Mohegan Sun Casino, Children and Screens and the Connecticut Council on Problem Gambling; has participated in surveys, mailings, or telephone consultations related to internet use, addictions, impulse-control disorders or other health topics; has consulted for and/or advised gambling and legal entities on issues related to impulse-control/addictive disorders; has provided clinical care in a problem gambling services program; has performed grant reviews for research funding agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events, and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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A Clinical Framework for Assessing Cannabis-Related Impairment Risk

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Clinicians play an important role in promoting safe and responsible medical cannabis use. One essential component to safe use is considering a patient's risk of neurocognitive impairment. However, there remains a lack of practical guidance on how clinicians can evaluate this risk for medical cannabis patients. Here, a practical framework is presented for clinicians to assess and stratify cannabis-associated impairment risk. The proposed framework is intended to practically guide healthcare providers in gaining a more comprehensive review of a patient's impairment-related factors. This framework can be used to assess impairment risk for patients currently using or considering medical cannabis and is recommended for all patients who perform safety-sensitive duties. Healthcare providers (HCP) managing patient's medical cannabis or those conducting assessments to determine risk of impairment for safety-sensitive workplaces can utilize this framework to stratify patients' risk of impairment. Such assessments can inform patient-specific needs for support, education, and guidance, to ensure cannabis is used safely and responsibly.

Keywords: cannabinoids, medical cannabis, THC, impairment, occupational safety, driving

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INTRODUCTION

As medical cannabis use increases worldwide, concerns have arisen over the potential for cannabis impairment during safety-sensitive work or activities (1). Currently, medical cannabis is most strongly indicated for chronic pain, spasticity associated with multiple sclerosis, chemotherapy-induced nausea and vomiting, and treatment of intractable seizures in Dravet and Lennox-Gastaut syndromes (2). Although evidence is less clear, medical cannabis is also commonly used to treat symptoms associated with neuropathic pain, fibromyalgia, arthritis, sleep disorders, anxiety, and depression (3–6). There are several routes of administration for cannabis, the most common for medical use are inhalation (e.g., smoking or vaporizing) and oral ingestion (e.g., oils or capsules) (7–9). Each route of administration has unique pharmacokinetic and pharmacodynamic properties, leading to different times of onset and duration of action (10, 11). Dosing and administration of medical cannabis is complicated by not only having multiple methods of administration, but also a wide variety of product types and chemovars. Cannabis products vary in their composition of the two primary cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD). Typically, cannabis treatment protocols are tailored to the individual patient, with the exact dose and administration protocol being dictated by patient-specific needs and goals of treatment (8). All of these factors influence the potential of cannabis-related impairment.

Cannabis has the potential to impair multiple domains of neurocognitive function (12, 13). Evidence to date supports that THC is the primary psychoactive component in cannabis responsible for causing impairment (14). THC is a partial agonist for Cannabinoid receptor type 1 (CB1) and binds to CB1 receptors in regions of the brain involved with cognition, memory, anxiety, sensory perception, and motor coordination (15). This pharmacological action is what causes the dose-dependent disruption of cognitive and psychomotor domains important for safety-sensitive work or activities, such as driving motor vehicles (16, 17). In contrast, CBD, the other primary cannabinoid in cannabis, is generally considered non-impairing at low and moderate doses (See **Figure 1**) (18). Current evidence suggests CBD may cause sedation in some individuals at higher doses (19, 20). However, evidence is inconclusive and dose ranges are unclear. Some studies and reviews report no sedation at higher doses of 1,000–1,500 mg of CBD (11, 19, 21, 22), while others, primarily in pediatric epilepsy populations, report sedation at more moderate doses of 5–10 mg/kg/day CBD (20, 23, 24). Further investigation is needed to assess if there is a true dose-dependent effect or if sedation is due to the co-administration of other drugs such as antiepileptics or CNS depressants, which may lead to drug interactions resulting in increased sedation (20, 25, 26). As such, when discussing impairment there are a myriad of other factors that are important to consider beyond just the dose of THC that can contribute to an individual's risk (12).

Education and risk mitigation are important components of a clinician's role in promoting the safe and responsible medical cannabis use. Determining impairment risk has been a significant challenge for many clinicians. There is a lack of suitable testing metrics for determining cannabis impairment with a lack of established correlation between measurement of bodily fluids and level of impairment. Additionally, there is a lack of available well-rounded guidance or consensus recommendations to assess a patient's impairment risk. An additional challenge is the lack of literature available specifically focused on medical cannabis-related impairment. Here, we present a practical framework for clinicians to assess and stratify cannabis-associated impairment risk. Current evidence is interwoven within this practical framework.

FRAMEWORK FOR ASSESSING IMPAIRMENT

This impairment framework has been developed to help guide healthcare providers (HCPs) assessing a patient's impairment risk (**Table 1**). The idea for this practical guide was born from a needs assessment conducted by author CM for continuing education programs, as well as recent published reports revealing a HCP need for practical guidance on assessing the many aspects of cannabis-related impairment (27, 28). This framework was developed through a combination of expert clinical opinion, reviewing common questions in medical education sessions conducted by the authors, and reviewing the available literature. The first step in developing this framework was translating the clinical processes used by authors CM, MB, and MSA when assessing patient impairment risk in-clinic into a step by step framework. The next step was a collaborative discussion reviewing common questions and points of concerns asked during medical education run by authors, these were then incorporated in the framework. A practical overview of the literature was then conducted to elaborate on each framework component and make final adjustments to content. Finally, author consensus based on expert clinical opinion and relevant literature categorized factors into higher, moderate, and lower risk of impairment. The outcome of this process resulted in a practical framework that can help guide clinicians when assessing their patients' potential risk of cannabinoid-related impairment. It is best practice to complete an assessment of impairment risk for patients being considered for or who are currently using medical cannabis, especially those in safety-sensitive occupations (e.g., driving, operating heavy machinery, dealing with hazardous materials, or working in a safety-sensitive workplace).

Cannabis Initiation

How Is the Patient Using or Intending to Use Cannabis?

Clinicians should engage with their patients to understand the reasons why they are using cannabis. Medical and recreational cannabis have different goals of use (29, 30). In a strictly medical context, cannabis and certain cannabinoids are used to manage symptoms associated with a medical condition and improve an individual's ability to function (31). Patients with HCP authorizations for medical cannabis should have a formal diagnosis and documentation of their medical condition. In clinical settings, it has been observed that these patients typically titrate to the lowest dose required to obtain symptom relief, with acceptable side effects, and follow consistent and standardized dosing procedures (8). This pattern often leads to lower cannabinoid doses, thus reducing impairment risk and may support side effect tolerance development (8, 32). It is important to determine if cannabis was initiated by a knowledgeable, licensed HCP and if there is regular ongoing monitoring and support, as lack of education and guidance can increase the risk of misuse and possible impairment. Additionally, individuals reporting the use of medical cannabis, but are not under the guidance and monitoring of a knowledgeable HCP, may have use patterns more similar to recreational users (31).

Recreational cannabis is generally used by those seeking relaxation, euphoria and/or impairment. Recreational users often consume larger THC doses over a shorter period of time in order to obtain the desired effect. This pattern is associated with an increased risk of adverse effects and impairment (15, 33, 34). Recreational use also tends to be more inconsistent in product type and pattern of use (31, 35). This can lead to unpredictable effects, thus increasing the risk of impairment.

Some medical patients will also use cannabis recreationally. This too may increase risk of impairment as the effects and risks of THC are additive due to its highly lipophilic properties and accumulation of THC in adipose tissue (14). Clinicians are encouraged to approach the topic non-judgmentally. Consider one of the following approaches: "A number of my patients also

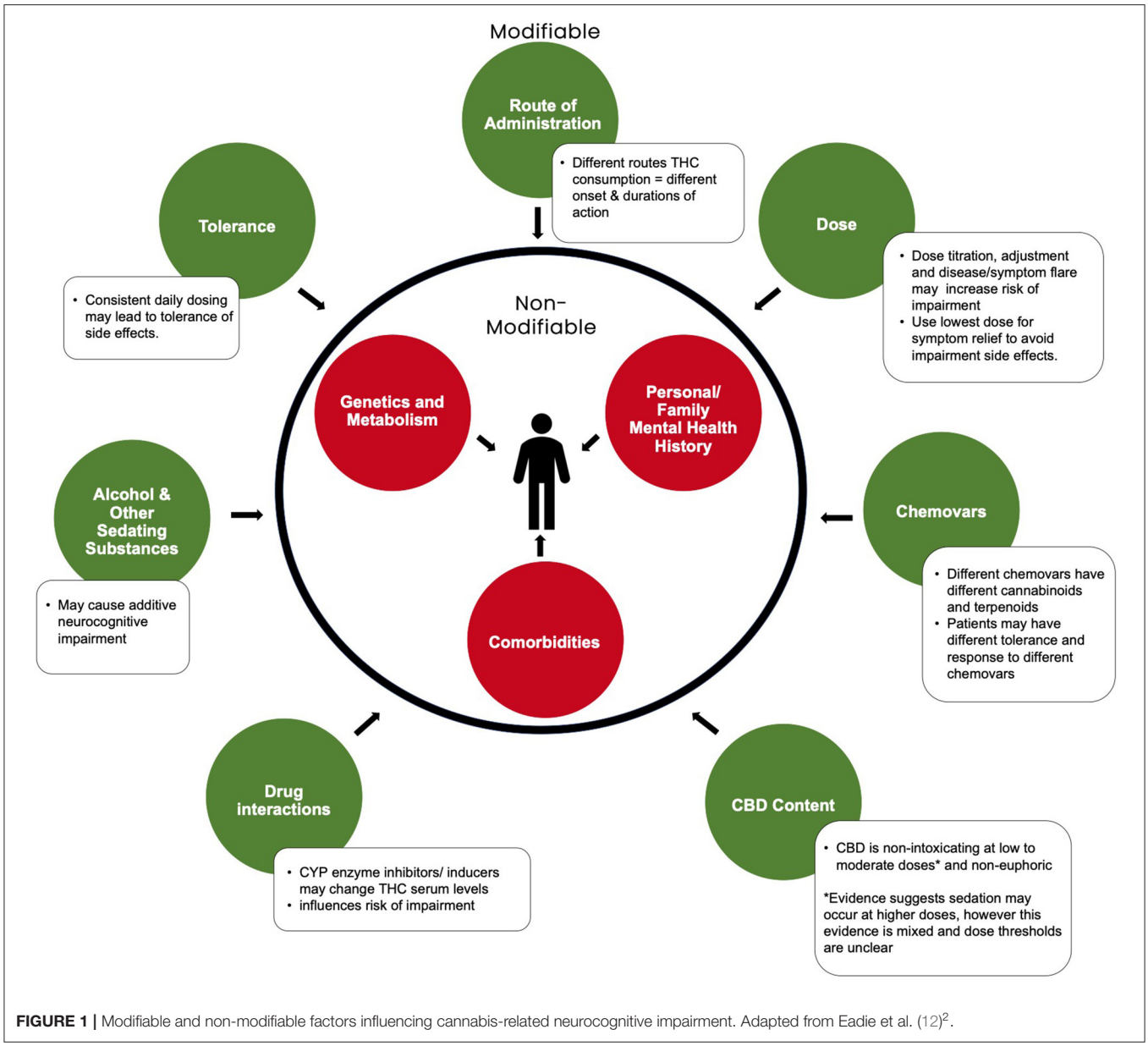

FIGURE 1 | Modifiable and non-modifiable factors influencing cannabis-related neurocognitive impairment. Adapted from Eadie et al. (12)[2].

use cannabis recreationally; do you use cannabis recreationally as well?" or "How often do you also use cannabis recreationally?".

Cannabis Product(s) Being Used

What Are the Methods of Cannabis Administration?

Different routes of cannabis administration have unique pharmacokinetic properties that dictate the duration of potential impairment and will when it is safe to engage in safety-sensitive activities (10, 36). It is important to understand the timeframe where a patient may be at risk in order to determine when cannabis can be used safely. Oral ingestion is a long-acting dosage form, with an onset of action within 1–2 h, lasting an average of 6–8 h (10, 37). Oral formulations are often ideal for medical use but there is also a greater period of potential impairment, and a risk for delayed impairment (38).

Inhalation is a short-acting dosage form, with an onset of 5–10 min, lasting an average of 1–4 h (14, 39). As a result, inhaled medical cannabis is commonly used for acute symptoms and presents a shorter period for potential impairment. However, there can be difficulties with accurate dosing, since length (time) and depth of inhalation significantly impact the cannabinoid dose consumed. This may increase risk of unintentional impairment.

We advise against the use of concentrated dosage cannabis forms for medical use (e.g., dabbing) as they are commonly associated with excessive impairment and health risks (40, 41). To date, local application of topical cannabinoids to intact skin does not appear to be associated with central effects, and thus can be used without risk of impairment (42).

TABLE 1 | Framework for assessing medical cannabis risk of impairment.

Cannabis initiation
How is the patient using or intending to use cannabis?
Cannabis product(s) being used
What are the methods of cannabis administration?
Is the cannabis source regulated, third party tested?
Dose, frequency, and length of use
What amount of THC and CBD is being used?
What is the frequency and time of day cannabis is being taken?
How long has the patient been stabilized on this dose and frequency?
Risk factors for impairment
Does the patient have any impairment-related adverse effects?
Are there patient factors that increase risk of impairment?
What other prescription or recreational drugs are being used?
Is the patient involved in a safety-sensitive occupation or duties?
How long between cannabis use and engaging in safety-sensitive activities?
Factors that may mitigate impairment
Does cannabis manage conditions that are associated with impairment?
Is the patient using CBD containing products?
Is there ongoing education and monitoring?

TABLE 2 | Adverse effects that may be associated with an increased impairment risk (9, 16).

Impairment-related adverse effects
Neurocognitive
• Cognitive effects (e.g., impaired short-term memory, decision-making, decreased concentration, divided attention)
• Dizziness
• Drowsiness
• Fatigue
Sensory-perceptual
• Ataxia or discoordination
• Blurred vision
• Headache
Mental health
• Anxiety
• Euphoria
• Psychosis/ paranoia
Cardiovascular
• Orthostatic hypotension
• Tachycardia (if results in anxiety, dizziness, syncope, or myocardial infarction)
Gastrointestinal
• Cannabis hyperemesis syndrome

Is the Cannabis Source Regulated, Third Party Tested?

Ensuring the cannabis product being used is from a regulated, third party tested supplier is important. Products from illicit sources may have mislabeled cannabinoid contents, presenting a risk of unexpected impairment. One study evaluating CBD products sold online, found that 21% of these products contained sufficient THC to produce impairment (43). Further, non-regulated products, especially purchased online, may contain synthetic cannabinoids or be more likely to be highly potent, increasing risk of impairment (40). Regulated products can provide some confidence that the label matches the product's cannabinoid content. Regulated products normally have strict regional requirements (state, provincial, or federal) for labeling and testing (40, 44).

Dose, Frequency, and Length of Use

What Dose of THC and CBD Is Being Used?

Different chemovars (strains) will have different cannabinoid content. Cannabis dosing takes into consideration the THC and/or CBD content of each plant chemovar. In dried cannabis flower it is labeled as a percentage of cannabinoid in the total weight (%/g), or by concentration in cannabis oils (mg/ml). The majority of impairing adverse events are THC-dose dependent (12, 45). Of note, tetrahydrocannabinolic acid (THCA) is the carboxylic acid form of THC in the "raw" plant. THCA is non-intoxicating and non-impairing (46) unless decarboxylation through heating occurs (47, 48).

There is increasing evidence to support that CBD is non-impairing. High oral doses of 100 mg of CBD up to supratherapeutic doses of 1,500 and 4,500 mg of CBD have not produced detectable effects on cognitive or motor function (11, 21, 22).

Determining what THC dose will elicit impairment remains highly patient-specific, regardless of the method of administration. Given the multiple factors responsible for impairment (**Figure 1**), it is challenging to separate effects of THC dose, specifically in determining a "safe" dose that will be non-impairing for all patients. Experimental studies utilizing neuropsychological battery tests, simulator or on-road testing, were conducted to assess the influence of cannabis on driving, cognitive, and psychomotor ability. In healthy, infrequent cannabis users, acute oral THC doses of 7.5 and 15 mg slightly impaired time perception, therefore also affecting motor response preparation and execution processes, impulsivity and inhibition (49), as well as episodic memory and learning (50). However, these same doses did not significantly alter performance on the Digit Symbol Substitution Test, Hopkins Verbal Learning Task, Digit Span Forward, Go/no-go, or the Delay or Probability discounting tasks (49). Other studies report that relative to placebo, 10 mg of oral THC did not appear to alter cognitive or psychomotor performance among healthy, infrequent cannabis users (51). Importantly, participants of these studies would not have been on stable doses of medical cannabis. A recent randomized, controlled trial found low, single doses of 0.5–1.0 mg inhaled THC did not result in impairment in processing speed (Reaction Time Test, RTI), episodic memory (Paired Associates Learning Task, PAL), working memory (Spatial Working Memory Test, SWM) or sustained attention (Rapid Visual Information Processing Test, RVP) in patients with chronic pain (52). While doses above 40 mg of THC are considered high and carry a substantial risk of impairment (32, 37). The risk of impairment for doses between these ranges

TABLE 3 | Factors to consider when assessing impairment risk (9, 10, 43, 50).

Consideration	Factors associated with a higher risk of impairment	Factors associated with a moderate risk of impairment	Factors associated with a lower risk of impairment
Cannabis initiation	**Not** initiated on medical cannabis by a HCP Patient is **not stabilized** on cannabis	Initiated by a HCP with **limited knowledge** of medical cannabis Patient has recently initiated cannabis or is still titrating dose of cannabis (**not stabilized)**	Initiated by a HCP **knowledgeable** in cannabinoid medicine Cannabis is used for a specific medical condition or symptoms *Patient has been **stabilized** on cannabis for **at least 2 weeks**
Product info	Products are **not** purchased from a regulated, third party tested supplier (19)	**Not all** products are purchased from a regulated, third party tested supplier (19)	All products are purchased from a regulated, third party tested supplier (19)
THC dosage	*Cannabis use includes use of **high dose THC** (above 40 mg THC/day) or use of cannabis concentrates (including dabbing)	*THC dosing **above 10 mg** THC/day but below 40 mg THC/day (9, 10)	*THC dosing **<**10 mg of THC/day Those working in safety-sensitive positions or workplaces may require even lower THC daily dose.
Restriction period	***Inhaled products:** <2 h prior to driving *__Inhaled products:__ <8–12 h after inhaling cannabis products for those in safety-sensitive positions/workplaces ***Oral ingestion:** <4 h prior to driving *__Oral ingestion:__ <12 h after ingesting cannabis products for those in safety-sensitive positions/workplaces	***Inhaled products:** <4–6 h prior to driving ***Oral ingestion:** <6–8 h prior to driving	**Inhaled products:** 4–6 h prior to driving (43). *__Inhaled products:__ At least 8–12 h after inhaling cannabis products for those in safety-sensitive positions/workplaces **Oral ingestion:** 6–8 h prior to driving (43). *__Oral ingestion:__ At least 12 h after ingesting cannabis products for those in safety-sensitive positions/workplaces Localized topical cannabis may be used on intact skin due to limited systemic absorption
Adverse events	*Reports **multiple** impairment related adverse effects of moderate to severe intensity	*Reports **one** impairment- related adverse effects of mild intensity	*Reports **no** impairment-related adverse effects
Concurrent medications and comorbidities	Patient has comorbidities associated with impairment (9, 50) *Using **≥ 2** other medications that may be impairing or result in additive sedation or adverse events	Patient has comorbidities that **may** increase risk of impairment (9, 50) *Using one medication that may be impairing or result in additive sedation or adverse events	Patient **does not** have any other comorbidities that increase risk of impairment (9, 50) ***No use of** other medications that may be impairing or result in additive sedation or adverse events
Recreational substance use	Patient **regularly** uses other recreational substances including recreational cannabis	Patient **occasionally** uses other recreational substances including recreational cannabis	Patient **does not** use any recreational substances including cannabis
Education and monitoring	**Not** monitored by a HCP (9). Only cannabis education was acquired from non-HCP sources	Monitored by a HCP with **limited knowledge** of medical cannabis (9) Basic education from HCP on safe medical cannabis use	Monitored by a HCP **knowledgeable** in cannabinoid medicine (9). Advanced HCP education on safe medical cannabis use

**Based on authors evidence-informed expert opinion.*

strongly depends on patient-specific factors. In alignment with previous literature (53), we believe *stable* doses below 10 mg/day generally carry a lower risk of impairment.

For dried product, evidence supports that most medical cannabis patients have therapeutic benefit from between 1 and 3 g of cannabis per day (44). Consuming over 5 g/day of dried cannabis flower is a potential flag of problematic use (37). Problematic use is associated with a high risk for cannabis impairment and should be intervened for a variety of health-related reasons.

What Is the Frequency and Time of Day Cannabis Is Being Taken?

Frequency and pattern of use are important in determining the total daily dose and the times of the day for which a patient may be at the highest risk of impairment. Greater frequency of use results in longer periods of potential impairment and less time between cannabis use and engaging in driving or safety-sensitive duties. Daytime THC use may present a greater safety risk, especially if the patient engages in safety-sensitive activities during the day. The pattern of use will depend on patient-specific goals. Assessing the timeframe between use of cannabis and driving or engaging in safety-sensitive positions/workplaces is imperative when assessing risk. If the frequency of use is such that an individual is using inhaled cannabis within 4–6 h prior to driving or 8–12 h prior to engaging in safety-sensitive positions/workplaces respectively, then the individual would be considered higher risk based on the frequency and time of day cannabis is taken. Given the longer duration of action of orally ingested cannabis, longer timeframes are recommended (**Table 3**).

How Long Has the Patient Been Stabilized on This Dose and Frequency?

As with any pharmacotherapy, periods of medication titration or dose adjustment increases the risk of adverse events. Chronic and continuous medical cannabis use can lead to tolerance to many potential adverse side effects such as fatigue, dizziness, and acute intoxication (54). This is similar to other prescription medications used in this patient population.

A recent systematic review and meta-analysis found that regular cannabis users experienced less impairment in discrete driving-related cognitive skills compared to occasional users following acute consumption of a single dose of THC (∼20 mg) (55). Other studies have corroborated these findings, reporting that frequent cannabis users (smoking ≥ 4 days/week) demonstrated less acute impairment across several neuropsychological tests compared to occasional users (smoking ∼1 day/week) as a potential consequence of tolerance (56). However, another recent systematic review of meta-analyses concluded that acute and non-acute, residual impairment (within minutes to hours post-acute intoxication phase) in executive function, processing speed, verbal learning and memory, and attention may occur with regular, mostly heavy, consumption despite potential tolerance (13). It is important to note that this low-to-moderate quality evidence was extracted from a heterogeneous group of studies which varied in the operationalization of cannabis use history (frequency), cognitive tests used, cannabis dose, and control variables employed. As evidence is still varied on whether regular consumption of cannabis can lessen the risk of acute impairment as a result of developed tolerance, it cannot be assumed that patients frequently using cannabis, even at medically appropriate doses, are not at risk of impairment.

Clinicians should actively discuss dose stability with patients to determine if tolerance is developing. HCPs should be cautious in recommending safety-sensitivity activities even in a patient with potential tolerance. Tolerance to cannabis, as with other substances, may not equate to complete lack of impairment.

Risk Factors for Impairment

Does the Patient Have Any Impairment-Related Adverse Effects?

Adverse effects are a common sign of an excessive cannabis dose. Common cannabis-related impairment adverse effects are not experienced by the majority of patients using medical cannabis when the THC starting dose is low and titration is slow. The presence of certain adverse effects may result in impairment (**Table 2**). Generally, if a patient experiences these adverse effects, safety-sensitive activities should be refrained from and adjustments to the cannabis regimen are recommended.

Are There Patient Factors That Increase Risk of Impairment?

Patients with comorbidities that result in fatigue, dizziness, or cognitive slowing may compound impairment (8, 12). Notable conditions to consider include, but are not limited to, older age, concurrent mental health conditions, substance use disorders, neurodegenerative disorders, sleep disorders, and chronic pain conditions (8, 57–59). These conditions alone, and in combination with cannabis, may impair an individual's ability to be alert and engage in normal cognitive or motor function. Additional patient factors that are important to consider are concurrent medications and driving/safety-sensitive occupations, which are discussed below (8, 12, 58, 59). Patients with factors that may cause additive impairment should be monitored more closely to ensure absence of adverse effects.

What Other Prescription or Recreational Drugs Are Being Used?

Drug interactions may increase risk of impairment. Medical cannabis patients commonly take other impairing medications to manage their condition(s). While cannabis is believed to be safe to use with most medications, clinicians should assess all other medications for potential interactions (60). Common prescription or over-the-counter medications that may pose a risk for additive impairment or sedation when combined with THC include antiepileptics, antipsychotics, benzodiazepines, opioids, tricyclic antidepressants, dimenhydrinate, diphenhydramine, or muscle relaxants (61). The use of recreational substances such as alcohol as well as other illicit substances can also cause increased impairment.

Since cannabis is metabolized in the liver by CYP 450 isoenzymes (THC: CYP2C9, CYP2C19, CYP3A4, and CBD: CYP2C19, CYP3A4), CYP inhibitors or inducers may cause pharmacokinetic drug interactions, which can impact the blood serum levels of cannabinoids or the interacting medication (61). It should be noted that there is an indirect potential for impairment with moderate to high doses of CBD when taken with other CYP3A4 inhibitors (e.g., anti-seizure medications such as clobazam) (62). Additionally, drug interactions that increase or prolong the availability of THC may lead to prolonged impairment. In patients with potential drug interactions, increased monitoring and drug levels, when appropriate, should be carried out until absence of impairment or adverse effects are ruled out.

Is the Patient Involved in a Safety-Sensitive Occupation or Duties?

The patient's specific lifestyle should be considered when determining risk of impairment. If a patient does not drive or work in a safety-sensitive position or workplace, the outcomes of impairment are generally less serious. Safety-sensitive activities can include such tasks as operating transportation, use of heavy machinery, and dealing with hazardous materials. The consequences of even mild impairment can be more profound in these circumstances, impacting the worker, their colleagues, the community, and the environment. Extra precaution and focus on mitigating impairment risk should be taken for those who work in a safety-sensitive position or workplace.

How Long Between the Use of Cannabis and When the Patient Engages in Safety-Sensitive Activities?

Although driving a personal motor vehicle is considered a safety-sensitive activity, those who work in safety-sensitive occupations, where impairment may lead to catastrophic consequences in

the workplace, may require more stringent restrictions in dose and timing of administration of cannabis. The more complex the task, the less likely individuals can compensate for the mild to moderate impairments associated with cannabis use. Due to the significant hazard associated with any impairment, tighter restrictions for those in safety-sensitive occupations should be considered and an abundance of caution is reasonable and recommended (63).

Regarding driving a car, a patient is generally considered low risk when driving the morning after inhaling a stable dose of THC the previous evening. Educating patients on windows of impairment in which driving should be avoided is critical. The 2021 Canadian Cannabis Survey revealed that 21% of people reporting cannabis use in the last 12 months had driven within 2 h of smoking or vaporizing. Of individuals reporting driving within 2 h, 78% reported they did not feel impaired and 22% reported that they thought they could drive carefully (64). This highlights the importance of HCP guidance to mitigate potential harms.

It is important to know the route of administration as each has a different duration of action and periods of potential impairment. This should be considered in the context of when cannabis is being used and when an individual is safe to operate a motor vehicle or performs any safety-sensitive duty.

A review containing six RCT's in medical cannabis populations found impairment resolved within 2–4 h post dose,[2] in line with several other clinical trials (56, 65, 66). However, until there is more robust literature for medical cannabis populations, a cautious approach of consuming THC at least 4–6 h, if inhaled, and 6–8 h, if ingested, prior to operating a personal motor vehicle is suggested (6, 29).

Longer duration between timing of dose and the start of work, as well as tighter restrictions on dosing of THC may be required for patients who work in a safety-sensitive position or workplace. We advise waiting at least 8–12 h, if inhaled, and 12 h, if ingested, prior to engaging in safety-sensitive positions or workplaces.

Factors That May Mitigate Impairment

Does Cannabis Manage Conditions That Are Associated With Impairment?

Certain medical conditions can increase the risk of impairment. Studies have shown conditions such as multiple sclerosis, insomnia, epilepsy, anxiety, and depression have an increased risk of motor vehicle accidents (67–69). Reducing or eliminating the symptoms associated with these medical conditions can therefore decrease risk of impairment. If medical cannabis is successful in controlling symptoms that may impact motor or cognitive function on their own, individuals may actually have a lower risk of impairment (70).

Is the Patient Using CBD Containing Products?

Evidence is still varied on whether or not CBD can lessen the impact of THC-associated side effects (71), but using products that contain CBD may allow for a reduced THC dose required due to synergistic effects (72). THC and CBD combinations were also associated with positive effects on symptoms, while experiencing significantly less paranoia and anxiety than THC-only products (72). From a clinical and safety standpoint, CBD is a preferred choice for individuals that engage in safety-sensitive activities. It is important to note that many CBD-dominant products still contain low levels of THC.

Is There Ongoing Education and Monitoring?

Many individuals consume medical cannabis without proper safety education (73). As per best practice standards, HCPs should provide education on side effects, product/chemovar selection, activity limitations, dosing and titration, method of administration, and treatment monitoring to reduce the risk of patient harm (8, 32). The frequency of monitoring will depend on patient specific circumstances, clinician experience, and guidelines by local regulatory bodies. HCPs are advised to tailor the frequency of monitoring to reflect the benefit and risk considerations for the individual patient.

DISCUSSION

The lack of suitable testing metrics poses a challenge in determining cannabis-related impairment. The proposed framework is intended as a practical guide for HCP's to comprehensively assess and stratify the potential risk of impairment in their patients. This information guides discussion and patient education regarding these potential risks and allows for adjustments to mitigate or reduce the risk of impairment. This is especially important for individuals who perform any safety-sensitive activities.

Whether it be returning to work, driving, or working in a safety-sensitive position or workplace, the potential for cannabis impairment should be evaluated. Factors associated with different levels of impairment risk are summarized in **Table 3**. To stratify risk for any patient, each factor must be considered and assessed. If any considerations fall under higher risk for impairment, the individual is considered higher risk, regardless of the number of risk factors in the moderate or lower risk of impairment categories. Similarly, if any considerations fall under moderate risk, with no higher risk of impairment considerations, the individual is considered at moderate risk of impairment. An individual can only be considered to be at lower risk of impairment if all considerations fall under the lower risk category.

The framework presented in this piece is intended as a proposed guide to help clinicians assess risk of cannabinoid-related impairment in their patients. However, it is not without limitations. Although the framework discussed is commonly used in-clinic by authors, it has not been formally evaluated. Thus, we cannot formally speak to its reliability or validity. Despite this, the current lack of available guidance on the topic gives merit to share available guidance while more standardized processes are developed. Second, cannabis-related impairment is a complex topic, as there is a wide range of domains through which impairment may occur and there is notable variability between patients. While this framework is meant to provide a general overview, it should not be forgotten that each patient requires an individualized assessment and may have

unique factors that influence impairment risk. Third, using this framework relies on patients providing honest and complete information. Without this, the guidance could be misinformed and could cause liability for HCPs and those relying on the risk assessment (employers for example). This stresses the importance of developing good rapport and trust with the patient to promote open and honest conversation. Additionally, taking the time to educate the patients on the danger of engaging in safety sensitive activities or work and how to mitigate this risk is key.

Future directions in this work should look at the reliability and validity of this framework more formally. Developing a points system may be a useful avenue to pursue to help consider all risk factors more clearly. Medical cannabis patients are a heterogenous population, thus another avenue would be investigating how cannabis-related impairment differs between medical populations, and if there are differing key factors that may promote or mitigate impairment.

CONCLUSION

Factors discussed in the framework can impact the degree and duration of impairment. Although this framework is guided by the current evidence, more research in this area can provide stronger guidance on potential risk factors for cannabis-related impairment. Each patient will have unique considerations. Proper screening and evaluation of a patient can help promote the safe and responsible use of medical cannabis.

AUTHOR CONTRIBUTIONS

CM was primarily responsible for the conceptualization and overall intellectual leadership of this project. In collaboration with CM, LL wrote the first draft of this manuscript with additional support from CP. AC, MB, and MS-A contributed to revising the manuscript with additional intellectual input. All authors contributed to the article and approved the submitted version.

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The impact of cannabis legalization for recreational purposes on youth: A narrative review of the Canadian experience

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Cannabis legalization for non-medical purposes (subsequently referred to as "cannabis legalization" or "legalization") took place in Canada in October 2018. One of the federal government's stated goals with cannabis legalization was to protect Canadian youth from cannabis-related harms. The main objective of this narrative review is to describe the impact of cannabis legalization on Canadian youth. To that end, we discuss the regulation of the Canadian cannabis market, outline changes in the epidemiology and parameters of cannabis use (modes of use, potency of cannabis) among youth, and discuss prevention and education initiatives related to cannabis. The Canadian model differs from other jurisdictions that legalized recreational cannabis use, especially with regard to a higher degree of government regulation of the cannabis market. Another difference is the development and endorsement of lower-risk cannabis use guidelines to educate the public and health professionals. The results available for this review cover only 3 years post-legalization. Cannabis legalization in Canada brought an apparent increase in use among Canadian older than 25. However, results for youth are mixed, with the majority of studies showing no pronounced increase. Notably, the trend of a decrease in adolescents' cannabis use seen pre-legalization may have reversed. Emerging evidence also suggests that cannabis-related hospitalizations and emergency department visits among Canadian youth may have increased due to cannabis legalization. Data about changes in the age of initiation, the influence of legalization on sex and gender, and race/ethnicity are limited, with evidence suggesting that the age of initiation slightly increased. So

far, there is limited data about the impact of cannabis legalization on Canadian youth. Further long-term monitoring and research to assess the effects of cannabis legalization on Canadian youth.

KEYWORDS

youth, adolescents, legalization, cannabis policy, Canada, cannabis (marijuana)

Introduction

Cannabis is one of the most globally prevalent psychoactive substances (1), with the onset of use usually in mid-adolescence (2, 3). Cannabis use has been linked to many short- and long-term adverse effects (4) including motor vehicle accidents (5), respiratory diseases (6), higher risk for acute myocardial infarction among people aged 15–22 (7), and cannabis use disorder (4, 8). In addition, youth who use cannabis are at increased risk for adverse mental health and cognitive outcomes, including development and exacerbation of early-onset psychosis (9), depression and anxiety (10), suicidal ideations and suicide attempts (11), alteration of brain development and structure (12, 13) lower educational attainment (14, 15), lower cognitive function, and decreased motivation (13). Also, individuals using cannabis during youth are at increased risk for addictive behaviors later in life (4).

The production, distribution, and consumption of non-medical cannabis were legalized in Canada at the federal (national) level in October 2018 (16). The federal government determines the types of cannabis products that can be legally sold. At the time of legalization, dried or fresh cannabis, cannabis oil, and cannabis seeds were the legal products. Edibles, extracts and topicals became legal 1 year later, and drinks 2 years after that (17).

Unsurprisingly, proposals for cannabis legalization for non-medical purposes (subsequently referred to as "cannabis legalization" or "legalization") were controversial in Canada, especially in the context of protecting youth. The federal government stated that it was taking a public health approach, and that the *Cannabis Act* had three main goals: to "keep cannabis out of the hands of youth, keep profits out of the pockets of criminals, [and] protect public health and safety by allowing adults access to legal cannabis" (16, 18). The *Canadian Medical Association Journal* published an editorial in 2017 stating that the proposed legislation would fail to protect Canadian youth (19), to which others responded that prohibition was also harmful to youth and that legalization would provide the opportunity for strict regulation that would reduce cannabis-related harms (20, 21). In general, Canada's public health and substance use sectors were in favor of cannabis legalization for non-medical purposes (22, 23) while its medical community tended to be against it (24). As part of its approach to cannabis legalization, the federal government endorsed Canada's lower-risk cannabis use guidelines (25), which were designed as an evidence-based means of educating the public and health care professionals to reduce cannabis-related harms (25, 26).

TABLE 1 Information sources used for this narrative review.

- Electronic databases searches (e.g., Google scholar) for relevant journal articles
- Internet hands searches of the references of the retrieved literature (e.g., policy reports, periodical surveys, governmental websites)
- Professional experience in writing several documents on cannabis legalization for recreational purposes in Canada
- Discussion with experts in the field of cannabis legalization for recreational purposes in Canada

This narrative review will focus on the impact of cannabis legalization on youth in Canada. This review aims to provide a broad description of the Canadian experience that may be of interest for jurisdictions considering the legalization of cannabis for non-medical purposes. We will describe the regulation of cannabis legalization for non-medical purposes and changes related to cannabis use and cannabis-related behaviors. Specifically, we will look at the prevalence of cannabis use, alternative modes of consumption, the potency of cannabis, age of first use, negative consequences related to use, and education regarding cannabis. This paper will use the World Health Organization's youth definition of ages 15–24 (27).

Methods

Information used to write this narrative review was collected from the sources listed in Table 1.

Cannabis regulation in Canada

Cannabis legalization in Canada took place with the passage of the *Cannabis Act* (16). While the *Cannabis Act* applies to the entire country, due to the nature of Canada's political system, some aspects of cannabis regulation have been set by the federal government and others by the governments of Canada's 10

provinces and three territories. Here we will discuss the elements of Canada's cannabis regulations most relevant to youth.

Minimum age

The *Cannabis Act* set the minimum age for legal cannabis purchases at 18, with the provision that provinces and territories could raise (but not lower) it if desired (16). All but one opted to harmonize the minimum age for cannabis and alcohol, resulting in a minimum age of 19 everywhere except Alberta and Québec, where it was left at 18; later, Québec raised the minimum age for cannabis to 21. Notably, Québec's provincial public health institute opposed the increase in the minimum age, recommending instead that youth aged 18–20 be allowed to purchase only lower-risk products (maximum 10% THC) and smaller amounts (maximum 10 g of dried cannabis) (28).

The Act also states that underage individuals cannot legally possess more than 5 g of cannabis—in other words, youth under 18 cannot legally acquire cannabis but technically can possess under 5 g without legal consequences. This measure is "ostensibly in place to ensure that youth are not arrested for possessing small amounts of the drug" (29). Minors possessing over that amount may be charged under the *Youth Criminal Justice Act*, which prioritizes extra-judicial measures in order to avoid criminalizing youth (30). Provinces have also implemented their own penalties for underage possession of cannabis; generally, it is treated like underage possession of alcohol, punishable by a fine (31). This is further discussed below.

The *Cannabis Act* also raised the penalties for adults providing cannabis to a person under the age of 18 and for "using a youth to commit a cannabis-related offence," both to a maximum of 14 years imprisonment (16).

Possession and consumption

The *Cannabis Act* set upper limits on personal possession of cannabis by adults, with provinces and territories able to lower those limits if desired. Individuals above the minimum age can hold a maximum of "30 g of legal cannabis, dried or equivalent in non-dried form" in public (16). They can also grow up to four cannabis plants at home. However, two provinces (British Columbia and Québec) also placed limits on the amount of cannabis that can be possessed by a household (1 kg and 150 mg, respectively), and two provinces (Manitoba and Québec) banned home cultivation entirely (32).

Regulation of public cannabis use is left to provinces and territories (16). All limit the public smoking or vaping of cannabis in some way. Seven provinces and territories ban public cannabis smoking and vaping altogether. The other six allow cannabis smoking and vaping only in locations where tobacco smoking and vaping are allowed (32).

Retail sales

Regulations in this area are determined by provinces and territories. Five have adopted public retail systems, in which government-owned entities are responsible for cannabis sales, online and/or in storefronts [several jurisdictions in Canada have this type of system in place for alcohol sales (33)]. Two have adopted private retail systems, in which sales are left to the private sector. Six have hybrid public/private (but private-dominant) systems, typically with a government entity responsible for online sales and in-person retail left to the private sector (32). The availability of legal cannabis varies accordingly: jurisdictions with private retail systems tend to have far higher numbers of stores per capita than those with public retail (34, 35).

Provinces and territories also differ with respect to limitations on retail locations (32):

- Five jurisdictions have a requirement that cannabis stores maintain a certain distance from schools—generally 150 m. Three allow communities to determine such requirements for themselves. Of note, the remaining five jurisdictions with no formal limitations have public retail systems, meaning that those provincial/territorial governments have direct control over where cannabis stores will be established.
- Eight jurisdictions allowed municipalities to opt out of hosting cannabis stores. We are not aware of any reviews of municipal cannabis store bans across Canada. However, Ontario, Canada's largest province by population, gave municipalities a one-time opportunity to opt out of having cannabis stores within their boundaries, and 19% (77 of 414) chose to do so—though 10 municipalities later reversed that decision (36). As a result, currently, about 18% of Ontario's population lives in municipalities where cannabis stores are not allowed and legal cannabis must be purchased online or by travelling to a municipality where stores are permitted.
- Significantly from a public health perspective, no province or territory has a formal limit or cap on the overall number of cannabis retail locations.

The packaging and labeling requirements described below apply to all cannabis products; the *Cannabis Act* also prohibits products that are appealing to youth (16). Further, cannabis edibles, extracts, and topicals are subject to THC limits: edibles, for instance, may contain no more than 10 mg of THC per package (37). For comparison, the state of Colorado sets a maximum potency for cannabis edibles of 10 mg of THC

1. The standardized cannabis symbol
2. The brand name of the cannabis product
3. THC and CBD content
4. Health warning message
5. Other brand element

FIGURE 1
The anterior side of cannabis packaging in Canada. Source: ©All rights reserved. Packaging and Labelling Requirements. Health Canada, modified 2019. Adapted and reproduced with permission from the Minister of Health, 2021.

6. Other required information about the cannabis product
7. Non-required information about the cannabis product
8. Nutrition facts table
9. List of ingredients
10. Bar code

FIGURE 2
The posterior side of cannabis packaging in Canada. Source: ©All rights reserved. Packaging and Labelling Requirements. Health Canada, modified 2019. Adapted and reproduced with permission from the Minister of Health, 2021.

per serving, but allows up to 100 mg of THC per package (38). In Canada, illegal edibles seem to contain more THC than legal ones, with one study finding illegal products with over 150 mg of THC (39).

Legal sources of cannabis are slowly replacing illicit ones. The percentage of people who use cannabis aged 15+ who reported obtaining at least some of their cannabis from legal sources rose from 23% in 2018 to 47% in 2019 and 68% in 2020 (40).

Advertising, marketing and promotion

The *Cannabis Act* determines regulations in this area and they apply to the whole country. In addition to age restrictions, the federal government cites rules in this area as key to "protecting youth" (16). Advertising rules are quite strict: advertising is essentially banned outside of the point of purchase (i.e., cannabis stores) and celebrity endorsements are not allowed (37). In addition, cannabis products must be sold in plain packaging with standardized fonts (see Figures 1, 2 below); minimal brand elements are allowed. There is certain required information, including THC and CBD content and a standard health warning.

In summary

Since the federal government introduced the *Cannabis Act* in 2016, it has continually emphasized the protection of youth as its main reason for cannabis legalization (36). Its stated rationale is that prohibition failed to curtail youth cannabis consumption, and legalization would provide the opportunity for cannabis to be strictly regulated (41). However, in promoting the *Cannabis Act*, the federal government went further, stating on numerous occasions that cannabis legalization would "keep cannabis out of the hands of kids" (36). While this claim was widely questioned [see (36) for a discussion], this priority of protecting youth is reflected in the legislation itself, which states at the outset that its purpose is to "protect the health of young persons by restricting their access to cannabis; [and] protect young persons and others from inducements to use cannabis" (37). As discussed below, so far there is limited data about the impact of cannabis legalization on Canadian youth. For now, we can simply point out that Canada's regulatory model looks very different from that of other jurisdictions with legal cannabis, especially those in the United States.

The most apparent difference between Canadian and American cannabis regulation is in the area of advertising and promotion: no US state has a ban on advertising or

a requirement that cannabis be sold in plain, standardized packaging [due to constitutional protection of "commercial speech," such regulations may not be possible in the US (42)]. There is emerging evidence that Canada's plain packaging makes cannabis less appealing to youth (43). Since there is strong evidence that youth are particularly susceptible to tobacco and alcohol advertising (44, 45), the ban on cannabis advertising is also noteworthy. Both of these regulations are among the measures recommended to the federal government by experts in the public health and substance use sectors (22, 46). However, violations of advertising rules by licensed cannabis firms seem widespread on the Internet, especially on social media (47); in addition, the cannabis industry has been lobbying for the ability to advertise and for plain packaging to be eliminated (48).

Cannabis use prevalence among Canadian youth

This section will discuss trends in youth cannabis use since Canadian cannabis legalization. In Canada, a number of periodic surveys track the prevalence of cannabis use. We will present the available results from the surveys including individuals below 18 years old. Two of the surveys are specifically cannabis-related: The National Cannabis Survey (NCS) and The Canadian Cannabis Survey (CCS). The main aim of both surveys is to evaluate the impact of the *Cannabis Act* on cannabis-related behaviors/approaches (49, 50). The CCS is an online cross-sectional survey that has been conducted annually since 2017 with participants 16 and above (49). The NCS is another cross-sectional survey that has been conducted quarterly since 2018 (40). Other surveys that will be discussed do not focus primarily on cannabis. The Canadian Student Tobacco, Alcohol and Drugs Survey (CSTADS), is a cross-sectional survey, sampling students from grades 7–12 every 2 years (51, 52). The Cannabis use, Obesity, Mental health, Physical activity, Alcohol use, Smoking, and Sedentary behavior (COMPASS) is a survey with both cross-sectional and longitudinal data of high school students from four provinces in Canada (53, 54). And the Tobacco and Vaping Survey, which is a multi-wave survey conducted in Canada, England, and the United States (55). Table 2 presents the prevalence of cannabis use in the Canadian youth population before and after legalization by the different surveys; when applicable, the rate of daily or almost daily use is presented. We included only studies that presented pre- and post-legalization (2017–2021) data.

Before cannabis legalization for non-medical purposes

Canada has one of the highest youth cannabis use rates in the world (61, 62), and the prevalence of use among Canadian youth is about double the prevalence of use among people 25 years and older use (49). Nonetheless, data from pre-legalization years show a decreasing trend in adolescents' cannabis use (63–65).

After cannabis legalization for non-medical purposes

A 2018 Canadian survey found that a substantial proportion of Canadian youth intended to try cannabis for the first time or increase their use following cannabis legalization (66). Accordingly, data collected in the CCHS throughout 2018 (67) show that use prevalence has increased to 16.3%, compared to 10.7% in 2017 among those aged 12–24 years old (64). CCS data also report an increase in the prevalence of past-year use between 2018 and 2020. In 2018, 36% of Canadian aged 16–19 years old endorsed cannabis use. In 2019 and 2021 this figure increased to 44% (56–58). This survey also showed an increase in cannabis use among Canadian aged 20–24, with the prevalence of increased from 44% in 2018 to 51% in 2019 and 52% in 2020 (56–58). Results from waves 1–3 of the Youth Tobacco and Vaping Survey also found that cannabis use prevalence increased significantly between 2017 and 2019 (55). This study also showed a significant increase in daily use [adjusted odds ratio (AOR) = 2.49] (55).

However, other data collected after legalization show no marked change in youth cannabis use. Results from the 2020 NCS report an increase in past-3 months use and daily use among 18- to 24-year-old Canadians compared to 2018 (pre-legalization) and 2019; however, the change is not statistically significant (40). Similarly, cross-sectional data from the COMPASS survey suggests an unremarkable increase for "ever use" (AOR = 1.05) in 2018–19 compared to 2016–2017 among Canadian high-school students, while no significant change was recorded in current and regular use. Longitudinal data from this study suggest that the differences between pre and post-legalization cohorts are minor (53). Data from the 2018 CSTADS found no change in use prevalence among students in grades 7–12 compared to 2016–17 (60).

Importantly, the most recent data from the 2021 CCS show a statistically significant decrease in youth cannabis use compared to 2020, with 37 and 49% of participants aged 16–19 and 20–24 (accordingly) reporting past year cannabis use, compared to 44 and 52% in the same age groups in 2020 (59). Unfortunately, so far, there are no other available survey results representing cannabis use in 2021 or 2022.

In summary, there are mixed results related to youth pre- and post-legalization cannabis use. Most studies show no pronounced/statistically significant increase; a few found an increase in youth cannabis use, and the most recent 2021 CCS, found a decrease in youth cannabis use. There is contradictory evidence regarding regular and daily or

TABLE 2 The prevalence of Cannabis use in the Canadian youth population before and after legalization.

Survey name	Age group	Time period	Prevalence of use (%)[mathbfe]	Prevalence of daily/almost daily use (%)[f]	1-6 times per week	Regular use
Canadian Cannabis Survey	16–19	2017	41	N.A.	N.A	N.A
(49, 56–59)		2018	36	N.A	N.A	N.A
		2019	44	N.A	N.A	N.A
		2020	44	21	N.A	N.A
		2021	37	20	N.A	N.A
	20–24	2017	45	N.A	N.A	N.A
		2018	44	N.A	N.A	N.A
		2019	51	N.A	N.A	N.A
		2020	52	26	N.A	N.A
		2021	49	29	N.A	N.A
National Cannabis Survey (40)	15–17	2018 Q1	[a]	[a]	N.A	N.A
		2019 Q1	[a]	[a]	N.A	N.A
		2020 Q4	19.2[b]	[a]	N.A	N.A
	18–24	2018 Q1	28.1	9.9[b]	N.A	N.A
		2019 Q1	34.3	12.5[b]	N.A	N.A
		2020 Q4	35.6	16.3[b]	N.A	N.A
Canadian Student Tobacco, Alcohol, and	Grade 6–12 students	2014–15	17	N.A	N.A	N.A
Drugs Survey (60)	Grade 7–12 students	2016–17	17	N.A	N.A	N.A
		2018–19 (October 2018 and June 2019)	18	N.A	N.A	N.A
Cannabis use, Obesity, Mental health,	Grade 9–12 students	2016–17	15.9	3.9	5.5	9.4
Physical activity, Alcohol use, Smoking, and		2017–18[c]	16.4	3.9	5.6	9.5
Sedentary behavior (COMPASS)[g] (53)		2018–19[d]	16.9	3.7	6.1	9.7
Tobacco and Vaping Survey (55)	16–19	2017	22.5	12.7	N.A	N.A
		2018[c]	23.4	13.7	N.A	N.A
		2019	27	17.6	N.A	N.A

[a]Unreliable to be published; [b]use with caution; [c]pre-legalization; [d]post-legalization; [e]all the results represent past-year prevalence, besides the National Cannabis survey in which results present prevalence of past- 3 months use; [f]for COMPASS study and the Tobacco and Vaping Survey the results present current daily use; Q1, The first quarter; Q4, The fourth quarter; N.A, Not available.

almost daily use, with some results suggesting no pronounced change and others suggesting an increase in youth daily use. Importantly, pre-legalization, Canada witnessed a trend of a decrease in adolescents' cannabis use. The initial evidence from the 2 years post-legalization suggests a possible reversal of that trend; however, the most recent study representing 2021 shows a decrease in cannabis use among both adolescents and emerging adults. Overall, results should be taken with caution as they are mixed and represent only up to 3 years post-legalization. This is important as a previous cross-national study suggests that the link between youth cannabis use and cannabis liberalization may only be statistically significant 5 years post-liberalization (68). Additionally, the surveys which target high school students might represent an underestimate since young who dropped out of school have higher rates of cannabis use (69).

The effect of the COVID-19 pandemic

In March 2020, following the onset of the COVID-19 pandemic, Canadian provinces enacted new public health measures, including social distancing and closures of in-person schools (including high schools, colleges and universities) (70). Given the interference of those changes in daily routines, it was speculated that a shift in cannabis-related behaviors would be seen. So far, studies conducted in this context only evaluated the early and mid-stages of the COVID-19 pandemic. Their results are presented below.

One study found that fewer Canadians aged 16–18 reported cannabis use after social distancing practices started, but those who used reported increased frequency of use (71). Another study found that cannabis use among high school students increased between 2019 and 2020 (after the start of

social distancing practices). However, this increase was smaller compared to the 2018–2019 period. In this study, the youth already using cannabis did not increase their use (72). Cross-sectional repeated data from the CCS 2020 and 2021 show that in 2020 many people who use cannabis have either increased or decreased in 2020 (56). However, in 2021 more people who use cannabis have increased their cannabis use in both age groups: 16–19 and 20–24 years old (59).

Interestingly, in a longitudinal study covering 4 months pre-pandemic and 3 months post-pandemic, participants aged 19–25 years who followed the recommendation to self-isolate were using 20% more cannabis than those who did not follow self-isolation recommendations. Using cannabis to cope with depression predicted an increased quantity and frequency of cannabis use during the pandemic (73).

In summary, both increases and decreases in cannabis use were observed in the early stages of the COVID-19 pandemic. However, more recent data suggest an overall increase in cannabis use among Canadian youth. Self-isolation and using cannabis to cope with depression were associated with increased cannabis use. Also, the majority of the available data represent the early period of the pandemic, and there is a need for evidence representing later and post-pandemic periods and also evidence about vulnerable populations, such as people that deal with mental health disorders.

Cannabis potency

Cannabis potency is typically defined as the percentage of delta-9-Tetrahydrocannabinol (THC) (the main psychoactive component) in the cannabis product (74). In the past decades, there has been a strong increase in cannabis potency (4, 75–77). For example, in the United States, the mean potency of cannabis plant material increased from 8.9% THC in 2008 to 17.1% THC in 2017 (76). This trend is concerning, as higher-potency cannabis is associated with more short and long-term health risks (74, 78). While THC levels have increased over time, cannabidiol (CBD) levels have not substantially changed (77) CBD is another major component of cannabis. Evidence suggests that CBD is well-tolerated and has relatively very few serious adverse events, such as drug-to-drug interactions, pneumonia, hepatic abnormalities, diarrhea, fatigue, vomiting and somnolence (79, 80). CBD is correlated with several positive effects, such as neuroprotective (81), anxiolytic (82), and antipsychotic (83) effects. Of note, with higher THC to CBD ratios, there is a potential to exacerbate the adverse effects of THC [see (84) for a review].

CCS cross-sectional data show that in 2020, 35.5% of people who use cannabis between the ages of 16–19 reported using strains with high THC, as did 32.9% of people who use cannabis aged 20–24. 5.1% of the 20–24 years old group used only THC (unfortunately, data about the use of only THC is unavailable for the younger age group in 2020) (85). The 2021 CCS showed that around one-third of people who use cannabis ages 16–19 and 20–124 reported using cannabis strains with higher THC and lower CBD and around 8% used strains with only THC (85). Another study that tracked the potency of legal and illegal cannabis products for 2 months following legalization in Canada found a mean THC concentration of 16.1% in the legal market and 20.5% in the illegal market (86). These studies both took place after legalization; to the best of our knowledge, no published study has assessed changes in cannabis potency in Canada before and after legalization.

In summary, data suggest that in the last few years, higher-potency cannabis has gained popularity; however, there is no available data about changes in potency before and after legalization. Research is needed to monitor future changes in this area.

Changes in modes of cannabis use

Data from the US suggest that modes of cannabis use other than smoking (e.g., vaping and edibles) increased in popularity along with the liberalization of cannabis (87). This finding is important, as edible cannabis products tend to have higher potency and delayed effects compared to smokable products, and thus may lead to over-intoxication (88, 89). Also, when removed from their packaging, they may look like food, thus increasing the risk for unintentional consumption, especially by children (89). Vaping cannabis is also a concern. Although it exposes the individual to fewer toxins compared to smokable cannabis, it has been associated with cases of acute lung injury and often involves high-potency cannabis products, which increases long and short-term risks (90). Potent cannabis extracts also increase the risk of over-intoxication, and limited evidence suggests that frequent extract use is linked with problematic cannabis use, cannabis use disorder and mental health problems (89). The long-term health impact of these alternative modes of cannabis use is unknown (89).

One study suggests that smoking was still the most prevalent mode of use among Canadians aged 16–19, with no significant changes between 2017 and 2019. However, in those years, e-cigarettes and extracts have gained popularity (AOR for e-cigarette use was 2.39 and the AOR for extract use 1.61 in 2019 compared to 2017) (55). Data from COMPASS show that 42.4% of Canadian high school students expanded their modes of use in 2018–19 compared to 2017–18. High school students who consumed cannabis in multiple modes were significantly more likely to binge drink alcohol, vape, use cannabis regularly, and endorse experiencing more depressive symptoms (53).

In summary, data suggest that after cannabis legalization, the Canadian youth extended modes of cannabis use, including more potent forms of cannabis. However, there is no data regarding whether youth using cannabis are obtaining it from

a legal or illegal source. This distinction is important, as legal edibles, extracts, and topical products are subject to THC limits.

Legalization and youth cannabis use: Special considerations

In this section, we will discuss special considerations such as the age of initiation, the influence of sex and gender, as well as race and ethnicity.

Age of initiation

Delaying the age of initiation of cannabis use is an important priority for public health, as early initiation of cannabis use (e.g., before age 18) has been clearly shown to increase the subsequent risk of cannabis dependence (91) and has the potential to lead to more severe and long-lasting cognitive and neurodevelopmental adverse effects (92, 93). Among youth aged 16–19 in the CCS, the mean age of initiation increased slightly from 2018 (15.2 years) to 2019 (15.6 years), with less of an increase to 2020 (15.7 years) that fell back to 15.6 years in 2021 (85, 94). These estimates are slightly higher than data from previous youth surveys have suggested. For example, Canadian youth data from 2004/05 to 2014/15 from the CSTADS found a mean age of initiation of cannabis use of 13.8 years, which did not vary significantly over the time period from 2004/2005 to 2014/2015 (65).

In summary, the limited data available suggest that the age of initiation of cannabis use might have increased slightly from pre- to post-legalization but has likely not decreased.

Influence of sex and gender

Both sex and gender impact cannabis use and effects. Animal models have shown that females are more sensitive to the effects of THC and other cannabinoids and that gonadal hormones (e.g., estrogens) directly impact THC metabolism and endocannabinoid system signaling (95). Cannabis use and cannabis use disorder have a more significant effect on self-reported mental health quality of life among women than men (96). Human laboratory research has suggested that females experience the same subjective effects as males after smoking less cannabis, which recapitulates some of the sex differences in acute cannabinoid effects observed in animal models (97, 98). Human research has shown that gender significantly impacts access to cannabis and patterns of cannabis use, with men/boys significantly more likely to use cannabis than women/girls (99). For example, the 2018 CCS found that 26% of men reported past-year use of cannabis compared to 18% of women (100). A recent analysis of federal data in Canada has suggested that men/boys might be increasing their use of cannabis to a greater extent than women/girls. Using data from the 2018 (pre-legalization) and 2019 (post-legalization) cycles of NCS found an increase in past-3-month cannabis use from 17.5 to 20.3% in men/boys aged 15+, compared to an increase from 12.3 to 13.4% among women/girls aged 15+. However, in the 2020 NCS data, for the first time, there was no statistically significant difference in the prevalence of past-3-month cannabis use between men/boys (21.1%) and women/girls (18.4%) (40). The difference in past-year cannabis use was still significantly different by sex (31% for males, 23% for females) in the CCS data that included Canadians aged 16 years or older (94). Unfortunately, these data rarely provide a breakdown of gender differences by age group, so it is not clear how the legalization of cannabis might have impacted boys and girls differently. In addition, no data were located that included gender-diverse or non-binary youth. In the CCS data, the frequency of daily or near-daily cannabis use in the past 12 months was broken down by both sex and age, showing a greater sex difference in adults aged 25 or older (30% for males, 19% for females) than in young adults aged 20–24 years (26% for males, 20% for females) and in youth aged 16–19 years, where the prevalence of daily or near-daily use was actually higher in females (20% for males, 23% for females). In a study assessing youth seeking support in a concurrent disorder treatment program, the proportion of boys/men sourcing cannabis from dealers increased, while the proportion decreased among girls/women after legalization. There was no other significant gender-related change between pre and post-legalization (101).

In summary, it appears that the prevalence of cannabis use is becoming more similar among men/boys and women/girls, though it remains unclear to what extent this might be due to legalization, and the data are too sparse to know if this is specifically true in youth, or if this is a trend mainly observed in adults.

Influence of race/ethnicity

Data that speak to racial/ethnic differences in cannabis use comparing pre-and post-legalization could not be located. As discussed by Haines-Saah and Fischer, the lack of racial/ethnic data on cannabis-related outcomes in Canada is a significant problem, as youth of color (especially Black and Indigenous youth) have been disproportionately targeted by policing and criminal justice systems in Canada (102). While not specifically focused on youth arrests, Owusu-Bempah and Luscombe recently showed that Black and Indigenous people in five major Canadian cities were significantly more likely to be arrested for cannabis possession than white people (103). How cannabis legalization has impacted youth of color in Canada and whether the disproportionate targeting and surveillance of Black and Indigenous youth in Canada have lessened with cannabis legalization is an important topic of further research. Starting

in 2020, the CCS began to report past-12-month cannabis use by ethnicity, sex, and age group, though the data on youth were often suppressed due to high sampling variability or small sample size. Data broken down by Indigenous status showed a high prevalence of cannabis use among Indigenous youth aged 16–24 years—where 62.3% of First Nations (North American Indian) youth reported past-12-month use, 56.1% of Métis youth reported past-12-month use (the Métis people are Indigenous peoples native to the provinces of Manitoba, Saskatchewan, Alberta, parts of Ontario, British Columbia, and the northern United States), while 48.3% of youth who did not identify as Indigenous reported past-12-month use (94). Comparable data from the 2021 CCS were not available due to high sampling variability or low sample size. When data were broken down by ethnicity, only data on white youth in the 16–19 year age group were available (49.2% reported past-12-month use), though data on other ethnicities were available for young adults aged 20–24. In this age group, 58.8% of white young adults reported past-12-month use, compared to 36.2% of South Asian young adults, 40.3% of Black young adults, 47.7% of Latin American young adults, and 53.1% for young adults who fell into "Other" ethnicity. In the 2021 CCS, 56.3% of white young adults reported past-12-month use, 32.9% of South Asian youth, and 29.1% of East/Southeast Asian youth, while data from other race categories were not available (85).

In summary, more data are needed to clarify how cannabis legalization might have impacted youth of color in Canada.

Impact of cannabis legalization for non-medical purposes on other cannabis-related outcomes among youth

While there has been substantial focus on the impact of cannabis legalization on cannabis use prevalence and frequency among youth, considerably less attention has been paid to cannabis-related harms among youth.

Emerging evidence suggests that cannabis-related hospitalizations and emergency department (ED) visits among Canadian youth may have increased due to cannabis legalization. Using data that was collected during the initial 5–6 months following cannabis legalization, two studies evaluated the impact of legalization of cannabis in Canada on youth cannabis-related hospitalizations, defined in both studies as admissions for poisonings or for mental or behavioral effects of cannabis using the 10th revision of the International Classification of Diseases (ICD-10). The first study (conducted in the province of Quebec) found no significant evidence of an increase in cannabis-related hospitalizations among youth, comparing a pre-legalization period (October 17, 2017–March 31, 2018) to a post-legalization period (October 17, 2018–March 31, 2019). However, in boys aged 10–14 years, there was a significant increase in the proportion of substance-related hospitalizations involving cannabis, from 39.3% pre-legalization to 70.0% post-legalization (104). The second study, a retrospective chart review of cannabis-related visits to an academic ED in Hamilton, Ontario, did find a significant 56% increase in ED visits following cannabis legalization among young adults aged 18–29 years (105). A recent repeated cross-sectional study conducted in Ontario evaluated ED visits and related hospitalizations involving cannabis exposure covering a long period pre- and post-legalization (between January 2016 and March 2021) (106). This study identified a total of 522 ED visits due to cannabis exposure over the study period; 81 visits occurred during the pre-legalization period (January 2016–September 2018), 124 visits occurred during the period immediately after the legalization of cannabis flower products (October 2018–January 2020), and 317 visits occurred during the period after commercial sale of cannabis edibles was legalized (February 2020–March 2021), which represented a significant pre-post increase for both post-legalization time periods. Importantly, even after adjusting for the increasing time trend of cannabis-related hospitalizations over the study period, the period following the legalization of commercial sale of cannabis edibles remained significantly associated with an increase in ED visits (106). Another study conducted in the province of Alberta found that while there was not an overall increase in the volume of pediatric cannabis-related ED visits in a post-legalization period (October 1, 2018–March 1, 2020) compared to a pre-legalization period (October 1, 2013–September 30, 2018), there was a significant increase in unintentional ingestions of cannabis among both children and older adolescents (107). Finally, a retrospective chart review of ED visits at a pediatric hospital in Ottawa, Ontario found an increase in pediatric ED visits related to unintentional exposures to cannabis, though the absolute number was still relatively low (5 visits in the 5-year period prior to legalization, 32 visits in the 2-year period following legalization) (108).

Data on cannabis-involved driving among youth are limited and mixed. Preliminary results from the NCS suggested that the percentage of young adults (aged 18–24 years) reporting driving within 2 h of using cannabis in the past 3 months actually decreased following legalization, from 16.4% pre- to 9.7% post-legalization. Being a passenger in a vehicle operated by a driver who had consumed cannabis within 2 h of driving in the past 3 months similarly decreased from 15.2% pre- to 11.9% post-legalization. CCS data are somewhat harder to compare, as cannabis-involved driving questions changed slightly with each new year of data. In 2018, 26.7% of youth aged 16–19 who used cannabis in the past 12 months reported having driven within 2 h of using cannabis, compared to 16.0% who reported having driven within 2 h of smoking or vaping cannabis in 2019, which was nearly identical in 2020 (16.1%) (94). In support of these findings, a recent study found no significant association between cannabis legalization and traffic injury ED visits among youth

drivers (aged 14–17 years in the province of Alberta, 16–18 years in the province of Ontario) (109). However, a recent study utilizing data collected from four trauma centers in the Canadian province of British Columbia between January 2013 and March 2020 indicated an increased prevalence of injured drivers under age 30 with a THC concentration of at least 2 ng/mL in blood, which is a threshold to define cannabis-impaired driving in some jurisdictions (110).

Cannabis legalization has the potential to impact youth seeking mental health support. A recent study analyzed data from one pre-legalization cohort and one post-legalization cohort of youth accessing treatment through an outpatient addictions and concurrent disorders treatment program for youth offered by the Centre for Addiction and Mental Health in Toronto, Ontario. They found no significant differences in a range of cannabis-related outcomes associated with legalization, including no changes in youth polysubstance use and no changes in mental health or substance dependence symptoms (101). Using a similar retrospective observational design, another study examined data from patients at least 12 years old who had visited a psychiatrist in the emergency unit of the Centre hospitalier universitaire de Sherbrooke (CHUS), comparing a period of 5 months post-legalization to a period of 2 years prior to legalization. They observed a significant increase in diagnoses of a cannabis use disorder, which was especially prominent among patients aged 18–24 years (from 17.3% pre-legalization to 25.9% post-legalization), though there was no significant increase in diagnoses of a psychotic disorder. This study also reported a significant increase in active use of cannabis among young adults presenting for psychiatric services, from 37.9% pre-legalization to 52.3% post-legalization. These data suggest that extra care should be taken to screen for cannabis use and potential cannabis use disorder among youth presenting for psychiatric services (111).

In contrast to potential harms associated with legalization, recent evidence about legal encounters suggests a possible net benefit to youth. Using data from the Canadian Uniform Crime Reporting Survey (UCR-2), a recent study found that implementation of the *Cannabis Act* was associated with a significant decrease in police-reported cannabis-related criminal offences among youth aged 12–17 years, an effect that was significant among both boys and girls. Importantly, no association was observed between the implementation of the *Cannabis Act* and property crimes or violent crimes among youth, providing preliminary evidence that cannabis legalization was not associated with overall increases in youth crimes (112). Data reported by the Canadian Centre for Justice Statistics similarly found a decrease of 36% in cannabis possession cases among youth (aged 12–17 years) from 2017 to 2018 (113). Finally, a recent report using data from Statistics Canada found a dramatic reduction in the number of cannabis possession charge counts among youth aged 12–17 years in Canada, from 9,383 cases in 2017 to just 740 cases in 2019 (114).

In summary, data on changes in cannabis-attributable harms associated with cannabis legalization among youth are limited and mixed. Though very preliminary, the current data do suggest an increase in cannabis-related hospitalizations among Canadian youth, which is possibly related specifically to the legalization of commercial sale of edible cannabis products. Unlike in the United States (Colorado, Washington State), the limited data do not suggest any major changes in driving under the influence of cannabis among youth, though an increase in THC-positive drivers under age 30 that were involved in car accidents was noted in British Columbia. Data from one university health center in the province of Quebec found an increase in cannabis use disorder diagnoses among young adults immediately following legalization, but it is unclear whether this generalizes to the rest of the country. Encouragingly, cannabis legalization appears to have led to a significant decrease in cannabis-related criminal offences among youth, with no significant changes in property or violent crimes.

Implications of legalization for education/prevention, treatment, and clinical practice

Health Canada committed CAD$100 million over 6 years to support education, awareness, and surveillance related to cannabis (115). Within the provinces and territories, the approach to prevent cannabis-related harms varies. So far, little data exists to determine if these approaches have been effective in reducing cannabis-related harms among youth or not. However, starting in 2019, the CCS began collecting data on exposure to and attitudes toward cannabis educational campaigns. In 2019, among youth aged 16–19 years, only 11.0% reported not noticing any cannabis-related education campaigns or public health messages. The most common locations for exposure to cannabis education campaigns or messages included social media (73.2%), school (58.1%), TV/radio (46.7%), or posters/billboards displayed publicly (46.7%). Also, in 2019, respondents were asked if their knowledge of cannabis-related harms increased since the new cannabis law came into effect; 30.9% of youth aged 16–19 years said "yes," while 39.5% said "no," and 25.4% said "somewhat." In 2020, respondents who reported seeing educational messages were additionally asked about the perceived credibility of the education campaigns, public health or safety messages. Overall, 71.3% of youth aged 16–19 years found the messages to be credible, while 21.0% found the messages "somewhat" credible (94). Thus, it appears that youth in Canada are being exposed to cannabis-related public health messaging, and the messages are being perceived as credible and trustworthy, but further data are needed to evaluate if these messages are having a positive impact on the cannabis use behaviors of youth, especially in regards to cannabis-attributable harms.

At the level of the school, data from the COMPASS study have described disciplinary approaches to cannabis use policy violations in Canadian secondary schools (116, 117). While punitive options (e.g., suspension from school, alerting the police) were more common than supportive options (e.g., encouraging participation in a substance use education program), the results showed that schools were less likely to use alerting the police as a punitive option for students violating cannabis use policies in the year post-legalization compared to the year pre-legalization (116). Clearly, more resources are needed for schools and school boards to facilitate implementation of supportive approaches to cannabis use policy violations in Canadian high schools.

A few educational interventions targeting youth were identified that have been evaluated since cannabis legalization or are currently under evaluation. For example, the Check Your Cannabis brief intervention is an anonymous digital health brief intervention based on normative feedback, harm reduction, and motivational interviewing, which has been evaluated as a potential tool for cannabis-involved driving concerns among youth, but can be tailored to focus on other cannabis-related concerns (118). The use of low-cost digital health interventions may be particularly useful to target youth who experience more cannabis-related problems. Another example is the University of Calgary's *Cannabis Café*, a novel harm reduction educational initiative that follows Canada's Lower-Risk Cannabis Use Guidelines and scientific evidence and targets post-secondary students (119).

In summary, data suggest that Canadian youth are being exposed to cannabis-related health messaging, which is encouraging. However, it is unclear how effective these messages are. More data are needed to evaluate the impact of cannabis legalization in Canada on education and prevention.

Conclusion

Cannabis legalization for non-medical purposes took place in Canada in October 2018. One of the federal government's stated goals in legalizing cannabis was to protect Canadian youth from cannabis-related harms (16). In this narrative review, exploring the impact of cannabis legalization on Canadian youth, we described the Canadian experience in detail. We discussed the regulation of the Canadian cannabis market, outlined changes in the epidemiology and parameters of cannabis use among youth, and discussed cannabis related prevention and education initiatives. The purpose of this review is to provide a broad description of the Canadian experience that may be of value to jurisdictions considering the legalization of cannabis.

The Canadian model differs from other jurisdictions which legalized recreational cannabis use in a number of aspects. First and foremost, the level of cannabis market regulation is much more extensive, with strict limits on packaging and labeling as well as advertising, marketing and promotion. Another difference is the government's endorsement of Canada's lower-risk cannabis use guidelines (25) as a way to educate the public and public health professionals (26).

Despite being legalized at the federal level, many rules are set at the provincial/territorial level, and thus impacts are likely to vary across the country. Although it is too early to ascertain, there are indications that Canadian provinces and territories with looser cannabis retail sales regulations have seen a higher increase in use compared to those with stricter regulations (120). This would be consistent with the alcohol and tobacco literature, which suggests that relative increases in availability are associated with increased consumption (33, 35). From a public health and youth protection perspective, provinces and territories should develop and enforce limits on retail density (35).

The *Cannabis Act* includes a requirement that the federal government review the legislation 3 years after it comes into effect. This review is expected to be conducted in 2022. According to the Act, the review must prioritize the impact of cannabis legalization on "public health and, in particular, on the health and consumption habits of young persons in respect of cannabis use" (24). The cannabis industry has been pushing for a repeal on many of the Act's regulations, notably the requirement for plain packaging and the restrictions on advertising, marketing and promotion (48, 121). It is critical that these regulations be maintained, from a public health perspective, as it is less appealing for youth compared to non-plain packaging (35).

While cannabis legalization brought an apparent increase in use among Canadians older than 25 years of age (40, 56), results for youth are mixed. Most studies show no pronounced increase, a few studies suggest an increase and the most recent national survey suggest a decline in youth cannabis use. Overall, however, the results suggest that the trend of a decrease in adolescents' cannabis use seen pre-legalization (64) may have reversed.

Data about changes in the age of initiation, the influence of legalization on sex and gender, and race/ethnicity are limited, with evidence suggesting that the age of initiation slightly. Also, data collected after legalization suggests that the prevalence of cannabis use among Canadian Indigenous youth is higher, compared to other ethnical groups (94). Notably, data on changes in cannabis-attributable harms among youth associated with legalization are limited and mixed, with emerging evidence suggesting an increase in youth hospitalization and ED visits as a result of cannabis legalization. Canadian youth are being exposed to cannabis-related health messaging, which is encouraging. However, it is unclear how effective these messages are.

The results presented in this review might support effective policies and educational initiatives. In particular, the finding that the trend of a decrease in adolescents' cannabis use has

either reversed or stopped can further support educational endeavors. This finding can also be used by the public health sector advocating for continuing the strict packaging restrictions. In addition, the finding of increased cannabis use among indigenous youth, compared to other ethnical groups (94) stresses the need for prevention and treatment programs targeting specific groups. Thus far, there is limited evidence linking specific policies to public health consequences. Future research about it can be a useful resource for both Canada and other jurisdictions considering the legalization of cannabis for recreational purposes.

The results available for this review cover only 3 years post-legalization; thus, it is not surprising that the data is limited and mixed. Further monitoring and research are needed to assess the impact of cannabis legalization on Canadian youth and the current results should be taken with caution.

Author contributions

DR-K, J-FC, JM, and BL contributed to the conceptualization and methodology. DR-K, J-FC, and JM contributed to writing the original draft preparation. All authors contributed to the review and editing, read, and approved the final manuscript.

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Conflict of interest

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Publisher's note

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Variations of cannabis-related adverse mental health and addiction outcomes across adolescence and adulthood: A scoping review

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Introduction: Evidence supporting associations between cannabis use and many health outcomes is growing, however it remains unclear how such associations vary across the lifespan. We therefore aim to answer the following questions: (1) Are the risks of cannabis's adverse effects on mental health and addiction-related outcomes different in adolescents than in adults? (2) What are the relationships between these cannabis's adverse effects and (a) an individual's age at first cannabis use, (b) age at assessment, and (c) duration of cannabis use?

Methods: We searched Medline, Embase, CINAHL, and PsychINFO from inception to 18 October 2021. Two reviewers independently screened studies and descriptively synthesized results.

Results: We included 140 studies. Cannabis effects on mental health and addiction-related outcomes were worse in adolescents, early cannabis initiators and cannabis users who consumed for longest periods. Evidence of worse long-term adverse effects in adolescents was substantial for psychosis, cannabis, and nicotine use disorders; mixed for depression, suicidality, other substance use and disorders; and limited for anxiety. Additionally, acute cannabis exposure had the opposite trend with adults more often reporting adverse effects than adolescents.

Conclusion: The available evidence suggests that cannabis use should be delayed as late as possible in adulthood and shortened in duration across the lifespan to decrease the risk of negative outcomes, while emphasizing the

need for adapted harm reduction approaches. This scoping review provides evidence on the role of age and duration of exposure as determinants of cannabis-related adverse effects, which may inform prevention and harm reduction strategies.

Systematic review registration: https://doi.org/10.17605/OSF.IO/BYG72

KEYWORDS

addictive behavior, adolescent, adult, cannabis, mental health

Introduction

Around the world, almost 200 million people consumed cannabis in the past year, making it the most used psychoactive substance after nicotine and alcohol (1–3). Cannabis use prevalence is particularly high among adolescents and young adults (3). Consumed for recreational purposes and its therapeutic properties, cannabis can also adversely impact users' health (4, 5). Cannabis exposure has been associated with a myriad of physical, mental, and psychosocial adverse health outcomes affecting all age groups (5). Notably, early cannabis initiation while the brain is still developing has been hypothesized to distinctly predispose adolescents to detrimental effects and increase risks specifically for mental health, cognitive and addiction problems (6). For example, adolescent cannabis use has been associated with psychiatric disorders such as schizophrenia (7–12), depression, and suicidal behavior (13). The probability for cannabis users to transition to cannabis use disorder (CUD) range between 9 and 27%, depending on the sample population, diagnosis definition and age of exposure onset (14, 15). Some evidence also suggests that early cannabis consumption may lead to the use of other substances (16, 17).

With the prevalence of cannabis use on the rise in many contexts and some jurisdictions liberalizing controls (including legalization) for recreational use (18), the establishment of a strong evidence base is needed to guide best public health strategies, harm reduction interventions, and policies. Existing initiatives have traditionally employed a precautionary approach assuming higher risks of harms in youth than in adults, thus suggesting broadly to avoid early and generally delay exposure to cannabis. While the body of evidence on associations between cannabis use and health outcomes is progressing, however, most of the existing literature reviews on cannabis harms on mental health and addiction in humans focused on a narrow set of mental health outcomes (7, 19) or on specific age groups (20). Consequently, it remains unclear how such associations may vary across the lifespan and whether they do similarly for all outcomes. To map the existing evidence as well as to identify any knowledge gap, we conducted a scoping review to answer these research questions (RQs): (1) Are the risks of cannabis's adverse effects on mental health and addiction-related outcomes different between adolescents and adults? (2) What are the relationships between these cannabis's adverse effects and (a) the user's age at first cannabis use (b) participant's age at assessment, and (c) duration of cannabis use?

Methods

We followed the Joanna Briggs Institute (21) scoping review methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes extension for Scoping Reviews (PRISMA-ScR) guidelines (22) to prepare our prospectively published protocol (23).

Eligibility criteria

Human studies were included if they: (i) reported adverse mental health or addiction outcome(s) related to cannabis use, (ii) reported relationship(s) between cannabis's adverse mental health or addiction outcome(s) and cannabis use onset or duration, (iii) included adolescents (<18 years old) and adults (≥18 years old), (iv) were published in peer-reviewed journals, and (v) were available in English, French, or Spanish. Editorials, letters, research protocols, and commentaries were excluded. To retrieve a full text that could not be obtained through institutional holdings, a librarian, the author, or the journal editor was contacted.

Data sources and search strategy

We searched for publications in three main electronic databases (MEDLINE, Embase, and PsychINFO) from inception to 27 October 2020. However, due to unforeseen circumstances caused by the COVID-19 pandemic, our scoping review got bit delayed therefore, to ensure inclusion of latest publications, we updated our search strategy on 18 October 2021. We consulted a specialized librarian to develop and execute a

specific search strategy for each database. The search concepts were: (i) cannabis, (ii) adolescents and adults OR age of onset or initiation, and (iii) adverse or negative effects OR mental health OR addiction. Supplementary Appendix 1 presents our first and updated search strategies for Medline that were adapted for other databases. Furthermore, we manually searched through the reference lists of all identified records for retrieving additional relevant studies.

Study selection process

All citations were imported into the EndNote X9 software. A screening form was developed *a priori*. Distiller SR® was used for data extraction and study selection. We followed a three-step study selection process. First, all duplicate publications were removed. Second, two reviewers (GB and VM, JG and CT/NK, FM and LG, NK, and HB) screened titles and abstracts with the screening form. Third, full texts meeting the inclusion criteria were reviewed and relevant studies were selected. Two independent reviewers (GB and VM, FM/JG and LG, NK, and HB) screened and extracted data from the full texts and a third reviewer (DJ-A/NK) resolved discrepancies between reviewers.

Data charting and synthesis

From each study, the following information was extracted: first author's name, publication year, country of study, study design, sample size, and cannabis use definition and findings. The main outcomes of interest were mental health, addiction and addictive behaviors related to cannabis use among adults and adolescents, relationships between cannabis's adverse mental health and addiction effects AND (a) participant's age at first cannabis use OR (b) participant's age at assessment OR (c) duration of cannabis use. In this scoping review, the "participant's age at assessment" is defined as the participant's age at study participation. Data were synthesized descriptively, and study characteristics were presented in a tabular form including structured summaries of the study characteristics and findings.

Results

Search findings

In total, 1986 studies (Medline n = 933; Embase n = 876; PsychINFO n = 110; and manual sources n = 67) were identified. After removing duplicates, 1,679 remained. Of these, 1,354 ineligible studies were excluded, and the remaining 325 full texts were reviewed. Finally, 185 studies were excluded leaving a total of 140 studies included in this scoping review (**Figure 1**).

Characteristics of included studies

Among the 140 included studies, 135 were in English (9–13, 16, 20, 24–151) three in French (152–154), one in Spanish (155) and one was available both in French and English (7). There was one meta-analysis (88), one systematic review (7), two combined meta-analyses and systematic reviews (13, 20), 11 literature reviews (33, 61, 76, 86, 87, 90, 95, 110, 124, 136, 152), four randomized controlled trials (79, 100, 112, 134), 61 cohort studies (10, 16, 26, 28, 29, 32, 35, 36, 40–45, 47–50, 55, 60, 62, 64, 68, 69, 71, 74, 78, 80, 83, 92, 96, 98, 104, 106–109, 111, 116, 118, 119, 123, 125, 128, 130, 132, 133, 135, 138–147, 149–151), 52 cross-sectional studies (11, 12, 24, 25, 27, 30, 31, 34, 37–39, 46, 51–54, 57–59, 66, 67, 70, 72, 73, 75, 77, 81, 82, 84, 85, 89, 91, 94, 97, 99, 101–103, 105, 113, 115, 117, 120, 121, 126, 127, 131, 137, 148, 153–155), three repeated cross-sectional studies (93, 122, 129), one naturalistic study (56), two retrospective cohort studies (65, 114), and two case-control studies (9, 63). Characteristics of the included studies are presented in **Supplementary Tables 1–4** and the main findings are described below.

Main findings

Research question 1: Are the risks of cannabis's adverse effects on mental health and addiction higher in adolescents compared with adults?

Supplementary Table 1 summarizes the 12 studies comparing cannabis's adverse mental health and addiction effects between adolescents and adults.

(i) Psychotic symptoms

Two studies by Mokrysz et al. (100, 134) reported that adults acutely exposed to cannabis experienced more psychotic-like effects than adolescents. Kelley et al. (99) found that daily cannabis use in adolescents tripled and in adults doubled the rate of onset of psychosis. Albertella et al. (10) reported that younger frequent cannabis users showed increased negative schizotypy while older frequent users showed reduced negative schizotypy.

(ii) Anxiety

Mokrysz et al. (100) observed that adults acutely exposed to cannabis rated their anxiety higher than when exposed to placebo while adolescents reported no such difference.

(iii) Suicidality

Levine et al. (110) concluded adolescent cannabis users are at higher risk of later suicidality.

(iv) Cannabis use and cannabis use disorder

Adolescents reported using cannabis more often than adults (115). Four studies (24, 31, 91, 105) reported 1.3–2.5 increased odds of developing a CUD in adolescent compared with adult cannabis users. Mokrysz et al. found that adolescents felt less stoned, felt the drug less, wanted more cannabis following exposure (100) and scored lower on negative experience (77) compared with adults.

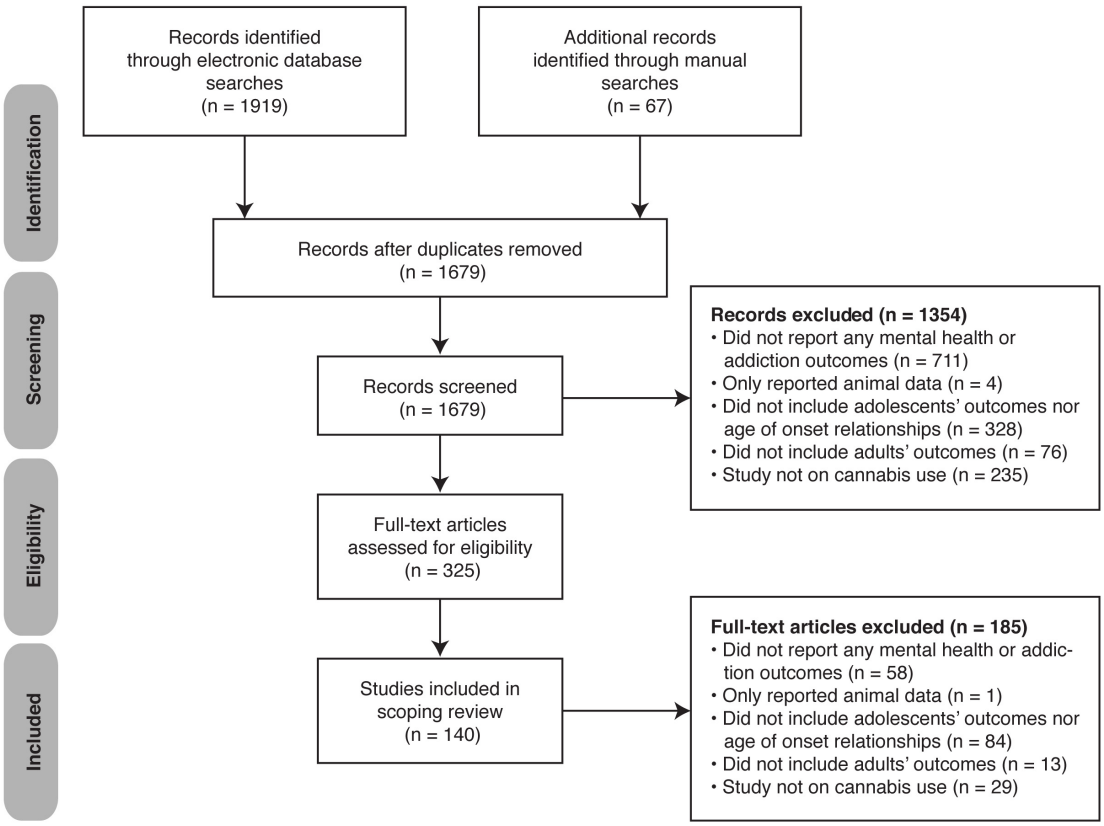

FIGURE 1
PRISMA flow diagram of the search and study selection process.

(v) Other substance use disorders

Wang et al. (102) concluded that the odds of co-occurring nicotine dependence greatly varied with age of cannabis use, reaching peak values during adolescence and late adulthood. Levine et al. (110) reported that adolescent cannabis users were at increased risk of addiction to several substances.

(vi) Other adverse effects on mental health

Hawke et al. (115) found that adolescent cannabis users were more likely to have an externalizing disorder such as attention deficit hyperactivity disorder than adult users. Levine et al. (110) indicated that adolescent cannabis users are at increased risk of psychiatric morbidity.

Research question 2: What are the relationships between cannabis's adverse effects and (a) participant's age at first cannabis use, (b) participant's age at assessment, and (c) duration of cannabis use?

(a) **Supplementary Table 2** summarizes the 115 studies on relationships between cannabis's adverse mental health and addiction effects and participant's age at first cannabis use.

(i) Psychosis and related disorders

Forty-four studies reported that early cannabis initiation was associated with psychotic outcomes, including earlier age of onset of psychosis (7, 9, 53, 61, 64, 65, 73, 75, 82, 97, 99, 101, 138), higher risks of psychotic symptoms (12, 38, 56, 66–68, 70, 71, 75, 94, 95, 103, 111, 116, 127, 131, 150) and greater severity of these symptoms (20, 61, 89), higher risks of psychosis (61, 86, 90, 131, 147), and higher risk of psychotic disorder (7, 59, 87, 95, 136, 152) compared with later initiation or non-use of cannabis. Two studies (73, 82) revealed that the onset of psychosis followed cannabis initiation on average 7–8 years after. Two studies (59, 89) associated the risk of cocaine-induced psychosis to an earlier age of cannabis use. A review (86) suggested that the higher risk of psychosis in early cannabis users was dose dependent. Eight studies (63, 80, 92, 97, 112, 116, 125, 128) found no association between psychosis outcomes and the age of cannabis initiation. Curran et al. (121) reported opposite results with older age of cannabis initiation associated with more psychotic symptoms.

(ii) Anxiety

Five studies (87, 106, 128, 142, 143) reported that early-age cannabis users had between two and three times the odds of anxiety disorders compared with non-users, while five studies (13, 68, 92, 132, 149) including a meta-analysis (13) and a cohort study (149) found no such association after adjusting for demographics and childhood adversities. Another study indicated that such increased risk was limited to early and frequent cannabis users (78). Late cannabis

initiation was associated with a fourfold increase in odds of developing an anxiety disorder as compared with non-users (128) a finding supported by another team reporting similar probability (92). Of the four studies comparing the risk or incidence of anxiety disorders between early and late cannabis users, only one (96) found a fourfold increased odds while the other three (92, 107, 132) found no difference. Dragt et al. (71) reported that age at first cannabis use positively correlated with age of onset of anxiety symptoms while two other studies (67, 112) found no such correlation. Two studies (61, 87) concluded that early cannabis initiation is a risk factor for anxiety disorders for frequent cannabis users. Hosseini et al. (7) indicated that too low quality of evidence exists on anxiety for recommending a minimum age for cannabis use for preventing this outcome.

(iii) Depression

Fifteen studies (13, 29, 33, 37, 61, 68, 72, 87, 88, 98, 119, 139, 142, 143, 152) reported that early cannabis initiators had between 1.1 and 8.8 times the odds of depression compared with non-users, while eight studies (37, 48, 50, 67, 78, 98, 128, 149) reported similar odds, incidence or no association. Four studies (72, 128, 139, 150) found that late cannabis initiators had between 1.6 and 3.3 times the odds of depression compared with non-users while two studies (29, 119) reported similar odds. These increased odds of depression disappeared after covariates adjustment in three studies (37, 142, 143). Lynskey et al. (37) revealed that depression risk was increased only in dizygotic twins discordant for early cannabis use, but not in monozygotic twins, before confounders adjustment, indicating a genetic modulatory effect. Harder et al. (48) found 2.6 times increased odds of depression only in males with problematic cannabis use in adolescence compared with those without problematic cannabis use. Three studies (54, 96, 132) showed that early cannabis initiators were between 1.2 and 1.9 times more likely to develop depression compared with late initiators, while another study (26) found similar likelihood. Out of three studies (37, 67, 71, 112) assessing correlations, one (71) found a positive correlation between age of cannabis initiation and age of onset of depressed mood.

(iv) Suicidality

Five studies (13, 37, 104, 128, 142) including a meta-analysis (13) reported that early cannabis initiators had 1.5–4.2 times the odds of considering suicide and 1.7–8.7 times the odds of attempting suicide compared with non-users (13, 37, 88, 104). However, these relationships in some instances became non-significant after covariates adjustment (37, 128, 142) and two studies (50, 106) reported no association. Silins et al. (88) found that the higher risk of suicide attempts in early cannabis users depended on cannabis use frequency, with daily cannabis use having the highest odds. Late cannabis users had a similar risk of suicide ideation (104, 128) and suicide attempts (104) compared with never users. When comparing early with late cannabis users, the suicidality risk was increased twofold in the early users (132). Savage et al. (112) reported that age of cannabis initiation negatively correlated with suicide risk rating.

(v) Other cannabis use outcomes

Baggio et al. (83) reported higher proportions of early compared with late cannabis users who felt high, relaxed, laughed a lot, and did crazy things the first time they tried cannabis. Ellickson et al. (40) indicated that a younger age at cannabis initiation was associated with negative consequences such as concentration problems. A cross-sectional study (39) found that early-age cannabis users (<16 years old) had increased odds of problematic cannabis use than later-age users. Bravo et al. (120) observed that younger age at first cannabis use was associated with less reliance on cannabis protective behavioral strategies. A cohort study (144) reported that early cannabis use increased the likelihood of continued cannabis use in adulthood.

(vi) Cannabis use disorder

Five studies (34, 88, 108, 123, 128) found that, depending on use frequency, cannabis users starting in adolescence had between two and 300 times the odds of subsequent cannabis dependence compared with non-users. When controlling for covariates, these odds ratios remained significant and varied between two and 253 (34, 55, 88, 108, 128). Furthermore, rates of dependence were between four and 14 times higher in early-age cannabis users compared with never users (143). Two cohort studies (36, 107) and two cross-sectional studies (25, 85) reported similar risk of dependence in early-age compared with later-age cannabis initiators. Three cross-sectional studies (34, 85, 131) and three cohort studies (32, 69, 151) found 2.0–2.7 times increased risk of developing cannabis abuse or dependence in early compared with later-age cannabis initiators. Interestingly, each year older at first cannabis use reduced the odds of developing dependence by 11% (84). People who develop cannabis dependence are more likely to have a younger age of initiation than non-problematic cannabis users (46). The time from first cannabis use to cannabis dependence diagnosis increased from 28 years in cannabis initiators starting before age 13, to 47 years in initiators starting after age 19 (57). The increased risk of dependence among young cannabis initiators was further supported by three narrative reviews (95, 124, 152) and a cohort study (145). Four studies further associated early initiation with risky cannabis use (81), severe cannabis dependence (126), and CUD (148).

(vii) Other substances use

Four studies found that early cannabis users were more likely to consume tobacco than non-users (68) or late cannabis users (49, 103, 130). Three studies (44, 85, 96) supported this finding but only for daily tobacco use, and this association was non-significant after covariates adjustment in another study (149). Moore and Budney (27) reported a younger age at first cannabis use among tobacco smokers compared with non-smokers. Mixed evidence was found among the three studies (85, 93, 96) measuring alcohol use. Moss et al. (85) found

no difference between early cannabis users and non-users for monthly and yearly alcohol use, while Buu et al. (93) noted an increased risk of heavy alcohol use for both early and late cannabis users compared with non-users. Few et al. (96) revealed that early cannabis users had twice the odds of regularly using alcohol compared with their late using co-twin. Stanley et al. (137) reported that while late cannabis users had 16 times the odds of misusing prescription drugs compared with non-users, early cannabis users had 47 times these odds. Early cannabis initiators had twice the odds of misusing prescription opioids compared with non-users (135), and nearly twice the risk of prescription opioid misuse compared with late users (129). This contrasts with Moss et al. (85) findings of similar prevalence of pain reliever misuse between early cannabis users and non-users. Hall et al. (95) reported that majority of the 17 studies reviewed associated early cannabis use with other illicit substance use. Early cannabis users had between two and 14 times the odds of using other drugs compared with non-users (34, 41, 42, 68, 88, 135). After covariates adjustment, these odds were increased to between two and 17 times (34, 62, 88, 135), or became non-significant (149). These results are in line with increased prevalence of a range of illicit drug uses among early cannabis users compared with non-users (47, 85), especially in frequent cannabis users (143). Early cannabis users were sometimes as likely (39, 79) and sometimes more likely (96, 103) to use illicit substances than late users. Finally, the age of cannabis initiation negatively correlates (medium effect size) with illicit drug use frequency (40).

(viii) Other substance use disorders

Early cannabis users were more likely to develop nicotine dependence than non-users (45, 55, 128) or late users (44, 45, 131). However, two studies reported no difference either in this risk between early cannabis users and non-users (85) or in the incidence of nicotine use disorder in early versus late cannabis initiators (107). The risk of developing an alcohol dependence was also higher for early cannabis users compared with non-users (55, 128, 143) or late users (36). However, this relationship sometimes became non-significant after covariates adjustment (55, 143). Another study (107) found similar incidence of alcohol use disorder in early- and later-age cannabis users. When controlling for confounders, early cannabis initiators had between 2 and 66 times the odds of illicit substance use disorder (SUD) (29, 128) or drug abuse (62) and twice the prevalence of illegal drug dependence (85) compared with non-users. The review by Dervaux et al. (152) further supported these results. Four studies (34, 118, 131, 145) found that the risk of illicit drug use or dependence depended on the age at first cannabis use and the type of other drug involved. For example, it was the highest in cannabis initiators starting before age 13 and became non-significant after age 15 (118). Moreover, it was higher for cocaine/stimulants, and opioids (34) but similar for methamphetamines (131) and sedatives (34).

(ix) Other mental health outcomes

As reviewed by Rubino et al. (76) three studies reported that early cannabis initiation increased the odds of psychological distress (103), subclinical psychotic experience (66), or non-suicidal injury (96) compared with later cannabis initiation. When compared with non-users, early and frequent cannabis use increased the odds of anxiety and depression two to threefold while late and frequent cannabis use increased it twofold (43). Estrada et al. (11) reported a positive correlation between age at first use and age of onset for psychiatric illness. Shah et al. (114) found that early cannabis initiation predicted progression to a cannabis-induced psychotic or mood disorder. Eight studies (35, 36, 40, 67, 92, 113, 149, 155) found no relationship between age of cannabis initiation and psychiatric disorders.

(b) **Supplementary Table 3** summarizes the 12 studies on relationships between cannabis's adverse mental health and addiction effects and participant's age at assessment.

(i) Depression and anxiety

The associations between cannabis use and depression symptoms differed with age (133). When depression and anxiety were measured together, however, Meier et al. (133) found no evidence of an association with age. When assessed separately, one cohort study (74) confirmed that cannabis use at younger age was associated with increased depressive symptoms compared with older age. Conversely, although Patton et al. (146) did not directly compare age groups in their cohort, the association between daily cannabis use and depression and anxiety during adulthood was stronger for past-year adult use than for adolescent use in women only (similar in males).

(ii) Suicidality

Fergusson et al. (141) showed that the strength of association between cannabis use frequency and suicidal ideations and attempts decreased with increasing age (14–21 years old).

(iii) Cannabis use and cannabis use disorder

Fergusson et al. (140) indicated that the cumulative risk of cannabis dependence increased gradually from 0% at age 16 to 9% at age 21. Wagner et al. (30) showed a moderate risk for developing CUD following early cannabis use. Madruga et al. (148) indicated that odds of current or past-year cannabis use decreased with progressing age. Chen et al. (144) reported that early age is a predictor of ongoing cannabis use. Padovano et al. (117) reported that adolescents experienced a greater subjective high experience than young adults.

(iv) Other substances use and substance use disorders

Two studies (16, 62) indicated that the odds of other illicit substance use following cannabis use declined with increasing age. One study (16) confirmed similar significant associations for other substance use. Another study (155) reported that younger age is associated with SUD among cannabis users. Finally, Fergusson et al. (141) showed that the strength of association between cannabis use frequency and illicit drug use decreased gradually with increasing age (between ages 14 and 21).

(v) Other mental health outcomes

A cross-sectional study (155) showed that age was associated with the presence of Axis I psychiatric disorders other than SUD but not with Axis II disorders among cannabis users.

(c) **Supplementary Table 4** summarizes the 18 studies on relationships between cannabis's mental health and addiction adverse effects and duration of cannabis use.

(i) Psychosis and related disorders

Two studies (52, 60) found that a cannabis use duration of more than 5 or 6 years increased the odds of experiencing psychosis twofold compared with a shorter duration or no cannabis use. Two studies (97, 147) found no correlation between cannabis use duration and age of onset of psychotic disorder (97) nor transition to psychosis (147).

(ii) Anxiety

Four (58, 94, 128, 133) out of the five studies (58, 94, 128, 133, 153) focusing on anxiety found a positive relationship with cannabis use duration. Cannabis users consuming for at least 11 years, between 2 and 10 years, and for 1 year or less had respectively 2.8, 2.3, and 1.6 times the odds of anxiety compared with non-users (58). Similarly, weekly cannabis users consuming for 16 years had 2.1 (2.5) times the (adjusted) odds of anxiety compared with non-users whereas those who weekly used for 8 years had 2.3 (2.8) times these odds (128). Although Cloak et al. (94) did not measure cannabis use duration *per se*, they found positive small-effect size correlations between cumulative lifetime quantity of cannabis and anxiety symptoms or phobic anxiety. Furthermore, Meier et al. (133) indicated that each additional year of weekly cannabis use increased the risk of anxiety and depression problems, when measured together. Another cross-sectional study (153) found no correlation between cannabis use duration and anxiety.

(iii) Depression and suicidality

Four studies associated a higher risk of depression (58, 72, 122, 133), one study associated depressive symptoms (153) and one study associated suicidal ideation (128) with long cannabis use duration. Two studies (58, 72) indicated that cannabis users who consumed cannabis for more than 11 years had nearly three times the odds of depression compared with non-users, whereas those who used between 2 and 10 years had twice these odds. Chabrol et al. (153) also reported a positive correlation between the depression score and cannabis use duration. Similarly, Meier et al. (133) indicated that each additional year of weekly cannabis use slightly increased the risk of depression. Conversely, Han et al. (122) reported a decreased depression prevalence for longer cannabis use duration (>3 years) than shorter duration (1–2 years) among adolescents.

(iv) Cannabis use disorder

Five (24, 84, 128, 154, 156) studies found an increased prevalence or risk with longer cannabis use duration. Von Sydow et al. (28) indicated that cannabis users develop cannabis abuse and dependence on average 2.0- and 2.4-years following initiation, respectively. Han et al. (122) reported an increased prevalence of CUD among adolescents and adults (adjusted prevalence of CUD in adolescents increased from 10.9 to 20.6% and in adults from 5.6 to 10.5% between the first and the fourth year of cannabis use).

(v) Other substance use disorders

Two cross-sectional studies (155, 156) and two cohort studies (128, 149) confirmed an increased prevalence or risk of SUD with longer cannabis use duration whereas Degenhardt et al. (51) found the opposite association. Han et al. (122) reported that after long cannabis use periods, both adults and adolescents developed other SUDs related to nicotine, alcohol, cocaine, hallucinogen, tranquilizers/sedatives, and opioids.

(vi) Other mental health outcomes

Three studies found positive small-effect size correlations between cannabis use duration and borderline personality disorder (153), and obsessive-compulsive scores (94). Cuenca-Royo et al. (155) found similar odds of psychiatric diagnosis in cannabis users consuming for 5–7 years compared with those consuming from 1 to 4 years.

Discussion

Our scoping review's results indicate that cannabis use is overall associated with higher likelihood of adverse mental health and substance use outcomes among adolescents, early cannabis initiators and cannabis users who consumed for longest periods. The strength of evidence varied based on the types of mental health and addiction outcomes. Substantial evidence was found for psychotic disorders, as well as cannabis and nicotine use disorders. Mixed evidence was obtained for depression and suicidality, other substance use, and other SUDs while it was limited for anxiety. Acute cannabis exposure led to the opposite trend with adults more often reporting adverse effects compared with adolescents. While our findings are overall consistent with three other recent reviews (7, 13, 95) on specific outcomes (i.e., psychosis, depression, other substance use, and suicidality) of cannabis exposure, we identified several knowledge gaps in the literature with some inherent limits and strengths in this scoping review.

Nearly half of the studies evaluating the effect of age of use initiation on cannabis-related harms compared early cannabis users with non-users instead of later-age users. Consequently, it was impossible to disentangle the effects of cannabis use from age at first use other than by comparing results with those obtained in similar studies conducted in older samples. Moreover, studies divided their age groups using different age categories, and most of the included studies measured cannabis consumption using self-report data. This type of measurement may be prone to recall and social desirability biases. More importantly, it prevents from accurately identifying exposure to specific cannabinoids (i.e., tetrahydrocannabinol and cannabidiol) and the level of such exposure. Future research

should use complementary biological sampling to improve measurement of cannabis and cannabinoid exposure, like did few authors (11, 100, 113, 114, 131, 134). This is even more important with the continuously changing concentrations of tetrahydrocannabinol and cannabidiol especially in cannabis products obtained from the unregulated market (157–159). These ongoing changes in cannabis composition and potency also highlight the need for repeated assessments of the risks of cannabis use, which may fluctuate over time, as different products are made available to consumers across all age groups.

Age of cannabis use initiation and duration of cannabis use were main factors influencing the magnitude of cannabis-related harms. Other important contributors and potential effect moderators include cannabis potency (160), use frequency (161), familial medical history (162), and peer influence (163, 164). However, not all studies controlled for these potential confounders and among those who did, the associations were sometimes non-significant. This suggests that young age, early initiation, and longer duration of cannabis use represent only some of a complex array of risk factors that contribute to potential adverse outcomes of cannabis exposure. Overall, there was no clear evidence of a specific age of use at which cannabis-related harms could be avoided; such threshold would likely vary according to specific outcomes of interest. This prevents us from advising an age limit for "safe" cannabis consumption and highlights the challenging nature of such efforts. Notwithstanding the limitations of the available literature, it is reasonable to suggest that delaying cannabis consumption as late as possible and limiting the duration of use could decrease the risk of both short- and long-term adverse effects, aligned with the recommendations of the Lower Risk Cannabis Use Guidelines (165). Equally important, and as has been proposed by others, efforts are required to further standardize measurement of cannabis exposure, outcomes to prioritize, and potential confounders to facilitate knowledge synthesis.

Beyond the restrictions of the available literature as described above, this scoping review has its very own strengths and limitations. One of the key strengths of the present scoping review is that we used a broad search strategy and included highly heterogeneous study designs and measurement methods. This allowed us to obtain a wide overview of cannabis harms on mental health and addiction. Other outcomes related to mental health such as cognitive function, however, were outside the scope of this review and merit further attention. Also, we limited our selection to studies published in English, French, and Spanish. This could have introduced a small language bias that, however, seems to be unlikely to change our conclusions. Finally, in this review we broadly used the term "adulthood," which, at least in theory, included "senior age." Future research and knowledge synthesis efforts should pay specific attention to that age group to determine if and how some outcomes may specifically vary among older adults.

Conclusion

In conclusion, age of exposure seems likely to modulate cannabis use-related mental health and addiction outcomes. Cannabis' adverse effects on the long-term outcomes tended to be generally worse in adolescents, early cannabis use initiators and cannabis users who consumed for long periods. Thus, delaying cannabis use initiation to as late as possible in young adulthood and limiting cannabis use to short periods could decrease the risk of adverse cannabis use consequences. Using a harm reduction perspective, we advocate for providing youth with nuanced and accurate information on potential effects of cannabis use and develop interventions to promote safer cannabis consumption practices, taking into consideration specific risks associated with early-age cannabis use, which are not the same for all outcomes. Finally, we recommend that future research efforts on age-specific cannabis harms account for important confounding factors such as frequency and potency of cannabis consumed, and other key individual and environmental factors.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

DJ-A and NK: study conceptualization and supervision. NK: methodology. GB, LG, JG, VM-P, NK, HB, FM, and CT: study selection. GB, LG, JG, NK, HB, and VM-P: data charting and synthesis. NK, JG, LG, and GB: original manuscript draft writing. LG, GB, HB, NK, DJ-A, and BF: data interpretation. NK, GB, LG, JG, VM-P, HB, FM, CT, BF, and DJ-A: reviewing and editing of the manuscript. DJ-A: funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

LG was now employed by AbbVie Corporation who does not support any of the author's views and declares that this is the author's independent work. VM was currently employed by Indivior who had no input, control or review of this article and confirms it is the author's own independent work. DJ-A receives study materials from Tetra BioPharma and Cardiol Therapeutics for clinical trials funded by the Quebec's Ministère de la Santé et des Services Sociaux.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.973988/full#supplementary-material

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Minimizing policy-biased appraisals of the evidence on cannabis and psychosis

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Appraisals of the evidence on the relationship between cannabis use and psychosis are often biased by appraisers' pre-existing views on whether adult cannabis use should or should not be legal. This viewpoint gives examples of such policy-biased appraisals and suggests strategies for avoiding them.

KEYWORDS

cannabis, psychosis, causal inference, policy-biased appraisals, policy implications

The debate about whether cannabis use is a contributory cause of psychosis is often seen as critical to the policy debate about whether adults should be legally able to use cannabis (1). Proponents on either side of the debate implicitly assume that the case for cannabis legalization is weakened if we accept that the relationship is causal. Supporters of retaining criminal penalties for adult cannabis use often support their case by arguing that cannabis is a cause of psychosis [e.g., (2, 3)] while some who support more liberal cannabis policies argue that the association is not causal [e.g., (4)]. This alignment of views can lead to policy-biased appraisals of evidence, i.e., appraisals in which evidence is selectively interpreted to support a pre-existing policy commitment. We need to disentangle our appraisals of the empirical evidence from our policy commitments.

Defining some key terms

A psychosis is a serious mental disorder in which a person, most often a young adult, experiences hallucinations (e.g., accusatory voices) and develops delusional beliefs that other people want to harm them. Persons with these symptoms may have impaired cognitive and social functioning that interferes with their ability to form close personal relationships, prevents them from completing their education, and makes it difficult for them to earn a living (5).

In this article, regular cannabis use refers to the daily or near daily use of cannabis. This pattern of cannabis use predicts an increased risk of psychosis, especially when it begins in adolescence and continues into adult life.

The hypothesis that cannabis is a cause of psychosis does not imply that cannabis use is a necessary or a sufficient condition for developing a psychosis. It is not necessary because many persons who develop psychoses have not used cannabis; it not sufficient because only a minority of cannabis users develop a psychosis (6).

A more plausible hypothesis is that regular cannabis use is a *contributory cause* of psychosis (1). On this hypothesis, regular cannabis use is one of a combination of factors that increase the risk of psychosis, or brings forward the onset of the illness in persons who are at increased risk of developing a psychosis, e.g., by having a parent or sibling with a psychosis. The factors with which regular cannabis use may interact include genetic vulnerabilities to develop a psychosis and environmental exposures that increase the risk of psychosis, such as childhood abuse and other unknown factors (1).

The case for a contributory causal relationship

In longitudinal studies of representative samples of young people, there is a consistent evidence that daily or near daily cannabis use in adolescence and young adulthood predicts an increased risk of psychotic symptoms or a diagnosis of a schizophreniform disorder (7–10).

Those who argue that cannabis use is a contributory cause of psychosis use [e.g., (1, 9–11)]. point to coherence of a set of interlocking kinds of evidence, namely, that cannabis use typically precedes the onset of psychosis, and the earlier cannabis use begins, the heavier cannabis use is, and the longer regular use lasts, the greater the risk of experiencing psychotic symptoms or developing a psychotic disorder (9–11). The principal psychoactive ingredient in cannabis—tetrahydrocannabinol (THC)—acts upon CB_1 cannabinoid receptors in the brain (8, 12) and the cannabinoid system that they comprise, in turn, interacts with dopaminergic and other neurotransmitters systems that have been implicated in the production of psychotic symptoms (12). When THC is given under double blind conditions, it also produces dose related increases in psychotic symptoms in persons who do and do not have a psychosis (13, 14). Cannabis users who develop schizophrenia have a worse clinical course, if they continue to use cannabis than do peers with a psychotic illness who cease using cannabis (15, 16).

Alternatives to a causal explanation

Those who are skeptical that cannabis is a contributory cause of psychosis suggest two alternative explanations of the association.

The first is that psychotic symptoms are a cause of early and heavy cannabis use rather than vice-versa (17). A popular common version of this hypothesis is that persons with early symptoms of psychosis use cannabis to medicate its symptoms, such as depression, or the side effects of the medications used to treat psychosis (4). This hypothesis would explain why regular cannabis use is common among newly incident cases of psychosis (9).

The second possibility is that the association reflects the effects of shared risk factors for early and regular cannabis use and for psychosis. According to this hypothesis, shared risk factors increase (1) the risk of early and regular cannabis use in young adulthood and (2) increase the risk of developing a psychosis. These shared risk factors could be environmental factors such as childhood abuse, genetic factors, or some combination of the two (7).

The self-medication hypothesis

The support for the self-medication hypothesis is weaker than that shared risk factors hypothesis. First, people with psychoses who use cannabis provide the same reasons for using cannabis as persons who do not have a psychosis, namely, its effects feel good, they want to do what their peers do, and they like to have fun etc. (18).

Second, the self-medication hypothesis has not been supported epidemiological tests of it. Some epidemiological studies have only included data from participants who did not report psychotic symptoms before they began to use cannabis [e.g., (19)]. Others have recruited participants who did not have a history of psychotic symptoms [e.g., (20)] while other studies have statistically controlled the association for the effects of a prior history of symptoms of mental disorders (21, 22). These studies have generally found that cannabis use more often precedes than follows the onset of psychotic symptoms (9).

Third, in prospective studies, persons with psychoses who used cannabis before their diagnosis, and continue to do so after treatment, have poorer clinical outcomes than those who discontinue cannabis use (e.g., higher rates of relapse and more positive symptoms) (15, 16).

This finding is inconsistent with the self-medication hypothesis.

Shared risk factors

In epidemiological studies, a history of regular cannabis use in young adulthood predicts an approximate doubling of the risk of developing a psychosis. Skeptics have argued that this size of association could be explained by shared risk factors that have similar sized associations with the risks of using cannabis and of developing a psychosis (7).

The estimated doubling of risk, however, may be attenuated by measurement error. In many studies, for example, cannabis use is simply measured as daily or near daily cannabis use. Epidemiological studies that have used finer grained measures of the type and potency of cannabis suggest that the risk of psychosis is much >2 in persons who use cannabis with high

levels of THC and low levels of CBD (10). If the association with cannabis use shows a dose response relationship, then shared risk factors must also show a dose response relationship to both cannabis use and psychosis risk.

Longitudinal epidemiological studies have assessed the shared risk factors hypothesis by controlling and statistically adjusting for plausible confounders, such as, other drug use, personal characteristics that predict psychosis, and a history of psychotic symptoms [e.g., (19, 20, 22–24)]. The number and type of confounding variables has varied between studies. Fixed effects regression has also been used to control for the effects of *unmeasured* confounders (23).

One type of confounding presents challenges for the strategy of statistical control. This is the strong association between cannabis use and tobacco smoking, which is more common among persons who develop schizophrenia than among peers without these disorders (25). The authors of a systematic review of the epidemiological studies of tobacco use in schizophrenia (25) argued that there was good evidence that cigarette smoking plays a contributory causal role in the onset of schizophrenia.

Disentangling the potential causal roles of tobacco and cannabis smoking is difficult because these types of drug use are strongly correlated. Controlling for cigarette smoking may also be inappropriate if tobacco smoking is a contributory cause of cannabis smoking. One analysis of data from the Avon Cohort found that the association between cannabis use and psychosis was greatly attenuated after controlling for cigarette smoking (26). Other studies suggest that tobacco smoking does not explain the association between cannabis use and psychosis [e.g., (27, 28)], including a later follow up of the Avon cohort (28).

Epidemiological studies have also assessed whether the association between cannabis use and psychosis can be explained by shared genetic factors that increase both the risk of using cannabis and the risk of developing a psychotic disorder. A weakness with these genetic studies is that many have only measured cannabis use over the lifetime (or the past year) rather than daily or near daily use over a period of years. These measures limit the statistical power of these studies in testing competing hypotheses. Another weakness of genetic studies is that they have not been able to identify genotypes that accurately predict the risk of using cannabis or developing a psychosis.

Gillespie and Kendler (29) reviewed studies that used a variety of genetically informed research designs to assess genetic contributions to associations between cannabis use and schizophrenia. These included: studies of the size of the association in cohorts of people of varying levels of genetic relationships (e.g., twins, parents, siblings, cousins and unrelated), Mendelian randomization studies, and studies that used polygenic risk scores to adjust the size of the association between cannabis use and psychosis. Gillespie and Kendler argued that these studies have found evidence of shared genetic risks for cannabis use and psychosis. They have also found evidence that emerging symptoms of psychosis increase the risks of using cannabis but concluded, nonetheless, that there is consistent evidence that cannabis use played a small contributory causal role in the development of psychoses.

Moving beyond policy-biased appraisals of the evidence

Two things are needed to move beyond policy-biased appraisals of the evidence on cannabis and psychosis.

First, we need to use explicit criteria to assess the evidence for contributory causal relationships and apply them in an even-handed and consistent way. We should avoid the example of the tobacco industry in setting such a high standard of evidence for a causal inference that no evidence can satisfy it (30). We should also avoid accepting weaker evidence in support of causal explanations, for example accepting observational evidence that persons with psychosis who use cannabis have better social adjustment than those who do not as evidence of the cognitive benefits of cannabis use [e.g., (31)].

Second, we need more nuanced analyses of the relationships between evidence and policy than those often implicitly assumed [e.g., (32, 33)]. For example, accepting that regular cannabis use may play a contributory causal role in psychosis does not entail support for cannabis prohibition. There is experimental evidence, for example, that heavy alcohol use is a contributory cause of the psychosis delirium tremens (34). There is also observational evidence that sustained heavy alcohol use can produce psychoses that persist beyond alcohol withdrawal (35, 36). This evidence does not justify alcohol prohibition because policy makers have to consider the social and economic consequences of the policy, as revealed during national alcohol prohibition in the USA from 1920 to 1933 (37).

Ideally democratic pluralist societies should decide on an appropriate cannabis policy by weighing the costs and benefits of cannabis use and cannabis control policies (38, 39). Policy makers need to weigh the harms that may arise from cannabis prohibition, such as, criminal records for cannabis users, production of a large illicit market, police corruption and discriminatory enforcement of the criminal law (38). The costs of cannabis prohibition and the potential benefits of regulating and taxing cannabis have led a majority of US citizens to support the legalization of adult cannabis use (40).

If a government decides to legalize cannabis, however, the evidence on cannabis and psychosis is relevant in making decisions as to how cannabis should be regulated. Experience with alcohol (41), for example, suggests that we should discourage the use of high potency cannabis by basing taxes on the THC content of cannabis products or setting a cap on their THC content (42). The availability of cannabis retail

outlets could also be limited and restrictions on the legal age of purchase enforced to reduce adolescent access (41, 43).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Contemplating cannabis? The complex relationship between cannabinoids and hepatic metabolism resulting in the potential for drug-drug interactions

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The majority of states have fully legalized the use of medical cannabis (MC), and nearly all other states allow limited access to cannabidiol (CBD), a non-intoxicating constituent of cannabis often touted for a range of therapeutic indications. Further, the Agricultural Improvement Act of 2018 legalized hemp-derived products in all 50 states; typically high in CBD, these products are derived from cannabis varieties containing ≤0.3% delta-9-tetrahydrocannabinol (THC) by weight. The recent "green rush" has resulted in a striking increase in cannabis use among patients and consumers who often use a wide variety of novel product types, each with a unique blend of cannabinoid constituents. Importantly, however, several cannabinoids have the potential to cause drug-drug interactions (DDI) with other medications, primarily due to their involvement with the hepatic cytochrome P450 (CYP450) system. This article examines the potential for individual cannabinoids, particularly CBD, to interact with the hepatic metabolic system, which is concerning given its involvement in the metabolism of commonly-prescribed medications. CBD and other cannabinoids are metabolized extensively by the CYP450 system, and also inhibit many of these enzymes, potentially leading to variable serum levels of other medications, as well as variable levels of cannabinoids when other medications modify the system. As access and interest in cannabinoid-based products continues to increase, critical questions remain unanswered regarding their safety. The complex relationship between cannabinoids and the

hepatic metabolic system, including common potential DDI resulting from cannabinoid exposure, are explored along with the clinical significance of these potential interactions and monitoring or mitigation strategies.

KEYWORDS

medical cannabis, cannabidiol (CBD), drug-drug interaction (DDI), CYP450, hepatic metabolism

1. Introduction

Cannabis sativa is comprised of over 400 constituents, including more than 100 phytocannabinoids, many of which are known to have effects in the human body and demonstrate therapeutic potential (1). Until recently, despite widespread cannabis use, little research had elucidated the effects of cannabinoids on various biological processes. Two primary cannabinoids found in the plant are delta-9-tetrahydrocannabinol (THC), the most abundant cannabinoid and the primary intoxicating constituent, which has also demonstrated therapeutic benefits as an anti-emetic for chemotherapy-induced nausea and vomiting, pain, and muscle spasticity (2); and cannabidiol (CBD), often the second most abundant cannabinoid which is non-intoxicating and has been touted as therapeutic for a range of indications, including seizure disorders, anxiety, pain, and inflammation (3). In addition to THC and CBD, dozens of "minor" cannabinoids are found in the plant which are also often present in cannabis products, including cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), cannabidivarin (CBDV), tetrahydrocannabivarin (THCV), and the acid forms of THC and CBD (THCA and CBDA), among others. While little work thus far has focused on minor cannabinoids, studies have shown that these compounds have a variety of biological effects (1, 4), and the presence of minor cannabinoids in medical cannabis (MC) products is increasing (5–7) as consumers and patients become aware of their potential utility.

Medical cannabis use has increased dramatically in recent years; in the U.S., almost all states have passed legislation allowing the use of MC or CBD-containing products. The rapid legalization of MC has coincided with a significant increase in MC use; state registry data indicates a 4.5 fold increase in registered MC patients from 2016 to 2020 (8), and use among older adults has increased particularly rapidly (9). As of November 2022, 37 states plus the District of Columbia (D.C.) have fully legalized the use of MC; in addition, 21 states plus D.C. have legalized adult or recreational use of cannabis (10, 11). Additionally, the Agricultural Improvement Act of 2018 (colloquially known as the "Farm Bill") legalized hemp-derived products containing <0.3% THC by weight (12). While a synthetic form (dronabinol) and an analog (nabilone) of THC were approved by the U.S. Food and Drug Administration (FDA) in 1985 for treating chemotherapy-related nausea and vomiting, in 2018, the FDA approved Epidiolex, a plant-derived, purified CBD isolate for treatment-resistant, pediatric-onset seizure disorders. Epidiolex is the first (and only, to date) FDA-approved, cannabis-derived medication available in the U.S., while Sativex, a plant-derived 1:1 CBD:THC buccal spray, is available in several other countries (13). The convergence of legalization of cannabis and hemp, along with the more recent approval and availability of Epidiolex and Sativex, has resulted in a rapid increase in cannabinoid-based products available for purchase in dispensaries, through online retailers, and by prescription.

While the use of cannabinoid-containing products has increased significantly, relatively little work has focused on assessing potential drug-drug interactions (DDI) between cannabinoids and conventional medications. DDI can result in variable serum levels of substrates, leading to unexpected side effects, stronger drug effects than intended, or incomplete symptom relief due to lower efficacy (14). Several studies have demonstrated that cannabinoids interact with the cytochrome P450 (CYP450) enzyme system, the hepatic system responsible for the metabolism of most common medications, and the second phase of metabolism which further processes compounds for excretion (15–21). As these pathways are commonly implicated in DDI, increased cannabinoid use results in a major public health concern regarding potential DDI that has yet to be addressed. This article will provide a brief overview of the hepatic metabolic process and discuss potential areas of concern for interactions with cannabinoids (particularly CBD), the clinical significance of these interactions, and potential monitoring or mitigation strategies to minimize interactions which may help address public health concerns regarding DDI.

2. Hepatic metabolism: An overview

2.1. Phase I: CYP450 system

Drug metabolism primarily occurs in the liver, with secondary metabolism occurring at other sites including the

intestines, kidneys, blood plasma, and lungs (22). Phase I of metabolism involves hydrolysis, reduction, and oxidation (the most common type of metabolism) (22), resulting in a metabolite that is commonly still active (23). Two additional phases of metabolism often occur; Phase II reactions create inactive compounds with increased polarity, often *via* glucuronidation, that are water-soluble and thus able to be excreted, while Phase III (which is uncommon and not discussed here in detail) further metabolizes Phase II compounds to allow for excretion (23). Together, Phase I metabolism *via* the CYP450 system and Phase II glucuronidation account for the metabolism of over 90% of conventional medications (18).

The CYP450 system is the major hepatic metabolic enzyme system that catalyzes Phase I reactions and is involved in the metabolism of the majority of common medications (24, 25). CYP450 is a hemeprotein superfamily comprised of over 50 enzymes/pathways (22) named with a family number (e.g., CYP1) and a subfamily letter (e.g., CYP1A), along with another number to determine the specific isoform or enzyme (e.g., CYP1A1) (22). Importantly, these enzymes do not typically work in isolation; multiple enzymes are often involved in the metabolism of a single medication or substrate.

In a report describing the characterization and distribution of CYP450 enzymes, Zanger and Schwab (24) noted that the enzymes most often associated with metabolizing typical medications were CYP3A4/5 (metabolizing > 30%); CYP2D6 (metabolizing > 20%); CYP2C9 (metabolizing > 13%); and CYP1A2 (metabolizing ∼9%). Other research has reported similar findings, confirming the critical role these enzymes play in metabolizing the majority of "most often prescribed" medications (26). Multiple factors impact functionality of each CYP enzyme, including polymorphisms, age, inflammation, illnesses/disease, and sex (24); variability in enzyme function over time may lead to fluctuations in metabolism within the same person, as well as inconsistent and variable levels of metabolism when compared to other individuals.

Modification of the CYP450 system by exogenous substances can alter metabolism of other substrates in two primary ways–inhibition and induction. Inhibition of CYP450 enzymatic activity is primarily accomplished by competitive binding; by occupying the enzyme's active binding site, other substrates are displaced and are unable to be metabolized (27). The other main inhibitory method is non-competitive inhibition, in which the inhibitor binds to a different (allosteric) binding site than the substrate, changing the enzyme's shape or function such that the substrate's binding site is no longer available (27). Inhibition has the potential to result in incomplete metabolism and increased serum levels of concomitant medications, potentially leading to adverse events (28). Several medications are recognized as CYP450 inhibitors, including omeprazole, erythromycin, fluvoxamine, fluoxetine, haloperidol, ritonavir, and some antifungals including ketoconazole and fluconazole (27–29).

Induction is the second method by which exogenous substances typically modify the CYP450 system. Inducers activate a CYP enzyme, leading to increased enzymatic activity, which results in decreased bioavailability and increased clearance of certain medications (28). This is typically accomplished by activation of transcription factors resulting in increased expression of CYP enzymes (29). Many medications have been identified as CYP450 inducers, including carbamazepine, ethinyl estradiol, phenobarbital, dicloxacillin, and others [see Hakkola et al. for review (29)].

It is important to note that many medications with a narrow therapeutic index (TI), the ratio between a drug's toxicity and effectiveness, rely on metabolism by the CYP450 system. Common medications with narrow TIs include anticoagulants, beta blockers, antidepressants, and antipsychotic medications. The enzyme CYP2C9 is particularly important, given many of its substrates include those with a narrow TI (24). Disruption of enzymatic activity may result in clinically significant changes in serum levels of these drugs with a narrow TI, leading to inadequate symptom relief or even adverse events.

2.2. Phase II metabolism

Phase II metabolism involves adding hydrophilic groups to the substrate or its metabolites to create water-soluble products for excretion (23). It involves multiple mechanisms, including methylation, acetylation, conjugation with amino acids or glutathione, or sulfation, but primarily involves glucuronidation using uridine 5′-diphosphoglucuronosyltransferase (UGT) enzymes, which link glucuronic acid to the substrate in order to increase polarity (13). A variety of UGT enzymes are involved in this process, and typically multiple UGTs are involved in glucuronidation of a single compound. Four broad families of UGT enzymes are involved in human drug metabolism: UGT1, UGT2, UGT3, and UGT8 (30).

Many common medications rely on activity of these enzymes, including over-the-counter (OTC) products like ibuprofen and other non-steroidal anti-inflammatory drugs (mainly relying on the UGT1A and 2B subfamilies), acetaminophen (primarily glucuronidated by the UGT1A subfamily), and prescription drugs including valproic acid, sorafenib, and propofol (13). Given that common OTC medications and prescription medications rely on glucuronidation, significant DDI could occur for many individuals.

3. Cannabinoid involvement with hepatic metabolic pathways

Medical cannabis and cannabinoids are available across a range of product types with many possible modes of use

or routes of administration, resulting in variable impact with regard to metabolism. For example, inhalation (smoking or vaping) predominantly avoids first-pass metabolism (31) and is associated with a very rapid onset of action and relatively limited concern regarding DDI (15). Conversely, ingestion introduces cannabinoids through the gastrointestinal tract where they are processed, absorbed into the bloodstream, and travel to the liver where they undergo first-pass metabolism, resulting in a more delayed onset of action and raising significant concern regarding DDI (32). Cannabinoid metabolism may be impacted by medications that interact with hepatic metabolic pathways, potentially leading to greater side effects or unintended effects (such as intoxication), as well as directly impacting the metabolism of other substances relying on hepatic metabolism. Given the increasing availability and variety of cannabis and cannabinoid products, it is imperative to understand the potential interactions for both major and minor cannabinoids.

3.1. Cannabidiol (CBD)

Cannabidiol (CBD) has become increasingly popular given its potential therapeutic benefits without risk of intoxication. Given CBD-based products are typically used as edibles, capsules, or sublingual solutions/oils, and since CBD has been identified as the cannabinoid exhibiting the strongest interactions with the CYP450 system (21), CBD poses considerable risk for DDI.

Cannabidiol is metabolized extensively by the CYP450 system (13, 15, 17, 18), primarily by hydroxylation (21); while not all research agrees on the specific enzymes involved in CBD metabolism, it is clear that many are implicated. In addition to the CYP2C9, CYP2C19, CYP3A4, UGT1A9, and UGT2B7 enzymes involved in general cannabinoid metabolism (18), CYP2C8, CYP1A2, and CYP2B6 are also potentially implicated in CBD metabolism; several additional studies suggest that CYP2C9, CYP2C19, and CYP3A4 likely play the greatest role in metabolism of CBD (21, 33, 34).

Cannabidiol also modifies CYP450 enzyme function as an inhibitor and inducer. Several studies indicate that CBD inhibits CYP450 enzymes, typically due to competitive inhibition. Specifically, *in vitro* and *in vivo* studies have demonstrated that CYP2C9, CYP2C19, CYP2D6, and CYP3A enzymes are inhibited by CBD; CYP1A2, CYP2B6, and CYP2C8 may also exhibit reduced function after administration of CBD (15, 17, 18, 33). UGT1A9 and UGT2B7 are potentially inhibited by CBD administration as well (18, 35), indicating that not only is Phase I impacted, but Phase II inhibition is also possible. Additionally, CBD may modify the CYP450 system through induction; CBD may induce CYP1A2, CYP2B6, and CYP3A4 (20, 36). Other inhibitors or inducers of the CYP450 system may also affect the bioavailability of CBD, either increasing or decreasing serum levels, depending on the pathways implicated.

Investigations have only more recently begun to examine the potential clinical significance of interactions precipitated by CBD co-administration with other medications. While only a few studies have examined these effects, these investigations are especially useful in determining whether clinically meaningful interactions may affect the bioavailability of either CBD or concomitant medications. Bansal et al. (15, 16) precipitated interactions in a human liver microsome model and determined that strong interactions likely occur with high-dose oral CBD (700 mg) and CYP3A substrates, followed by moderate interactions with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 substrates. In a clinical study, Gaston et al. (37) assessed serum levels of antiepileptic drugs following titration from 5 to 50 mg/kg/day of CBD in patients with epilepsy. Increasing CBD doses were associated with changes in serum levels of clobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine, although levels remained within the acceptable serum range for each drug (37). Finally, in a recent clinical trial, Anderson et al. (38) examined CBD's impact on serum levels of several medications used to treat anxiety disorders (fluoxetine, sertraline, citalopram, escitalopram, and mirtazapine), finding that common doses of CBD-containing products (200–800 mg/day) resulted in significantly increased citalopram serum levels in patients taking citalopram or escitalopram. The full clinical significance of these alterations is yet to be explored.

In addition to the risk of DDI, many medications have the potential to cause liver damage; pre-existing liver disease can significantly impact drug metabolism, resulting in substantial DDI (39). Liver function tests (LFTs) are a common way to monitor liver health and provide an important indicator of hepatic disease. Clinical trials of Epidiolex reported elevated LFTs in some individuals, which increased as the daily dose of Epidiolex increased; further, co-administration of Epidiolex with valproate and/or clobazam resulted in a significantly higher risk of elevated LFTs (3, 36). It is possible that these LFT elevations are clinically significant and have the potential to be serious; further investigation is warranted regarding the impact of CBD on LFTs with and without concomitant medication administration. Importantly, however, the prescribed daily dose of Epidiolex typically ranges from 5 to 20 mg/kg/day, which is significantly higher than typical doses of full- or broad-spectrum CBD products proliferating in the marketplace, raising the question of whether lower-dose CBD products are less concerning.

3.2. Delta-9-tetrahydrocannabinol (THC)

Considered the most abundant cannabinoid in the plant, and often sought by both recreational consumers and medical patients, delta-9-tetrahydrocannabinol (THC) is also likely to

impact metabolic pathways, particularly the CYP450 system, causing potential DDIs. In their review, Kocis and Vrana (18) reported that CYP2C9, CYP2C19, CYP3A4, and UGT1A9 and UGT2B7 are the primary enzymes involved in cannabinoid metabolism, including THC. Several studies have demonstrated that THC may act as an inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP2J2 (17, 19, 20). THC may also induce CYP1A1 and CYP2C9 (20). While many edible THC products are available in the marketplace, a significant number of THC-containing products are designed to be inhaled (i.e., smoked and vaped), which bypass first-pass metabolism in the liver, potentially limiting concerns related to DDI for at least some products (15).

3.3. Minor cannabinoids

Despite increasing presence in commercially-available products, relatively little research has focused on the impact of "minor" cannabinoids, which are less abundant in the plant than THC and CBD, and include CBG, CBC, CBN, THCV, CBDV, CBDA, and THCA. Although many "minors" are often only present in trace amounts in the plant and were historically present in very small amounts in cannabis and cannabinoid-based products, recent interest in their potential clinical benefit has resulted in products focused on delivering isolated minor cannabinoids (e.g., CBG and CBN) as well as combination products containing multiple cannabinoids. Cannabinol (CBN) is the most commonly studied minor cannabinoid, which has demonstrated inhibition of CYP1A1, CYP2B6, CYP2C9, and CYP2E1 (17, 19, 40, 41). Recently, Doohan et al. (17) evaluated the inhibitory potential of cannabinoids including 10 minor cannabinoids (THCA, THCV, THCVA, CBDA, CBDV, CBDVA, CBN, CBC, CBG, and CBGA) against CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 *in vitro*. All minor cannabinoids except CBN inhibited CYP2C9, and most (CBDV, CBDVA, CBG, CBN, THCV, and THCVA) inhibited or partially inhibited CYP2C19. It is not clear from these *in vitro* studies whether minor cannabinoids inhibit the CYP450 system in a clinically meaningful way. Given their growing popularity and the increasing number of novel products in the marketplace containing considerable amounts of these constituents, additional research is needed to determine the likelihood of DDI related to minor cannabinoids.

4. Future directions

As access to MC products, particularly high CBD-containing products, continues to expand, critical questions remain unanswered regarding their safety. Although few studies have assessed the clinical significance of common DDI related to CBD exposure, evidence suggests moderate to strong interaction risks between CBD and drugs metabolized by a variety of CYP450 enzymes (15, 16), indicating that *interactions are likely at clinically-relevant doses of CBD*. Future studies are needed to fully evaluate the potential for cannabinoids to cause DDI; *in vivo* studies and human pharmacokinetic/pharmacodynamic (PK/PD) studies involving co-administration of multiple medications with cannabinoids will be particularly valuable in determining the clinical significance of any interactions. As DDI are also more likely with drugs with a narrow TI (17, 18, 22), additional co-administration studies are warranted, particularly for CYP2C9 substrates with a narrow TI (17). In addition, studies are necessary to assess whether DDI that result in changes in bioavailability actually lead to adverse outcomes in various clinical populations.

To date, potential mitigation strategies have not been studied. It is unlikely that an offset between administration of cannabinoids and concomitant medications of concern would completely address the issue, given the extremely long half-life of certain cannabinoids, which are lipophilic and remain detectable for days to weeks after use (42, 43); however, this should be evaluated directly. Monitoring strategies, including serial blood draws assessing serum levels of concomitant medications, and monitoring LFTs to avoid potential hepatic damage, could be utilized to minimize potential negative outcomes. Importantly, as the majority of older adults take medications involving the CYP450 system (44), this group is particularly important to monitor upon initiation of cannabinoid use. Consumers and health care providers alike should be informed regarding the potential for DDI when considering cannabis and cannabinoid use, and efforts should be made to eliminate or limit potential risk and harm.

5. Conclusion

The proliferation of medical cannabis and hemp-derived products has resulted in thousands of commercially available cannabinoid-based options in the marketplace. Many consider cannabis and cannabinoid-based products relatively harmless, especially those high in CBD which is non-intoxicating and often touted for its medical benefits. Unfortunately, concerns regarding the potential safety issues associated with their use in conjunction with other medications are often overlooked. While there is great promise in the use of cannabis and cannabinoid-based products for a range of conditions, researchers and healthcare providers should be aware of the potential for significant DDI and should counsel their patients regarding potential interactions whenever the use of cannabinoid-based products is disclosed or considered. As cannabis and cannabinoid use increases, particularly vulnerable groups (e.g.,

older adults) should understand the potential risks associated with using these products with concomitant medications.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

RS and SG designed and conceptualized the manuscript, responsible for writing and editing, and accountable for the full content of the manuscript. Both authors contributed to the article and approved the submitted version.

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Conflict of interest

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The clouded debate: A systematic review of comparative longitudinal studies examining the impact of recreational cannabis legalization on key public health outcomes

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Background: Ineffective cannabis regulatory frameworks such as prohibition have sparked interest in alternative solutions to reduce individual and societal harms. While it has been suggested that the recreational legalization process has yielded early successes, the relatively recent implementation of the novel policies has provided a modest time frame for a truly thorough establishment and assessment of key population-level indicators. The following systematic review focuses on identifying the downstream public health sequelae of cannabis legalization policies, including parameters such as cannabis consumption rates, hospitalization rates, vehicular accidents and fatalities, criminal activity, and suicidal behaviors, as well as other substance use trends.

Methods: An exhaustive search of the MEDLINE and Google Scholar databases were performed to identify high-quality (1) longitudinal studies, which (2) compared key public health outcomes between regions which had and had not implemented recreational cannabis legalization (RML) policies, (3) using distinct databases and/or time frames. Thirty-two original research articles were retained for review.

Results: Adult past-month cannabis consumption (26+ years) seems to have significantly increased following RML, whereas young adult (18–26 years) and adolescent (12–17 years) populations do not show a significant rise in past-month cannabis use. RML shows preliminary trends in increasing service use (such as hospitalizations, emergency department visits, or poisonings) or vehicular traffic fatalities. Preliminary evidence suggests that RML is related to potential increases in serious/violent crimes, and heterogeneous effects on suicidal behaviors. While the research does not illustrate that RML is linked to changing consumptions patterns of cigarette, stimulant, or opioid use, alcohol use may be on the rise, and opioid prescribing patterns are shown to be significantly correlated with RML.

Conclusion: The current data supports the notion that RML is correlated with altered cannabis consumption in adults, potentially increased criminal activity, and a decline in opioid quantities and prescriptions provided to patients. Future work should address additional knowledge gaps for vulnerable populations, such as individuals with mental health problems or persons consuming cannabis frequently/at higher THC doses. The effects of varying legalization models should also be evaluated for their potentially differing impacts on population-level outcomes.

KEYWORDS

cannabis, legalization, recreational, review, longitudinal

1. Introduction

It has been suggested that international cannabis prohibition mandates have failed to achieve key goals such as harm reduction, increased prevention and treatment, and have instead generated negative consequences, including increased contributions toward global disease burden over time (1, 2) and exacerbating social inequalities through disproportionate impacts on people of color (3, 4). As such, ineffective regulatory frameworks such as cannabis prohibition have sparked interest in alternative solutions to reduce individual and societal harms (5). Recently, countries such as Uruguay, Canada, and certain states of the United States have enacted recreational marijuana laws (RML). While the overarching frameworks vary between locations, certain RML laws propose to enhance the protection of vulnerable populations; strengthen health education programs; provide access to quality-controlled cannabis; and enable the close monitoring of public health outcomes through these new regulatory frameworks (6). Despite these beneficial aspirations, the enactment of cannabis legalization policies remains hotly questioned. Several thought leaders have denoted an opposition against the hasty implementation of legalization policies, warning against the escalation of use and related harms among the most vulnerable populations, such as youth (7), an increase in driving under the influence, or increased risk of using other drugs, including harder drugs (8). Despite having collected close to a decade of research evidence, we have yet to determine unequivocal findings to support either side of the discussion relating to recreational cannabis legalization laws.

Regarding the impacts of RML on general cannabis consumption, studies conducted in several states across the US have found discrepant results. Initial evidence in adult populations have found increases in cannabis use over time (9–11), decreases of use (12), or even a lack of change altogether (13). Youth populations also demonstrate varying effects, with evidence for overall exacerbated use (14), diminished use (15), or show no impact (16). Of importance, the largest source of data collected on consumption metrics relate to past month cannabis use, few have investigated frequent use, and sparse have examined trends in cannabis use disorder. As marijuana consumption trends may vary over time, using outcome metrics such as past month marijuana use may not provide an accurate reflection of true individual consumption trends over time. This may entail an over or under-estimation in the number of individuals at highest risk of adverse health consequences associated with cannabis use.

Beyond simple consumption patterns, several other population parameters have been monitored over time to determine the impacts of RML. Seminal work developed by Lake and colleagues highlighted the use of 28 indicators to monitor RML effects, including public safety measures such as vehicle injuries/fatalities and crimes; other substance use and overdose trends; and hospitalizations related to cannabis use (17). Research has suggested potential surges in vehicular fatalities and crimes–specifically, increases in crimes such as burglary, larceny, violent assaults, and so forth (18, 19). Preliminary evidence points to potential increases in healthcare service use related to cannabis (20–22). However, these initial assumptions seem to be skewed by an overrepresentation of increases in specific states, such as Colorado. Other substance use, such as alcohol, tobacco, or illicit drugs use, has seen trends of increases (23), decreases (11), and no changes (24).

The discrepant results in the current literature can be partially attributed to the methodology and sampling used in the research studies. Most are performed in a single location, thus omitting trends over the same time course in a comparator location. Thus, such studies may highlight changes that are not necessarily related to legalization *per se*, but may actually reflect other unspecific factors, such as the perception of harms, for instance. Other studies have used a comparator location but have collected data only post-legalization. These are both critical methodological aspects to consider, as certain locations may be already experiencing upticks in cannabis consumption prior to legalization, thus post-legalization patterns across regions should be interpreted with caution. Certain studies collect only a single datapoint prior to RML implementation, or only a

single datapoint post RML implementation, providing little information on the trends already occurring prior to RML implementation, as well as little information into long-term effects if studying a short post-RML period. Considering the limitations of studies using these methodological strategies, it would be beneficial to update the current state of the knowledge of RML impacts on population health metrics using longitudinal comparative studies.

As such, the following systematic review seeks to shed light on the clouded debate of the impacts of RML on key public health metrics. Importantly, we aim to perform a systematic review of studies which will provide a high level of insight: research articles which follow RML and non-RML states, with a baseline assessment of public health trends prior to RML implementation. This systematic review will focus on key metrics outlined by Lake et al. (17) to examine if RML implementation affects youth/young adult/adult cannabis consumption, service use, vehicular crashes/fatalities, crimes (unrelated to cannabis possession), and other drug use. The evidence provided in this review will help provide recommendations for future cannabis legalization policy research.

2. Methods

2.1. Search strategy

The search strategy was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (25). Potential articles were discovered through an exhaustive search of the MEDLINE database and Google Scholar for studies expanding from January 1, 2012–which corresponds to the year where recreational cannabis was legalized for the first time in Colorado and Washington–until February 1, 2022. The following terms were employed to direct our search for research articles: ("marijuana/marihuana," "cannabis," "illicit), the independent factor ("legalization," "recreational") and the outcomes of interest ("use," "consumption," "hospital*", "traffic," "crime," "alcohol," "stimulant," "opioid," "nicotine"). Cross-referencing of previous systematic reviews on the topic was also performed.

2.2. Eligibility criteria

Longitudinal observational studies were retained for the purposes of this systematic review. Specifically, we retained studies that: (i) had a baseline assessment (pre) prior to the implementation of recreational cannabis legalization, and a subsequent assessment (post) at least 6 months after the implementation of RML.; and (ii) which also longitudinally assessed at least one comparator location (control) which did not undergo RML. Of note, in some article, the same subjects were investigated over time, while in others, multiple measures were acquired over time in different samples of persons living within a state.

2.2.1. Exclusion criteria

In addition to the above-referenced criteria, studies were excluded if they evaluated medical cannabis legalization. We omitted studies which focused on solely on the impact of recreational cannabis legalization on arrests for possession of cannabis. Studies in languages other than English were also excluded. We did not retain studies that lacked a comparison group, or studies that did not have at least one pre-legalization evaluation and one post-legalization evaluation. There was an important number of publications which utilized overlapping databases and/or time points to study the effects of RML. As such, for all overlapping research initiatives, M.A. and S.P. identified the studies used for primary analyses purposes, which provided the latest data, included the highest number of participants and/or the highest number of states, and provided the longest follow-up period. Any overlapping studies which investigated single locations were retained for secondary analysis purposes when these studies reported data on specific outcomes that had not been reported in the primary analyses (example: specific effects in particular locations). The final decision on the inclusion and exclusion of studies was determined by consensus between M.A. and S.P.

2.3. Data extraction and quality assessment

The following information was extracted by two independent authors (M.A. and I.Z.): (1) type of population studied (including sample size (if available), average age, sex ratio); (2) RML locations studied; (3) non-RML comparator locations; (4) years assessed; (5) data source; (6) outcome measures analyzed; (7) confounding factors controlled for/considered in the analyses; (8) statistical models used in the analyses; (9) overarching results.

A quality assessment was then performed on the retained articles using an adapted version of the Newcastle - Ottawa Quality Assessment Scale for cohort studies (26). Briefly, studies were rated on strength of sampling selection, comparability, outcome, and follow-up time. As per the tool, studies were rated using a 3-point system (0–2 points), and accumulated scores on the 7 rated items qualified them as having either weak (0–4), moderate (5–9) or strong (10–14) reporting strength.

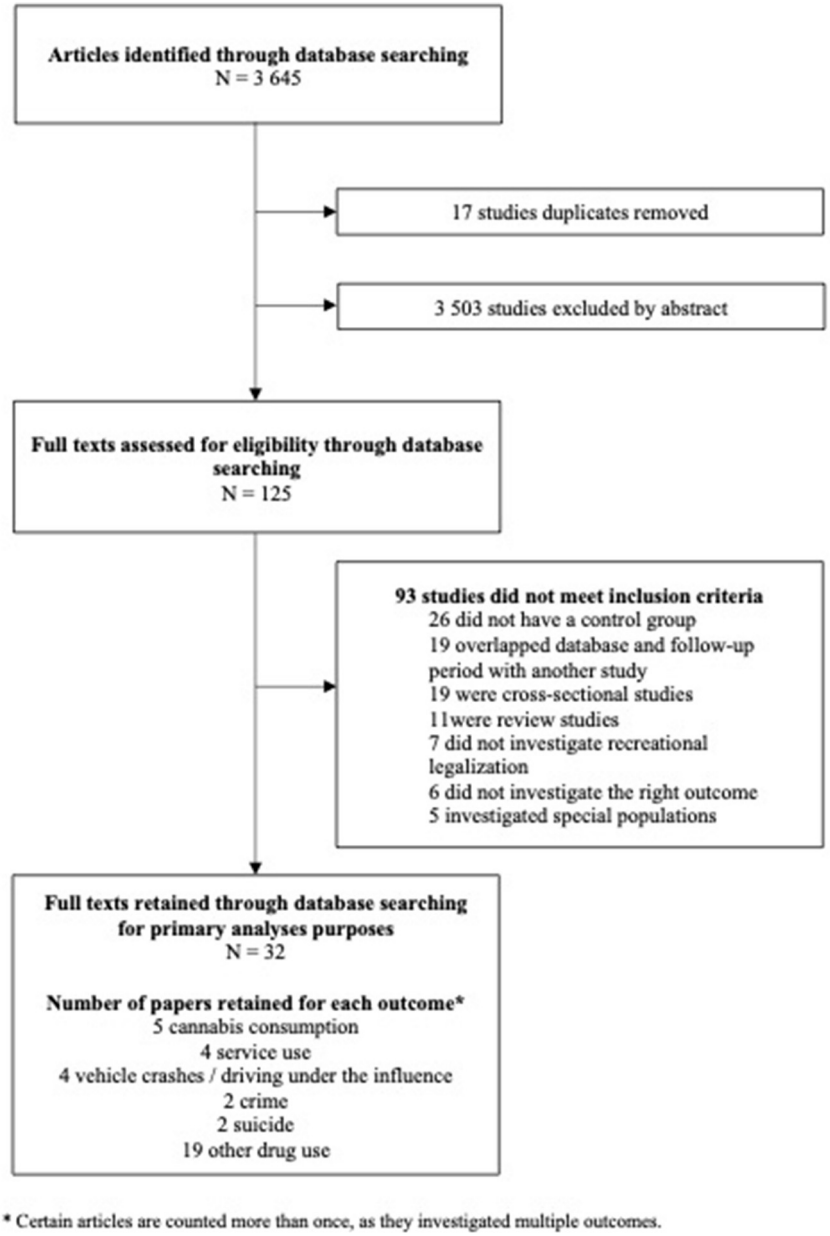

FIGURE 1
PRISMA flow Chart for the impact of the legalization of recreational cannabis on key public health outcomes.

3. Results

3.1. Study selection

Out of 3645 studies identified in the database search, 125 articles underwent full-text screening, whereby 93 articles were excluded, predominantly because they were not longitudinal in nature (26), did not include a comparator group (19), or the database and time frame used in the analysis overlapped with another study retained for review (20). Thirty-two unique articles stemming from this database search were included in the primary analyses (Figure 1 PRISMA flow chart).

3.2. Study characteristics

Studies investigating the effects of cannabis legalization on health outcomes are summarized in Table 1. Most studies

included in the review investigated multiple locations which had or had not implemented RML. While most studies accounted for a large number of covariates, including age, sex, socioeconomic status, prior education, and prescription drug monitoring programs, it should be noted that a few publications failed to account for more than a few basic confounders.

3.3. Study quality and reporting strength

As described in Table 2, the range of scores from the extracted articles varied greatly (between 5 and 12), with an average overall strong quality score of 10.25. As a quality score of 10 and above is considered as methodologically robust, 25 studies of the total 32 were deemed as good-quality evidence to accurately depict the relationships between RML and the selected population-level outcomes. Overall, the selected samples were representative of the targeted population; the nature of the studies yielded large sample sizes including thousands of persons. The intervention and comparator locations were clearly defined and represented a large number of states. The outcomes included relatively objective observable outcomes, mostly from government-mandated databases. A wide range in the years assessed was noted, whereby studies had a follow-up period of 4–18 years post-baseline assessment.

3.4. Results of study outcomes

3.4.1. Adult consumption

One research article examined the impact of RML on adult (26 years+) past-month cannabis use (11). Using the National Survey on Drug Use and Health (NSDUH) across 11 states. The authors determined that RML was associated with an increase in past-month adult consumption. One study evaluated past-month frequent use, as well as past-year CUD prevalence in adults using the NSDUH across 4 RML locations: Colorado, Washington, Alaska, and Oregon (10). The data yielded a significant increase in past-month frequent use (from 2.13 to 2.62%), as well as an increase in past-year CUD (from 0.90 to 1.23%).

3.4.2. Young adult (18–26) consumption

Three publications assessed the impact of recreational marijuana legalization on young adult past-month cannabis use in multiple RML states (9, 11, 27). While two studies demonstrate a lack of effect of RML, Bae and Kerr (9) found that college students in states with legalized recreational cannabis use had an increased prevalence of past-month use [adjusted Odds Rations (OR) of 1.23]. Three additional studies were retained for secondary analysis purposes and investigated the effects of RML specifically in in Colorado, Oregon, and Washington (28–30). In all three cases, RML was linked to increased past-month cannabis use in young adults. Regarding frequent use, Bae and Kerr (9) has found an increased adjusted Odds Rations (OR) of 1.18, whereas Cerdà et al. (10) failed to find evidence of increased past-month frequent use, or past-year prevalence of CUD, among young adults.

3.4.3. Youth (12–17)

Three primary articles investigated past-month cannabis use in adolescents (1, 31, 32). While Kim et al. (11) found a decrease in past month use, Coley et al. (32) did not find evidence for an increase or decrease in use, and Cerdà et al. (31) only found increases in past-month use of eighth and tenth graders. One additional study was retained for secondary analysis purposes and demonstrated that RML was associated with heightened past-month use in Alaskan youth (17). Cerdà et al. (10) did not report increases in past-month frequent use, however, did denote an increase in past-year CUD prevalence in youth (OR 1.25; 95%, confidence interval (CI) 1.01–1.55).

3.4.4. Healthcare-related service use

Four articles studied RML effects and service use, including cannabis-related hospitalizations, emergency department visits and reported cannabis exposures (33–36). Three studies denoted heightened service use in association with RML status, whereas Mennis et al. (37) found a decrease in cannabis-related treatments admissions in young adults in seven legalized states.

3.4.5. Multi-vehicle collisions, traffic fatalities or driving under the influence

Four studies assessed traffic-related accidents, injuries, and driving while intoxicated according to recreational legalization status. Delling et al. (33) extracted multi-vehicle collision data from the Healthcare Cost and Utilization Project database for the state of Colorado and found a significant impact of RML. These findings were echoed by Kamer et al. (38), who used Fatality Analysis Reporting System (FARS) data to demonstrate a link between a doubling in traffic fatality rates and RML in Colorado, Washington, Oregon, and Alaska. Lane et al. (39) utilized the Centers for Disease Control and Prevention Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER) database to show that Washington state experienced an increase in traffic fatalities, whereas Colorado and Oregon did not. While no information on location is provided, Benedetti et al. (40) extracted data from the Traffic Safety Culture Index (TSCI) and found no effect of RML status on driving while under the influence.

TABLE 1 Overview of longitudinal studies investigating the impact of cannabis legalization public health outcomes used for primary analyses.

Study	Year	Population	Location (s) studied	Comparator location (s)	Years assessed	Data source	Outcome (s) of interest	Ascertainment of outcome (s) of interest	Brief main findings of the impacts of RML
Alcocer	2020	All persons in participating states	CO	32 non-RML states	1999–2017	WONDER	Opioid mortality	Opioid overdose mortality rate per 100,000 in population	No significant difference
Alley	2020	18–26-year-old college students	All RML states	All non-RML states	2008–2018	NCHA-II	Other drug use	Self-reported use	Decreased odds of binge drinking, no significant difference for other drug use
Bae	2019	18–26-year-old college students	7 RML states	41 non-RML states	2008–2018	NCHA-II	Cannabis use	Self-reported past-month use (any), frequent use (>20 uses in last month)	Increased odds of cannabis use
Benedetti	2021	Adult drivers	All RML states	All non-RML states	2013-2017	TSCI	Driving under the influence of cannabis	Self-reported past-year driving within 1 h of marijuana use	No significant difference
Bhave	2020	All persons in participating states	CO, OR, NV, WA	Synthetic control	2012–2017	Retail scanner data from A.C. Nielsen	Nicotine use	Weekly cigarette sales in packs	Increased odds of nicotine use
Cerdà	2020	Persons 12+ in participating states	CO, WA, AK, OR	All non-RML states	2008–2016	NSDUH	Frequent use in the past month, past-year CUD overall	Self-reported past-month use, frequent use (>20 days or more of use in the past month), past-year prevalence of CUD (instrument that assessed symptoms corresponding to DSM-IV criteria)	Group 12–17 years: No increase in frequent use; increased past-year CUD prevalence Group 18–26 years: No difference for any outcome Group 26+ years: Increase in both outcomes
Cerdà	2017	High school students	CO, WA	45 non-RML states	2010–2015	MTF	Cannabis use	Self-reported past-month use (any)	Increased odds of cannabis use in youth in Washington (grades 8–10)
Chan	2020	All persons in participating states	All RML states	Non-RML states	1999–2017	NVSS	Opioid mortality	Means of opioid mortality rates (per 100,000 population)	Decreased odds of opioid mortality

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TABLE 1 (Continued)

Study	Year	Population	Location (s) studied	Comparator location (s)	Years assessed	Data source	Outcome (s) of interest	Ascertainment of outcome (s) of interest	Brief main findings of the impacts of RML
Coley	2021	Youth	6 RML states	Non-RML states	2015 and 2017	YRBS	Cannabis use, other drug use	Past-month marijuana, alcohol, cigarette, e-cigarette use (number of times)	No significant difference for cannabis use, small increased odds of cigarette use
Delling	2019	Inpatients in participating states	CO	NY, OK	2010–2014	HCUP	Service use	Total number of hospitalizations, length of inpatient stay, healthcare costs, hospitalization related to multi vehicle collisions	Increased odds of cannabis-related service use
Doucette	2021	All persons in participating states	CO, WA	Synthetic control	2000–2018	NCHS	Suicide rate	Annual, state-level deaths by suicide	Increased odds of death by suicide in Washington, no significant difference in Colorado
Drake	2021	All persons in participating states	CA, ME, MA, NV	Non-RML states	2011–2017	HCUP	Service use	Log opioid-related ED visit rates per 100,000 population in states	No significant difference in service use
Kamer	2020	All persons in participating states	CO, WA, OR, and AK	20 non-RML states	2008–2018	FARS	Traffic fatality rates	Traffic fatality rates	Increased odds of traffic fatalities
Kerr	2017	18–26-year-old college students	OR	6 non-RML states	2014 and 2016	HMS	Cannabis use, other drug use	Self-reported past-month use (any) of marijuana, cigarette and frequency of heavy alcohol	Increased odds of cannabis use only in recent heavy alcohol users
Kim	2021	All persons in participating states	AK, CA, CO, DC, MA, ME, NV, OR, WA	Non-RML states	2004–2017	NSDUH	Cannabis use, alcohol use	Self-reported past month marijuana use (any), past month alcohol use (any)	Increased odds of cannabis use only in adults

(Continued)

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TABLE 1 (Continued)

Study	Year	Population	Location (s) studied	Comparator location (s)	Years assessed	Data source	Outcome (s) of interest	Ascertainment of outcome (s) of interest	Brief main findings of the impacts of RML
Kropp Lopez	2020	All persons in participating states	CO	UT, MD	2007–2017	DEA ARCOS	Opioid prescriptions	Prescription opioid distribution for OUD treatment (oral morphine milligram equivalents)	Significantly increased oral MME
Lane	2019	All persons in participating states	CO, WA, OR	AL, AR, FL, GA, IN, IA, KY, MI, MS, MO, ND, NC, SC, SD, TN, TX, VA, WV, WI	2009–2016	WONDER	Traffic fatalities	Monthly traffic fatalities rates per million residents	Decreased odds of traffic fatalities only in Washington
Lopez	2021	Medicaid enrollees in participating states	AK, CA, CO, DC, MA, ME, NV, OR, WA	Non-RML states	2013–2017	Medicare Part D Prescription Drug Event database	Opioid prescriptions by orthopedic surgeons	Annual aggregate daily doses of all opioid medications (excluding buprenorphine) prescribed by orthopedic surgeons in each US state (and DC)	No association between RML and opioid prescriptions
Lu	2018	All persons in participating states	CO, WA	Non-RML states	1999–2016	FBI's UCR	Crimes	Monthly crime rates: violent, property, aggravated assault, auto theft, burglary, larceny, and robbery rates	No significant difference for violent crimes, only short-term increase in property crimes in Colorado
Lu	2020	All Medicaid enrollees in participating states	All RML states	Non-RML states	2005–2019	Consumer Expenditure Interview Survey	Alcohol use	Alcohol expenditures	Increase in alcohol use
Masonbrink	2021	Youth	CA, CO, DC, MA, WA	AZ, CT, DE, FL, IL, IN, MD, MN, MO, NJ, NY, OH, PA, UT	2008–2019	Inpatient Essentials database	Service use	Annual incidence of a hospitalization with a cannabis-related diagnosis (i.e., cannabis-related hospitalization)	Increased odds of service use

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TABLE 1 (Continued)

Study	Year	Population	Location (s) studied	Comparator location (s)	Years assessed	Data source	Outcome (s) of interest	Ascertainment of outcome (s) of interest	Brief main findings of the impacts of RML
Matthay	2021	All Medicare enrollees in participating states	All RML states	All non-RML states	2003–2017	Clinformatics Data Mart; Optum Inc	Self-harm, Crimes	Claims for self-harm and assault injuries based on International Classification of Diseases codes	Increased odds of self-harm injury in males <21 years old, increased odds of physical assault for males and females <21 years old
McMichael	2020	Patients at outpatient pharmacies in participating states	All RML states	MCL and no marijuana law states	2011–2018	Symphony Health's IDV® dataset	Opioid prescriptions	(1) the total number of MMEs prescribed by each provider, (2) the total days' supply prescribed by each provider, (3) the number of unique patients to whom each provider prescribed opioids, (4) the percentage of a provider's patients receiving any opioids, and (5) whether a provider prescribed any opioids.	Significantly decreased oral MME
Mennis	2021a	All young adults in participating states	All RML states	All non-RML states	2008–2017	SAMHSA (TEDS-A), NSDUH	Service use	Treatment admissions for cannabis (number of young adult's treatment admissions/young adult population),	Decreased odds of service use
Mennis	2021b	Youth	CO, WA	Non-RML states	2008–2017	SAMHSA TEDS-A	Service use	Mean observed treatment admissions rates (per 10,000 population)	Increased odds of service use in Colorado
Miller	2017	18–26-year-old college students	WA	National average	2005–2015	NCHA, NSDUH	Cannabis use, other drug use	Self-reported past-month use	Increased odds of cannabis use, no significant difference for other drugs

(Continued)

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TABLE 1 (Continued)

Study	Year	Population	Location (s) studied	Comparator location (s)	Years assessed	Data source	Outcome (s) of interest	Ascertainment of outcome (s) of interest	Brief main findings of the impacts of RML
Shi	2020	All persons in participating states	All RML states	Non-RML states	2010–2017	USNPDS	Service use	Cannabis exposures reported to the US National Poison Data System	Increased odds of service use (unintentional exposures and exposures without medical consequences)
Shi	2019	All Medicaid enrollees in participating states	CO, WA, AK, DC, OR, CA, MA, ME, NV	HI, MI, MT, NM, RI, VT	2010–2017	Medicaid State Drug Utilization Data	Opioid prescriptions	(1) Number of opioid prescriptions, (2) Total doses of opioid prescriptions (in quantity of MME)	Significantly decreased oral MME
Veligati	2020	All persons in participating states	All RML states	All non-RML states	1990–2016	NIAAA, AEDS, Tax Burden on Tobacco	Other drug use	Per capita consumption of alcohol and cigarettes as measured by state tax receipts	No significant difference
Wallace	2020	18–26-year-old college students	CO	National Average	2011–2015	NCHA	Cannabis use	Self-reported 30-day use of cannabis	Increased odds of cannabis use
Weinberger	2022	All persons in participating states	All RML states	Non-RML states	2004–2017	NSDUH	Cannabis use, nicotine use	Self-reported past-month cannabis use (any)	Decreased odds of cannabis use in youth, increased odds of cannabis use in adults, decreased odds of nicotine use in youth
Wen	2021	Patients with employer-sponsored health insurance	All RML states	Non-RML states	2009–2015	Truven Health MarketScan Commercial Claims and Encounters Database	Opioid prescriptions	Monthly MME per enrollee	Significant decreased of oral MME

RML, Recreational Marijuana Legalization; WONDER, Wide-ranging ONline Data for Epidemiologic Research; NCHA, National College Health Assessment; TSCI, Traffic Safety Culture Index; MTF, Monitoring the Future; NVSS, National Vital Statistics System; YRBS, Youth Risk Behavior Surveillance; HCUP, Healthcare Utilization Project; NCHS, National Center for Health Statistics; FARS, Fatality Analysis Reporting System; HMS, Healthy Minds Study; NSDUH, National Survey on Drug Use and Health; DEA ARCOS, Drug Enforcement Administration Automation of Reports and Consolidated Orders System; FBI's UCR, Federal Bureau of Investigation Uniform Crime Reporting; SAMHSA TEDS-A, Substance Abuse and Mental Health Services Administration Treatment Episode Data Set; USNPDS, US National Poison Data System; NIAAA, National Institute on Alcohol Abuse and Alcoholism; AEDS, Alcohol Epidemiologic Data System; MME, milligram morphine equivalent.

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TABLE 2 Bias assessment of longitudinal studies investigating the impact of cannabis legalization public health outcomes used for primary analyses.

First Author	Year	Representativeness	Sample Size	Non-respondents	Ascertainment	Comparability	Assess outcome	Statistical test	Follow-up time frame	Score
Alcocer	2020	1	1	1	2	2	2	1	2	12
Alley	2020	1	1	0	2	2	2	1	2	11
Bae	2019	1	1	1	2	2	2	1	2	12
Benedetti	2021	1	1	1	2	2	2	1	1	11
Bhave	2020	1	1	0	2	2	2	1	1	10
Cerdà	2020	1	1	1	2	2	2	1	2	12
Cerdà	2017	1	1	1	2	2	2	1	1	11
Chan	2020	1	1	1	2	2	1	1	2	10
Coley	2021	1	1	1	2	2	2	1	0	10
Delling	2019	1	1	1	2	2	2	1	1	11
Doucette	2021	1	1	1	2	2	2	1	2	12
Drake	2021	1	1	1	2	1	0	1	1	8
Kamer	2020	1	1	0	2	1	2	1	2	10
Kerr	2017	1	1	1	2	2	2	1	0	10
Kim	2021	1	1	1	2	2	2	1	2	12
Kropp Lopez	2020	1	1	1	1	0	2	0	2	8
Lane	2019	1	1	0	2	0	2	1	1	8
Lopez	2021	1	1	0	1	2	2	1	1	9
Lu	2018	1	1	1	2	0	2	1	2	10
Lu	2020	1	1	1	2	1	2	1	2	11
Masonbrink	2021	1	1	1	2	2	2	1	2	12
Matthay	2021	1	1	1	2	2	2	1	2	12
McMichael	2020	1	1	1	2	1	2	1	1	10
Mennis	2021b	1	1	1	1	1	2	1	1	9
Mennis	2021a	1	1	1	2	1	2	1	1	10
Miller	2017	1	1	0	2	2	2	1	2	11
Shi	2020	1	1	1	2	2	2	1	1	11
Shi	2019	1	1	1	2	2	2	1	1	11
Veligati	2020	1	1	1	2	2	2	1	2	12
Wallace	2020	1	1	0	1	0	1	1	0	5
Weinberger	2022	1	1	1	2	1	2	1	2	11
Wen	2021	1	1	1	1	1	1	1	1	8

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3.4.6. Crime

Two studies evaluated the effects of RML on crimes excluding arrests for marijuana possession. Lu et al. (18) reviewed data extracted from the Federal Bureau of Investigation's Uniform Crime Reporting Program for the states of Colorado and Washington. Between 1999 and 2016, the authors concluded that violent crimes did not significantly increase in either state due to RML, however certain property crimes rates were significantly heightened post-legalization. In Colorado, larceny seemed to drive property crime rate increases, whereas in Washington, rates of burglaries and aggravated assaults were predominantly affected. As well, Matthay et al. (41) used Clinformatics data to determine that RML status was associated was linked significant increases in assaults of persons younger than 21 years of age.

3.4.7. Alcohol use

A series of seven articles investigated the association between recreational cannabis legalization and alcohol use. Three studies provide evidence for an increase in alcohol consumption in RML states, as reported by the Consumer Expenditure Interview Survey (42), HCUP data (33), and the ACHA-National College Health Assessment II (NCHA-II) (23), across RML states. Curiously, 3 studies failed to show an association between legalization and alcohol use (24, 27, 32). One research article demonstrated a decrease in alcohol use following legalization in Colorado across 11 US RML states (11).

3.4.8. Cigarette use

Six studies were retained to evaluate cigarette consumption in response to RML implementation in the US. Most studies failed to find an effect of recreational legalization on tobacco use, as per data derived from the Healthy Minds Study database in Oregon youth/young adults (27), the NCHA-II in several RML states (23), the Tax Burden on Tobacco data (24), and the Youth Risk Behavior Surveys (YRBS) in six RML locations (32). Nonetheless, longitudinal data has also found evidence of potential increases in cigarette use in Colorado, Oregon, Nevada, and Washington (43), as well as decreases in use in almost 10 states (15).

3.4.9. Opioid metrics

3.4.9.1. Opioid use

One original research article evaluated the impact of RML on self-reported opioid use. Alley et al. (23) collected responses to self-reported past-month opioid use from the NCHA-II from over 800 000 college students and determined that legalization status was not associated with opioid consumption in young adults (23).

3.4.9.2. Opioid-related service use

Two research studies assessed the effects of RML on opioid-related service use. Drake et al. (44) examined the opioid-related emergency department visit rates per 100,000 population in California, Maine, Massachusetts, and Nevada using the Healthcare Cost and Utilization Project (HCUP) database. While they found initial decreases in opioid-related ED visits in RML states, the effects were abolished by the end of the study period (44). Mennis et al. (37) explored the impact of RML in adolescents and young adults (12–24 years of age) in Washington and Colorado compared to non-RML states regarding opioid-related treatment admission from the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Episode Dataset–Admissions database. The first difference-in-difference analyses determined that RML was not linked to treatment admissions. However, when analyzed separately, Colorado yielded a significant increase in opioid-related treatment admissions, while Washington demonstrated a significant decrease in opioid-related treatment admissions (37). In sum, the current data do not provide sufficient evidence to support the notion that RML is correlated with alterations in opioid-related service use.

3.4.9.3. Opioid prescriptions

Five studies assessed the impact of RML on opioid prescriptions. McMichael et al. (45) collected information from over 1 billion individual prescriptions derived from the Symphony Health's IDV® (Integrated Dataverse) dataset of patients of outpatient pharmacies in all RML and non-RML states. Using difference-in-difference analyses, the authors determined that recreational cannabis legalization corresponded with a significant decrease in the quantity of opioids (in morphine milligram equivalents or MMEs) prescribed to patients (45). This significant finding was echoed throughout three of the other four studies which investigated MMEs as their main outcome of interest. Wen et al. (46) retrieved MME data from patients with employer-sponsored health insurance between RML and non-RML states and found a significant 13% reduction in monthly MMEs in RML state patients (46). Shi et al. (47) extracted MME doses for Medicaid patients of RML vs. non RML states using the Medicaid State Drug Utilization Data and yielded total MME dose reductions for Schedule 3 opioids by 30% in RML states (47). Lopez et al. (48) used an indirect measure to investigate opioid use, through prescription opioid distribution numbers for opioid use disorder treatment (in MME equivalents) and found a reduction in this outcome in Colorado and Maryland–but not for the state of Utah. Only one study failed to establish a significant association between recreational cannabis legislation and MMEs (48). Shi et al. (47) also determined that the average number of opioid prescriptions written by physicians declined by 32% with the implementation of recreational cannabis legalization policies. In sum, the current data supports the notion that RML is correlated

with a change in opioid prescription practices, including a reduction of average MMEs prescribed to patients, as well as the number of prescriptions provided to patients.

3.4.9.4. Opioid-related deaths

One study observed trends in opioid-related deaths pre and post recreational cannabis legalization. Alcocer et al. (49) investigated a wide temporal range (1999–2017) in Colorado and extracted data from the CDC's WONDER database and found no evidence of RML effects on opioid overdose mortality rates per 100,000 population when compared to a synthetic control model (i.e., pooled data from multiple donor states to provide an accurate comparator) (49).

3.4.10. Suicide

Two studies evaluated the effects of RML on deaths by suicide. Matthay et al. (41) examined claims for self-harm injuries based on International Classification of Diseases codes from all RML states using the Clinformatics Data Mart. The analyses yielded a significant association between heightened rates of self-injury for your males in states that had legalized recreational cannabis (41). Doucette et al. (50) performed a more restricted analysis on data derived from Washington State and Colorado and found heterogeneous effects of RML. Specifically, Washington state youth and young adults demonstrated a link between deaths by suicide and RML status, whereas Colorado residents did not (50).

4. Discussion

The following review aimed to evaluate the evidence linking population-level health metrics with the implementation of recreational legalization policies. Through a literature review, we identified 32 studies which investigated key metrics, such as cannabis consumption, healthcare-related service use, crime, traffic crashes/fatalities, suicidal behaviors, and other drug use. Due to our stringent methodological criteria, all included studies in the review were performed in the United States of America. Overall, the evidence illustrates a lack of effect of RML on adolescent and young adult populations, and a possible increase in service use, vehicle related crashes and fatalities, and alcohol consumption. The data has not signaled an increase in nicotine use; however, it does correlate with a decrease in opioid prescriptions. It is also important to highlight the dearth of research with controlled designs related to the impact of recreational legalization of marijuana on criminality (excluding drug possession-related crimes), as well as deaths due to opioid overdoses or suicide.

To date, the evidence suggests moderate increases in past-month cannabis use in adult populations and no increase in adolescents or young adults (11). These data illustrate two central points. First, the lack of clearly detrimental effects seen in adolescence and early adulthood years is important considering that one of main concerns that was raised prior to RML was that such policy change could contribute to the development of ancillary impairments caused by increased cannabis use during early periods of brain maturation (51, 52). Second, the observation of increased consumption in adults is based on one single study which met the aforementioned methodological criteria. There is therefore a need to replicate these results in future research. As well, the results yielded from current studies refer to past-month use, which is an outcome that cannot differentiate between adult populations that are occasionally experimenting with cannabis from populations that are transitioning from occasional use to heavy use or cannabis use disorder. Early work by Montgomery et al. (53) has discerned potential increases in newly onset cannabis use in the adult population following RML, but not the underage population, suggesting heightened experimenting among adults who may not have otherwise tried cannabis, however these findings should be replicated before deemed as conclusive (53).

The data included in this review which evaluated frequent past-month cannabis use, and past-year CUD prevalence, across the age groups, was mainly extracted from a single study, and thus caution must be exerted when interpreting the findings. Nonetheless, the preliminary evidence points to increased frequent use, and CUD prevalence in the adult population. This evidence could potentially indicate a heightened rate of transition from occasional use to problematic use; acute monitoring of the situation is warranted in future studies. Among the research articles that did not meet the inclusion criteria (i.e., not comparative and/or longitudinal studies), the collected evidence is heterogeneous however does point to a potential increase as well [for a review, see (54)]. In the young adult population, the authors found no evidence of increased frequent use or problematic use, which may suggest limited enduring effects in this age group. Interestingly, in youth, authors have failed to establish altered frequent past-month consumption, however early evidence from the comparative longitudinal study by Cerdà et al. (10) highlights a heightened prevalence of past-year CUD. As cannabis potency has been continuously increasing over the last decades (55) is posited to be associated with increased adverse health outcomes, and as heavy cannabis use is associated with more harm to psychological and physical health than occasional use (56). Comparative and longitudinal studies on this issue are required in the future to evaluate the enduring impact of recreational cannabis legalization on youth marijuana consumption and health.

With respect to post-legalization trends of motor vehicles crashes, the evidence is mixed, however indicates potential increases. Specifically, the studies encompassing early adopter regions, such as Colorado, Washington, Oregon, and Alaska have shown increases in traffic crashes/fatalities (33, 38).

Other studies including a vaster range of states show more divergent effects (39, 40). It may be posited that the differing modalities of RML may be associated with differential effects, or that states which legalized recreational cannabis at a later time point learned from the experiences of states which had legalized recreational cannabis earlier on (57). Nonetheless, when drawing upon the evidence generated by non-comparative or non-longitudinal studies, patterns of increases also emerge (58–63). Careful surveillance of this key metric in future research is recommended to fully grasp the weight and extent of the impact of RML.

Service use trends more readily demonstrate increases, and were predominantly related to cannabis-related hospitalizations, however divergent trends were noted among youth, with one study demonstrating increases (34), and a second study yielding decreases in hospitalizations (35). Reasons for hospitalizations may vary substantially from one individual to another, so future studies will need to disentangle these differences. Otherwise, similar populations, locations, and timeframes were utilized to study this outcome, and it is difficult to determine at this time why opposing trends surfaced from the data.

Prior to the legalization of recreational cannabis use, certain assumptions were formulated about the anticipated impact of these types of policies on the use of other substances. On the one hand, it was hypothesized that the legalization of cannabis could lead to an increase in the co- use of other substances, presumably through a mechanism of cross-sensitization (64). Others proposed, on the contrary, that by legalizing cannabis, consumers would be less exposed to organized crime to obtain the substance, thus potentially discouraging additional access of other substances through this illicit point of contact (65). Finally, other authors, inspired by the theory of self-medication, postulate that by making cannabis more accessible, consumers could substitute their consumption of other substances by turning to cannabis (66). According to our review, we observe, in the case of tobacco, an absence of change in consumption, whereas in the case of alcohol, 3 out of 7 studies have shown an increase in the consumption of this substance. A lack of studies of non-prescription opioids does not allow for any concluding remarks to be made at this time. The reasons why we denote opposing effects of legalization on tobacco and alcohol are difficult to ascertain. In the future, research should focus on alcohol consumption, which remains, to this day, one of the substances with the highest social, economic and health impacts (67, 68).

One of the most robust associations observed in this systematic review is the correlation between RML and prescription opioids. Specifically, of the five studies which investigated the effects of RML on opioid prescription patterns, none reported a significant increase; only one reported a lack of effect; and the remaining five studies reported decreases in MMEs and number of prescriptions. These RML data parallel and align with previous medical marijuana legalization data, which report decreases in the number of opioid prescriptions provided to patients; the number of prescriptions filled by patients; the number of prescriptions discontinued early by patients; MMEs prescribed to patients, etc. (48, 69, 70). Most research articles included on this topic were evaluated as having high-quality evidence. As such, the evidence is sufficient to establish a potentially beneficial association between recreational marijuana legislation and prescription opioid patterns. Influencing prescription practices and restricting access to opioids are two public health strategies which have already been implemented by the Center for Disease Control (CDC) to contain the opioid epidemic (71); one may speculate that the reduction in prescriptions denoted in the current review may be accounted for by these strategies (72). However, the comparative nature of the articles retained in this review suggest that RML states find greater reductions in opioid prescriptions compared to non-RML locations, indicating that RML status may be contributing to a synergistic effect and amplifying these efforts. Beyond this general observation, future research should clarify the nature of this relationship. For instance, it remains to be determined if there are subgroups of healthcare practitioners or organizational services (i.e., surgeons, emergency medicine physicians, family physicians; hospital, community services, etc.) that are more strongly changing their prescription habits, and if there are subcategories of patients who are targeted by these declining practices (i.e., cancer patients, patients undergoing surgeries requiring pain management care, patients with chronic pain, etc.). Likewise, it remains to be determined if the changes in opioid prescription are directly related or not to the providing of alternatives to patients (i.e., medical cannabis prescriptions). Finally, it must be noted that a causational relationship has not yet been established between RML status and opioid prescription patterns.

While a changes in opioid prescription was observed, no effects of cannabis legalization were observed on opioid-related deaths. One can hypothesize that downstream cascading effects may require lengthier follow-up periods to capture differences. Alternatively, the lack of effect on mortality despite the decrease in opioid prescriptions could be explained by the fact that most opioid-related deaths are due to the consumption of particularly powerful opioids (i.e., fentanyl) procured outside of clinical settings. Nonetheless, it is important to note that the lack of effect on opioid-related deaths is based on a single comparative and longitudinal study. Data derived from research which was not selected as a part of this review show diverging patterns, exhibiting patterns of increases, lack of effects, and decreases (73, 74). Finally, it is worth mentioning that most studies on opioid-related outcomes failed to account for significant confounders such as policies related to the delivery of overdose healthcare services, and access to overdose treatment, including naloxone

and buprenorphine, which may directly impact opioid-related outcomes (75).

It is important to know that few studies corresponding to the above-reference inclusion and exclusion criteria investigated criminal activity (outside drug-relate possession crimes); evidence from non-comparative or non-longitudinal nature are conflicting, positing increases and decreases in crimes such as violent crime, property crime and sexual assaults (65, 76, 77). Similarly, only two longitudinal and comparative studies investigated the impact of RML on suicide, and none evaluated cannabis potency. Regarding the potency of cannabis, it has been steadily increasing decades before the enactment of any cannabis regulations, transitioning from an approximate 2% of delta-9-tetrahydrocannabinol (Δ^9-THC) in 1970, to close to 15% in 2016 (55). Stronger potency of Δ^9-THC content in cannabis products is vital to monitor, as it is most likely the main component responsible for the psychological, cognitive and health harms of cannabis (78, 79). We found no comparative and longitudinal study that has evaluated Δ^9-THC potency changes before, and subsequent to, RML implementation. To fully assess the consequences of recreational cannabis regulations on public health, it will be relevant to assess this outcome in the future.

Despite the narrow inclusion criteria of this review, it is relevant to compare current findings with population-level health data derived from other adult (recreational) regulatory frameworks, such as the ones in Uruguay and Canada. The Uruguayan experience of recreational legalization has yielded preliminary results which are largely in accordance with the present review, with noted potential increases in the prevalence of adult use, a lack of effect on use in youth, a lack of effect on other drug use, an increase in service use such as hospital visits for intoxication, as well as an increase in serious crimes such as homicides and traffic fatality rates (80–83). Despite the recent recreational legalization in Canada, several publications have yielded crucial insights to the impacts of RML on population health. Echoing most findings from the present publication, the primary evidence suggests adult consumption is on the rise, however CUD prevalence remains stable (12, 84); RML is associated with mixed, yet potentially minimal impacts on consumption in youth (85), and may be linked with possible increases in service use, such as emergency department visits or unintentional cannabis intoxications (86–88). Vast efforts are still ongoing across both nations to better grasp the implications of recreational legalization on public health outcomes.

5. Limitations of the current systematic review

The strengths of the studies collected in this systematic review include their longitudinal study design, which captures important temporal variations of outcomes; and that all studies included one or more comparator locations, which controls for diverging trends occurring outside of cannabis legislation policies. Despite these strengths, a few limitations should also be noted. First, there is a lack of longitudinal comparative studies to investigate key populational health outcomes, and stronger efforts in elucidating these outcomes are required to allow for informed policy decisions. For instance, no controlled study specifically examined the effects of RML on cannabis-related mental health outcomes. Second, the implementation of the comparator criteria entailed the exclusion of all studies derived from Canadian settings. In Canada, cannabis has been legalized across all provinces, thus makes it impossible to carry out studies with comparators locations. It is possible that the trends observed in the United States may not be representative of the Canadian experience of legalization, as there are notable differences in legalization modalities between countries. For example, the Canadian experience of recreational legalization is more standardized across regions than the US experience, is overall more restrictive in terms of licensing, home growing and possession, but more liberal in terms of age of consumption, location of consumption, and limits for driving under the influence (89). Nonetheless, the data extracted from Canadian settings seems to largely parallel findings from the United States, except for consumption data, demonstrating a mixed effect RML on daily cannabis use, whereas US data suggests a likelier increase in daily use (10, 84), and service use, with once again mixed effects in Canada, and more suggestive increasing patterns in the US (90, 91).

There are several confounding factors which are infrequently controlled for, though should be accounted for when analyzing the implications of RML on public health outcomes. For example, the proliferation of marketing strategies of edibles (92) mounted alongside several reports of non-compliant tactics, especially regarding youth (93, 94) may be contributing to an uptick in adverse public health outcomes, such as pediatric exposures to cannabis or emergency department visits (95, 96). Another notable confounder in the landscape of recreational legalization is its potential "spillover effect" to neighboring non-legalized states (19, 97). This could potentially give rise to the under-estimation of effects between legalization states, especially if these neighboring states are included as comparator locations in the analyses. In addition, several studies included in the current review did not differentiate between the legalization and the delayed enactment of recreation cannabis policies; this is a crucial variable to consider in future research, as prior data has already shown a correlation between the number of outlets opened and the prevalence of consumption (98, 99). Several studies analyzed data timepoints less than one-year post-enactment–thus limiting the ability to identify patterns which either require a lengthier time to be detected or identifying patterns which do not endure in time. Finally, the legalization of medical

marijuana has rendered it more difficult to scrutinize the consequences of recreational legalization, as the evidence has shown medical legalization influences public attitudes, opinions, and behaviors (100, 101).

6. Conclusion

Considering the entirety of the collected evidence, RML is preliminarily associated with increases in adult consumption of cannabis–but not youth consumption; however, little data from controlled studies is available on frequent/problematic cannabis use. RML is also linked to potential increases in service use, as well as traffic crashes and fatalities. Due to the lack of evidence, we could not determine any patterns associated to crimes and suicide. A potential increase in alcohol use has been observed, while no differences were observed in the case of nicotine. Interestingly, the data demonstrated a reduction of opioid prescriptions in RML states compared to non-RML states. We cannot determine if this effect yields an overall benefit or risk to mortality or morbidity of at-risk populations and thus should be a key focus for future research. Another gap in the field is the lack of controlled studies on the potential impact of RML on mental health outcomes. Finally, further research is clearly needed on the differences in RML policies.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

SP and MA conceptualized the systematic review and wrote the manuscript. MA and IZ performed the search and extracted the information. AD and IZ provided critical comments. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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On offer to Ontario consumers three years after legalization: A profile of cannabis products, cannabinoid content, plant type, and prices

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Introduction: Cannabis was legalized in Canada in October 2018, regulating the production, distribution, sale, and possession of dried cannabis and cannabis oils. Additional products were legalized 1 year later, including edibles, concentrates, and topicals, with new lines of commercial products coming to market. Ontario is the most populous province in Canada and has the largest cannabis market with the highest number of in-person retail stores and the most cannabis products available online. This study aims to create a profile of products available to consumers three years after legalization by summarizing types of products, THC and CBD potency, plant type, and prices of product sub-categories.

Methods: We extracted data from the website of the Ontario Cannabis Store (OCS)—the public agency overseeing the only online store and sole wholesaler to all authorized in-person stores—in the first quarter of 2022 (January 19–March 23). We used descriptive analyses to summarize the data. A total of 1,771 available products were mapped by route of administration into inhalation (smoking, vaping, and concentrates), ingestible (edibles, beverages, oils, and capsules) and topical.

Results: Most inhalation products included ≥20%/g THC (dried flower: 94%; cartridges: 96%; resin: 100%) while ingestible products had similar proportions of THC and CBD content. Indica-dominant products tend to be more prominent in inhalation products while sativa-dominant products tend to be more prominent in ingestible products. The average sale price of cannabis was 9.30 $/g for dried flower, 5.79 $/0.1g for cartridges, 54.82 $/g for resin, 3.21 $/unit for soft chews, 1.37 $/ml for drops, 1.52 $/unit for capsules, and 39.94 $/product for topicals.

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Discussion: In summary, a wide variety of cannabis products were available to Ontarians for different routes of administration and provides numerous indica-dominant, sativa-dominant, and hybrid/blend options. The current market for inhalation products however is geared towards the commercialization of high-THC products.

KEYWORDS

cannabis legalization, legal market, adult consumers, cannabis products, cannabis prices, cannabis potency, THC, CBD

Introduction

Canada was the second nation globally to legally regulate the production, distribution, sale, and possession of dried cannabis and cannabis oils in October of 2018 (1). A "second wave" of legalization came into effect in October 2019, regulating edibles, high-potency concentrates, and topicals (2), with new lines of commercial products available by early 2020. One of the main goals of legalization was to provide safe, legal access to cannabis products (3), enabling the legal industry to compete with the illegal market. The legalization of non-medical cannabis in Canada occurred under the Cannabis Act, which regulates cannabis nationally, but under Canada's constitutional division of powers, each of the 10 provinces and 3 territories developed their own laws and regulatory systems (1). Ontario, Canada's most populous province and largest cannabis market, follows a hybrid model where a public agency is the sole wholesaler to all authorized in-person stores—all of which are private—and also provides direct access to the public through the only online store.

Purchasing behaviors of consumers are influenced by cannabis prices and availability in the illegal and legal markets (4). In the US, cannabis use is higher in states that have legalized cannabis, with dried cannabis being the most dominant form (5). It is too early to determine the impact of legalization in Canada as the legal market continues to evolve, but early evidence suggests increased use in adults, mixed effects in adolescent use and on driving under the influence of cannabis, increases in pediatric emergency room visits and hospitalizations, and decreases in arrests and convictions (6–13). Given the acute and long-term health risks associated with cannabis containing high levels of THC (14–17), documenting the potency of the cannabis products available in the legal market is of interest to public health.

One year post-legalization, a Canadian study found that the top 10% of cannabis users (those with the highest cumulative cannabis use) accounted for about two-thirds of cannabis consumption, with 40% of the cannabis consumed in the form of flower products (18). At that time, legal cannabis sales covered about 33% of Canada's cannabis consumption (19). Two years post-legalization, there were a total of 1,183 legal cannabis stores in Canada (20). Three years post-legalization, Ontario had the highest number of in-person retail stores (n = 1,974) and the highest number of products available online (n = 1,685) among all the provinces and territories (21, 22). The legal market has expanded to an estimated 57% of sales as of the last quarter of 2021, making progressive gains in the displacement of the illegal market (23).

Our aim was to create a profile of the products available to adult consumers in Ontario—just over three years post-legalization—and report their THC and CBD potency, plant type (e.g., indica-dominant, sativa-dominant, hybrid), and price. To do so, we cataloged products listed on the website of the Ontario Cannabis Store (OCS), the public agency overseeing the only online store and sole wholesaler to all authorized in-person stores. We do not present sales data which are available elsewhere for approximately the same period (23).

Materials and methods

This is a cross-sectional study designed to produce a profile of the legal cannabis market in Ontario three years post-legalization. We extracted data from the OCS website to document the THC and CBD potency, plant type, and price of all products available to purchase by Ontario consumers over a span of two months (19 January–23 March 2022) (22). During data extraction, FT and YL manually entered information from each cannabis product into an Excel spreadsheet. Any unavailable or unlisted information was marked as "N/A". We used descriptive statistics [counts, means (M), standard deviations (SD), and ranges] using Excel functions. FT used pivot tables, sorted columns alphabetically, and counted each product individually to determine counts of high potency products and plant types. We also mapped the product categories and subcategories provided in the OCS website by route of administration to provide a more meaningful consumer perspective.

Products on the OCS website are listed with a range of values for both THC and CBD content (in%/g or mg/unit), rather than a single THC or CBD value as it is presented on the label of the individual product purchased by consumers. By design, regulations placed THC limits per package on ingestible products (e.g., maximum of 10 mg of THC per package for edibles). Thus, we calculated the average for each product THC and CBD range and then averaged the THC and CBD potencies of all products by their sub-category. Also, the OCS labels products that contain 20%/g or greater THC as "very strong THC" levels (OCS (22)). We calculated the frequency and proportion of very strong THC products using the unit%/g from each product. As the OCS does not define "very strong CBD" levels, we labeled any product with an average value above 5%/g as very strong CBD. We then calculated the number of very strong THC and CBD products by product sub-category using pivot tables, alphabetical sorting, and manual counting. For plant type, we sorted alphabetically and manually counted all the products categorized as blend, hybrid, indica-dominant, or sativa-dominant for each of the sub-categories.

In terms of price, a single product often had multiple selling prices listed depending on the quantity available for purchase, so we calculated the average of the lowest and highest selling price for each product and then calculated the average price for each sub-category (in $/g, $/0.1g, $/ml, or $/unit). In addition, we calculated the minimum selling price and the maximum selling price for each sub-category. These average selling prices allow us to approximate an estimate of how much money a consumer would spend to purchase a particular product in bulk.

Our study cataloged all the products available in the OCS during the period of observation and most dried flower products were only available in one or two quantities while pre-roll products were available in 20 different quantities (ranging from 0.25 to 30g), making it difficult to report average prices for pre-determined quantities as previous studies have done (24–27). Thus, the lowest and highest price per gram of every product was used for clarity.

The top 10 cannabis products by units sold in Ontario retail stores were listed in the OCS's January to March 2022 quarterly review (23). We used our Excel spreadsheet with the data extracted from the OCS website to provide more information about each of these ten products, including THC and CBD potency, plant type, and price.

Results

Product types and routes of administration

We mapped a total of 1,771 available products by route of administration into inhalation (smoking, vaping, and concentrates: n = 1,250), ingestible (edibles, beverages, oils, and capsules: n = 410), topical (n = 75), and other (pantry, seeds, and starter kits: n = 36) (Tables 1, 2). The sub-categories with the most products under each of the nine categories were: dried flower (n = 508), thread cartridges (n = 230), resin (n = 50), soft chews (n = 104), beverages (n = 106), oils-drops (n = 80), capsules (n = 39), and topicals (n = 75) (Table 2).

TABLE 1 Ontario cannabis store (OCS) product categories and sub-categories mapped by route of administration (RoA).

OCS categories	OCS sub-categories	RoA categories	RoA sub-categories
Flower	Dried flower	Inhalation—smoking	Dried flower
	Pre-rolls		Pre-rolls
	Seeds	Inhalation—vaping	510 thread cartridges
Vapes	510 thread cartridges		Pax pods
	Pax pods		Closed loop pods
	Closed loop pods		Disposable vape pens
	Disposable vape pens	Inhalation—concentrates	Hash
	Starter Kits		Kief and sift
Extracts	Oils		Resin
	Capsules		Rosin
	Hash		Shatter and wax
	Kief and sift		Isolates and distillates
	Resin	Ingestible—edibles	Soft chews
	Rosin		Chocolates
	Shatter and wax		Baked goods
	Isolates and distillates		Hard edibles
Edibles	Soft chews	Ingestible—beverages	Beverages
	Chocolates	Ingestible—oils	Drops
	Beverages		Spray
	Baked goods	Ingestible—capsules	Capsules
	Hard edibles	Topicals	Topicals
	Pantry	Others	Pantry
CBD and topicals	Topicals		Seeds
			Starter kits

THC and CBD potency

A large proportion of inhalation products were categorized as very strong THC products (percent of products with ≥20%/g THC and average THC): dried flower: 94%, 22%/g; thread cartridges: 96%, 74%/g; resin: 100%, 71%/g (Table 2). The trend of high-THC products continued across the inhalation sub-categories, with all sub-categories having over 64% of products being classified as having very strong THC levels and 100% for most concentrates and some vaping products. Apart from isolates and distillates and closed loop pods, all sub-categories had very strong levels of THC in over 88% of products. On the other hand, only 6% of dried flower and 5% of pre-rolls had CBD levels ≥5%/g. Except for isolates & distillates, all sub-categories had lower than 33% of products with very strong CBD levels. Topical products averaged 69 mg/product with a range of 0–500 mg.

No ingestible products exceeded the regulatory limit of THC per package (28). As such, ingestible products saw lower average THC values than inhalation products, including soft chews, beverages, and capsules at 4 mg/unit, and drops at 2%/g (Table 2). The average CBD content in ingestible products corresponded more closely to the THC levels within those products: soft chews: 4 mg/unit; beverages: 6 mg/unit; drops: 2%/g; capsules: 10 mg/unit; and topicals: 280 mg/product.

Plant type

The vast majority of products provided information on the plant type (i.e., blend, hybrid, indica-dominant, sativa-dominant) (Table 3); this information was missing for only 10 products (0.56%).

Relative to ingestible products, inhalation products tended to have a higher percentage of indica-dominant than sativa-dominant products (dried flower: 48% vs. 26%, cartridges: 34% vs. 28%, resin: 34% vs. 30%) while the opposite was true for ingestible products (soft chews: 11% vs. 14%, beverages: 2% vs. 25%, drops: 8% vs. 10%, capsules: 10% vs. 26%, and topicals: 7% vs. 17%).

Ingestible products had more hybrid and blend products available relative to inhalation products, with the majority of the

TABLE 2 Tetrahydrocannabinol (THC) and cannabidiol (CBD) potency by product type (first quarter of 2022).

Category	No. of products	*M (SD)* [Range]		No. of very strong products (%)	
		THC	CBD	THC (≥ 20%/g)	CBD (≥ 5%/g)
Inhalation—smoking (%/g)					
Dried flower	508	*22 (4)* [0–33]	*1 (2)* [0–20]	476 (94)	30 (6)
Pre-rolls	305	*21 (4)* [0–36]	*1 (2)* [0–20]	283 (93)	15 (5)
Inhalation—vaping (%/g)					
Thread cartridges	230	*74 (19)* [0–96]	*6 (7)* [0–90]	221 (96)	44 (19)
Pax pods	21	*74 (12)* [39–88]	*5 (12)* [0–46]	21 (100)	6 (29)
Closed loop pods	3	*59 (42)* [11–89]	*20 (34)* [0–61]	2 (67)	1 (33)
Disposable pens	16	*65 (29)* [11–92]	*18 (27)* [0–71]	14 (88)	5 (31)
Inhalation—concentrates (%/g)					
Hash	31	*44 (14)* [17–71]	*2 (6)* [0–34]	31 (100)	3 (10)
Kief and sift	17	*34 (4)* [25–47]	*1 (1)* [0–10]	17 (100)	1 (6)
Resin	50	*71 (16)* [15–96]	*4 (11)* [0–64]	50 (100)	11 (22)
Rosin	24	*68 (12)* [27–85]	*2 (2)* [0–10]	24 (100)	6 (25)
Shatter and wax	31	*75 (3)* [63–85]	*2 (2)* [0–10]	31 (100)	10 (32)
Isolates and Distillates	14	*46 (36)* [0–96]	*33 (39)* [0–102]	9 (64)	8 (57)
Ingestible—edibles (mg/unit, mg)					
Soft chews	104	*4 (3)* [0–10]	*4 (6)* [0–25]	N/A	N/A
Chocolates	46	*8 (3)* [0–10]	*3 (6)* [0–25]	N/A	N/A
Baked goods	16	*7 (3)* [2–10]	*1 (2)* [0–5]	N/A	N/A
Hard edibles	12	*2 (1)* [1–10]	*4 (8)* [0–20]	N/A	N/A
Ingestible—beverages (mg/unit, mg)					
Beverages	106	*4 (4)* [0–10]	*6 (8)* [0–45]	N/A	N/A
Ingestible—oils (%/g, mg/spray)					
Oils—drops	80	*1 (11)* [0–4]	*2 (25)* [0–11]	0 (0)	8 (10)
Oils—spray	7	*2 (1)* [0–5]	*2 (4)* [0–13]	0 (0)	N/A
Ingestible—capsules (mg/unit, mg)					
Capsules	39	*4 (4)* [0–10]	*10 (14)* [0–53]	N/A	N/A
Topicals (mg)					
CBD and topicals	75	*69 (116)* [0–500]	*280 (259)* [5–1500]	N/A	N/A
Other					
Pantry (mg)	4	*8 (5)* [0–10]	*250 (500)* [0–1000]	N/A	N/A
Seeds	30	N/A	N/A	N/A	N/A
Starter kits (%/g)	2	*42 (54)* [2–88]	*40 (56)* [0–84]	1 (50)	1 (50)

ingestible sub-categories carrying mainly blend or hybrid products. All edibles sub-categories classified over 75% of products as either hybrid or blend, with less than 25% being classified as indica- or sativa-dominant.

Price

Typically, products were available at a lower selling price when purchasing higher amounts (Table 4). This enables consumers to buy more cannabis for a lower price per gram. For example, if a product's lowest selling price was $39.95 for 4 g and its highest selling price was $129.95 for 14 g, the lowest price in $/g would be $9.99 for 4 g and $9.28 for 14 g. The consumer has the option to save $0.71/g by buying more cannabis. This was true in the vast majority of cases, but not in all cases.

The average selling price of cannabis products was $51.39 (4.50–259.95) for dried flower, $40.99 (15.95–89.95) for cartridges, $53.43 (20.96–124.95) for resin, $10.00/package (3.98–44.95) for soft chews, $37.20 (13.95–89.95) for drops, $26.79/package (9.50–74.95) for capsules, and $39.94 (8.95–82.20) for topicals.

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TABLE 3 Plant type by product type (first quarter of 2022).

Category	No. of products				
	Total	Blend	Hybrid	Indica-dominant	Sativa-dominant
Inhalation—smoking					
Dried flower	508	4 (1%)	125 (25%)	244 (48%)	133 (26%)
Pre-rolls	305	8 (3%)	87 (29%)	131 (43%)	77 (25%)
Inhalation—vaping					
Thread cartridges	230	36 (16%)	51 (22%)	79 (34%)	64 (28%)
Pax pods	21	3 (14%)	3 (14%)	6 (29%)	9 (43%)
Closed loop pods	3	0 (0%)	1 (33%)	2 (67%)	0 (0%)
Disposable pens	16	1 (6%)	6 (6%)	4 (25%)	5 (31%)
Inhalation—concentrates					
Hash	31	8 (26%)	11 (35%)	8 (26%)	4 (13%)
Kief and sift	17	1 (6%)	5 (29%)	6 (35%)	5 (29%)
Resin	50	1 (2%)	17 (34%)	17 (34%)	15 (30%)
Rosin	24	0 (0%)	8 (33%)	13 (54%)	3 (13%)
Shatter and wax	31	1 (3%)	15 (48%)	10 (32%)	5 (16%)
Isolates and distillates	14	3 (21%)	5 (36%)	0 (0%)	5 (36%)
Ingestible—edibles					
Soft chews	104	44 (42%)	34 (33%)	11 (11%)	15 (14%)
Chocolates	46	27 (59%)	17 (37%)	1 (2%)	1 (2%)
Baked goods	16	11 (69%)	1 (6%)	1 (6%)	3 (19%)
Hard edibles	12	11 (92%)	1 (8%)	0 (0%)	0 (0%)
Ingestible—beverages					
Beverages	106	60 (57%)	18 (17%)	2 (2%)	26 (25%)
IIngestible—oils					
Oils—drops	80	50 (63%)	13 (16%)	6 (8%)	8 (10%)
Oils—spray	7	3 (43%)	1 (14%)	1 (14%)	2 (29%)
Ingestible—capsules					
Capsules	39	12 (31%)	12 (31%)	4 (10%)	10 (26%)
Topicals					
CBD and topicals	75	30 (40%)	27 (36%)	5 (7%)	13 (17%)
Other					
Pantry	4	4 (100%)	0 (0%)	0 (0%)	0 (0%)
Seeds	30	0 (0%)	22 (73%)	2 (7%)	4 (13%)
Starter kits	2	2 (100%)	0 (0%)	0 (0%)	0 (0%)

The average price per unit of cannabis for the most numerous sub-categories was found to be 9.30 $/g (3.57–17.13) for dried flower, 5.79 $/0.1g (3.50–17.99) for cartridges, 54.82 $/g (13.97–109.90) for resin, 3.21 $/unit (0.43–8.95) for soft chews, 1.37 $/ml (0.47–3.60) for drops, and 1.52 $/unit (0.63–7.75) for capsules.

Many products in the flower and pre-roll sub-categories were sold at multiple price points due to the variety of quantities available for purchase. A product in the flower section could be available in multiple sizes, including 1, 3.5, 5, 7, 10, 11, 14, 15, 28, or 30 g. Similarly, products in the pre-roll section could be available in 0.25, 0.3, 0.32, 0.33, 0.35, 0.4, 0.42, 0.5, 0.6, 0.7, or 1 g. For each of these sizes, a different number of pre-rolls may be available, ranging from 1 to 70. Thus, one product could have multiple price points due to being available in a variety of quantities.

Top 10 cannabis products by units sold

In the first quarter of 2022, the top ten cannabis products by units sold in Ontario retail stores were mainly inhalation products (Table 5). Eight of the 10 products fall under the dried flower (n = 5) and pre-roll (n = 3) sub-categories. Two of the top 10 products sold were ingestible and fall under the soft chews sub-category. All inhalation products had "very strong" THC levels

TABLE 4 Average prices by product type (first quarter of 2022).

Category	Sub-category	*M (SD)* [range]	
		Price	Selling price
Inhalation—smoking		$/g	$
	Dried flower	*9.30 (3.33)* [3.57–17.13]	*51.39 (35.66)* [4.50–259.95]
	Pre-rolls	*11.85 (4.01)* [4.82–24.87]	*21.99 (12.65)* [4.88–135.95]
Inhalation—vaping		$/0.1g	$
	Thread cartridges	*5.79 (1.82)* [3.50–17.99]	*40.99 (10.72)* [15.95–89.95]
	Pax pods	*8.94 (1.88)* [5.79–11.99]	*43.43 (10.03)* [28.95–59.95]
	Closed loop pods	*9.66 (0.58)* [8.99–9.99]	*48.28 (2.89)* [44.95–49.95]
	Disposable pens	*12.06 (4.57)* [6.65–17.98]	*36.64 (10.96)* [16.95–44.95]
Inhalation—Concentrates		$/g	$
	Hash	*28.73 (13.24)* [9.99–49.95]	*36.39 (9.66)* [14.95–49.95]
	Kief and sift	*17.18 (3.59)* [10.47–22.95]	*24.01 (8.63)* [14.95–39.96]
	Resin	*54.82 (16.31)* [13.97–109.90]	*53.43 (16.22)* [20.96–124.95]
	Rosin	*62.92 (19.65)* [16.63–109.95]	*57.78 (20.08)* [24.95–109.95]
	Shatter and wax	*48.66 (13.37)* [26.48–79.90]	*44.50 (16.14)* [17.48–79.90]
	Isolates and distillates	*45.85 (8.62)* [32.95–65.90]	*37.23 (10.52)* [13.80–44.95]
Ingestible—edibles		$/unit	$/package
	Soft chews	*3.21 (1.92)* [0.43–8.95]	*10.00 (7.72)* [3.98–44.95]
	Chocolates	*4.34 (1.45)* [1.39–7.45]	*5.50 (1.49)* [2.48–10.20]
	Baked goods	*5.09 (2.33)* [1.65–9.75]	*7.50 (2.15)* [2.95–9.95]
	Hard edibles	*1.82 (0.67)* [1.00–3.33]	*10.08 (6.02)* [5.95–24.95]
Ingestible—beverages		$/unit	$/package
	Beverages	*6.11 (1.94)* [2.40–13.80]	*8.14 (4.47)* [2.95 –21.95]
Ingestible—oils		$/ml	$
	Oils—drops	*1.37 (0.60)* [0.47–3.60]	*37.20 (14.78)* [13.95–89.95]
	Oils—spray	*1.47 (0.36)* [1.20–2.00]	*25.66 (3.55)* [19.95–29.95]
Ingestible—capsules		$/unit	$/package
	Capsules	*1.52 (1.18)* [0.63–7.75]	*26.79 (13.05)* [9.50–74.95]
Topicals			$
	CBD and topicals	N/A	*39.94 (15.53)* [8.95–82.20]
Other		$/0.1g	$
	Pantry	N/A	*19 (22.33)* [3.95–51.95]
	Seeds	N/A	*46.59 (9.64)* [24.95–64.95]
	Starter kits	*8.29 (1.88)* [6.59–9.99]	*41.45 (10.03)* [32.95–49.95]

(Continued)

TABLE 4 (Continued)

with an average of 21%/g. Inhalation products had an average price of 6.49 $/g while ingestible products had an average price of 2.77 $/unit.

Discussion

This study describes the Ontario cannabis legal market three years after legalization by cataloging every cannabis product on offer to consumers rather than profiling a market based on a subset or a random selection of products. There was a large variety of products on offer to Ontario consumers with inhalation products being 2.5 times more numerous than ingestible products. The majority of inhalation products had very strong levels of THC. They also had a higher percentage of indica- than sativa-dominant products while ingestible products saw the opposite trend. The average price per unit of dried cannabis was $9.30/g, which is lower than self-reported data collected prior to legalization (29, 30).

Product variety included varying routes of administration, with 46% of items classified as smoking products, 16% as vaping, ~10% each for edibles and concentrates, and between 2 and 6% each for beverages, oils, capsules, and topicals. The breakdown of product types resembled that for total sales during the same time period, which was 50% for dried flower, 18% pre-rolls, 16% vapes, 5% each of edibles and concentrates, and 2% each of oils and beverages (23). We also found that eight out of the top ten products sold in retail stores were smoking products. In the 3 years post-legalization, consumer preferences for particular types of cannabis products have shifted, although smoking continues to be the most common route of administration (31). From 2017 to 2022, the Canadian Cannabis Survey—a national survey implemented by the Government of Canada to monitor the effects of legalization—reported a decrease in smoking (94–70%) and vaping using vaporizers (14–10%), and an increase in vaping using vape pens (20–31%) and edibles (34–52%) (31, 32). From 2020 to 2022, of those who vaped cannabis, liquid cannabis oil/concentrate use increased (60–74%) and dried flower use decreased (65–49%) (31, 33). This shift in consumer preferences is generally seen as a positive consequence of legalization as lower-risk cannabis use guidelines recommend avoiding routes of administration that involve smoking combusted cannabis products (15). However, the guidelines also caution consumers about the risk of ingesting larger than anticipated doses associated with

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TABLE 5 Characteristics of top 10 cannabis products by units sold in Ontario retail stores (first quarter of 2022).

Rank	RoA Sub-Category	Brand	Product name	Average THC	Average CBD	Potency	Plant type	Price	Selling price
1	Dried Flower	SHRED	Tropic thunder	21%/g	0.50%/g	Very Strong	Hybrid	4.56 $/g	$31.95/7g
2	Dried flower	SHRED	Funk master	21%/g	0.75%/g	Very Strong	Hybrid	4.56 $/g	$31.92/7g
3	Pre-rolls	Good supply	Jean guy pre-roll	21%/g	1.00%/g	Very Strong	Sativa dominant	8.65 $/g	$8.65/1g
4	Pre-rolls	Good supply	Grower's choice Indica pre-roll	21%/g	0.50%/g	Very Strong	Indica dominant	6.50 $/g	$6.50/1g
5	Dried flower	Spinach	GMO cookies	23%/g	0.08%/g	Very Strong	Indica dominant	9.99 $/g	$34.97/3.5g
6	Dried flower	Pure sunfarms	Pink kush	23%/g	0.50%/g	Very Strong	Indica dominant	6.56 $/g	$22.95/3.5g
7	Dried flower	SHRED	Gnarberry	20%/g	0.50%/g	Very Strong	Hybrid	4.56 $/g	$31.92/7g
8	Soft chews	Spinach	SOURZ by spinach - blue raspberry watermelon Indica	10 mg	0.10 mg	N/A	Indica dominant	1.56 $/unit	$7.80/1 pack
8	Soft chews	Wana	Pomegranate blueberry Acai 5:1 sour soft chews	10 mg	50.00 mg	N/A	Blend	3.98 $/unit	$7.95/1 pack
10	Pre-rolls	Good supply	Grower's choice Sativa pre-roll	19%/g	0.50%/g	Very strong	Sativa dominant	6.50 $/g	$6.50/1g

edibles, which have been linked with increased emergency room visits and hospitalizations, especially with pediatric populations (9, 10).

We observed that the current legal cannabis market for inhalation products is geared toward offering products with high THC potency with a lower availability of balanced THC-CBD or high-CBD options. The average THC potency in the current market is higher than the average potency of 10-13% reported by Health Canada prior to legalization (29), and higher still than the average 6–10% reported in the legal medical market that existed pre-legalization of non-medical cannabis (30). THC potency had already been increasing prior to legalization with a 212% increase from 1995 to 2015 (34). At the time of legalization in late 2018, the average THC potency of legal dried flower across a sample of legal retail stores in Ontario was 16% (31). As of early 2022, we observed that THC levels in dried cannabis on offer to Ontario consumers has an average of 22%. Consumers should be aware that high potency cannabis can have detrimental effects on mental health and addiction outcomes (16, 17, 35–37). Within this context, some have argued for imposing limits on THC in cannabis products, and others propose the use of excise tax based on THC levels to incentivize the use of less potent products (38). It is unknown to what degree THC levels impact consumer product choice; however, in various studies of consumer views on cannabis quality, the potency of cannabis was not mentioned as a marker (31, 39–41). In the latest Canadian Cannabis Survey, strength was ranked last among the factors that influence consumer purchases after price, safe supply, quality, convenience, proximity to retailer, and ability to purchase from a legal source (31). Public outreach around the safer use of cannabis should consider lower-risk cannabis use guidelines; one of the recommendations of which is the choice of lower-potency cannabis products (15). Given the availability of more potent cannabis, future experimental research into their health effects is needed as there is still uncertainty over whether consumers effectively self-titrate THC doses of higher potency products (42).

Despite strict regulations on testing requirements for cannabinoids and contaminants on cannabis products in the Canadian market, we are not aware of peer-reviewed, independent evaluations of the accuracy of product labels (43, 44). However, US studies have reported inconsistencies in cannabinoid labeling on commercial products (45–47). In addition, it has been shown that consumers have difficulties understanding and applying quantitative cannabinoid labeling and additional work should be devoted to improve the labeling of standard doses across routes of administration (48, 49).

The legal market offered a wide variety of products containing different plant types. Inhalation products had higher percentages of indica-dominant products relative to all other plant types, while ingestible products had higher percentages of sativa-dominant products. There were many offers of blend or hybrid options available in every product category. The taxonomical classification of cannabis into indica and sativa are mostly based on marketing considerations as they do not exist in nature due to historical cross-breeding and misuse of nomenclature (50, 51). However, cannabis users report differential subjective experiences between indica- and sativa-dominant products with greater preference for using indica in the evening while reporting feeling "relaxed, sleepy/tired"

and sativa during the day while reporting feeling "alert/energized" (52). Overall, offered products appear consistent with consumer preferences for a variety of indica-dominant, sativa-dominant, and hybrid/blend products.

Previous studies of cannabis pricing have typically been done by survey research (24, 25), by selecting a subset of products (e.g., most popular, least, and most expensive) (26), or by calculating the average price of a random sample of products at each pre-determined purchase quantity (27). These studies have typically reported on the average price of dried flower and pre-rolls at set quantities (e.g., the average price at 1, 3.5, 7, 14, and 28 g). In our study, the average price per gram of dried flower for all products on offer was found to be $9.30 and the lowest price was $3.41 per gram. Sales during that period suggest that the majority of consumer purchases were made in the lower price range, with most of the purchases between $3.00 and 6.50 per gram making up 48% of in-person purchases and 63% of online purchases (23). Our calculations suggest that spending more money on larger quantities would provide consumers with a "better deal," with the average selling price of dried flower products being $51.39. In line with 2022 self-reported data, consumers who had used recreational cannabis within the last 30 days spent an average of $65 ($46–$86) from legal sources per month, an increase from $55 in 2021 (31, 39). Participants who used cannabis for medical purposes spent an average of $75 in the past 30 days (31). For consumers that tend to spend above $50 a month on cannabis, buying dried flower products "in bulk" seems to be a reasonable approach for reducing the cost of cannabis per gram.

The average dried flower prices was lower than those reported in studies of the retail cannabis market in Canada pre-legalization and at the time of legalization (29, 30). Prior to legalization, the average self-reported price-per-gram of cannabis was $9.56, but this varied depending on the quantity purchased (24). In comparison to self-reported data collected several months post-legalization, the average price of legal dried flower has decreased slightly: 9.82 $/g in late 2018 versus 9.30 $/g in early 2022 (27). In comparison to self-reported legal cannabis prices in Canada from 2019, regardless of quantity, the average price of dried flower in 2022 is also lower, ranging from $23.16/1g to $9.95/3.5 g and $9.95/27.9 g in 2019 (25). Additionally, it was found that the price of dried flower from legal sources decreased post-legalization (25), consistent with our findings.

In a recent qualitative study from Canada, participants spoke of the benefits associated with the illegal cannabis market, including lower prices, incentives, discounts, and loyalties (41). The majority of participants in that study noted that legal cannabis is more expensive than illegal cannabis and that price was of highest importance when making purchasing decisions (41). This is in agreement with the Canadian Cannabis Survey in which 30% of participants in 2022 ranked price as the number one factor that influences purchases (31, 39). Users on social media platforms thought legal products were expensive in comparison to illegal cannabis and have also expressed concerns with difficulties with supply shortages in the legal market (53). Cannabis users have indicated that price, product quality, store location, and the inconvenience of purchasing from legal sources were key reasons for buying cannabis from the illicit market (54). However, if the average price per gram and average selling prices of the legal market continue to follow downward trends, then more Canadians may become motivated to purchase from legal sources (54). Recent Canadian research states that the divergence between legal and illegal cannabis markets is narrowing (25) and the legal share of the overall cannabis market is estimated to be 57% (23).

Conclusion

The Ontario legal market has a wide variety of cannabis products on offer to consumers. There is a wide array of products available for various consumer preferences in plant type, with numerous indica-dominant, sativa-dominant, and hybrid/blend options on offer. In line with lower-risk cannabis use guidelines (15), consumers would benefit from having access to more lower-potency, mixed THC-CBD ratios, and CBD-dominant products. Three years post-legalization, Canadian cannabis consumers have favorable perceptions of legal cannabis products in comparison to illegal products, apart from price (40).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

SR and PD conceived, designed, and directed the study. FT extracted the data with support from YL. FT analyzed the data and wrote the first draft of the manuscript. SR carried out substantial edits to the initial draft. All authors reviewed various drafts and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Development of cannabis use disorder in medical cannabis users: A 9-month follow-up of a randomized clinical trial testing effects of medical cannabis card ownership

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Background: Evidence for long-term effectiveness of commercial cannabis products used to treat medical symptoms is inconsistent, despite increasingly widespread use.

Objective: To prospectively evaluate the effects of using cannabis on self-reported symptoms of pain, insomnia, anxiety, depression, and cannabis use disorder (CUD) after 12 months of use.

Methods: This observational cohort study describes outcomes over 9 months following a 12-week randomized, waitlist-controlled trial (RCT: NCT*03224468*) in which adults (N = 163) who wished to use cannabis to alleviate insomnia, pain, depression, or anxiety symptoms were randomly assigned to obtain a medical marijuana card immediately (immediate card acquisition group) or to delay obtaining a card for 12 weeks delay (delayed card acquisition group). During the 9-month post-randomization period, all participants could use cannabis as they wished and choose their cannabis products, doses, and frequency of use. Insomnia, pain, depression, anxiety, and CUD symptoms were assessed over the 9-month post-randomization period.

Results: After 12 months of using cannabis for medical symptoms, 11.7% of all participants (n = 19), and 17.1% of those using cannabis daily or near-daily (n = 6) developed CUD. Frequency of cannabis use was positively correlated with pain severity and number of CUD symptoms, but not significantly associated with severity of self-reported insomnia, depression, or anxiety symptoms. Depression scores improved throughout the 9 months in all participants, regardless of cannabis use frequency.

Conclusions: Frequency of cannabis use was not associated with improved pain, anxiety, or depression symptoms but was associated with new-onset cannabis use disorder in a significant minority of participants. Daily or near-daily cannabis use appears to have little benefit for these symptoms after 12 months of use.

KEYWORDS

cannabis (marijuana), insomnia, pain, anxiety, depression, cannabis use disorder, medical cannabis, medical marijuana

1. Introduction

With growing state-level legalization of commercial cannabis markets, individuals are increasingly using cannabis products hoping to alleviate symptoms of various chronic medical conditions (1–3). In most US states, people seeking cannabis for medical or psychiatric symptoms must obtain state-specific medical cannabis authorization cards to purchase cannabis products from dispensaries (4, 5). Enrollment in medical cannabis programs increased 4.5-fold from 2016 to 2020 (6). While interest in using commercial cannabis products for medical conditions is high, rigorous data on its safety and effectiveness for symptom relief is sparse (7), and few studies assess longer-term outcomes.

The most common conditions for which individuals obtain medical cannabis cards are pain, insomnia, anxiety and depressed mood (8–10), but evidence for the efficacy of cannabis to treat these symptoms has been mixed (7, 11–18). Studies examining the effects of cannabis on chronic pain have generally had small sample sizes and null results (19), except for some evidence of efficacy for neuropathic pain (19–21). While patients using opioid medications for chronic pain have reported preliminary success in substituting cannabis for these medications (22, 23), electronic health records, including prescription drug monitoring program data from a large multisite medical cannabis program, demonstrated minimal to no change in either opioids or sedative hypnotics over the 6 months of medical cannabis use (24). An ongoing randomized controlled trial is currently assessing the effectiveness of cannabis for pain control and opioid dose reduction (25). A relationship between cannabis use and sleep has been theorized based on connections between the endocannabinoid system and circadian rhythms (26, 27) with research indicating improved sleep in the short term (28–31), but a disruption in sleep quality over long term use (32, 33). The use of cannabis as a therapeutic for anxiety or depression is controversial, as existing trials are limited by small sample sizes, as well as deficits in the overall study designs, which limit the clinical applications of findings (34, 35).

Unlike Food and Drug Association (FDA) approved medications, treatments approved by voter initiatives or legislative action come with little evidence to guide dosing to optimize benefits and minimize adverse effects. Further, recent US national data reports that 3 in 10 adults who use cannabis develop cannabis use disorder (CUD), with 23% developing severe CUD (36) often with tolerance to Δ9-tetrahydrocannabinol (THC) and withdrawal symptoms (37, 38). Data are lacking on whether adults using cannabis for medical purposes develop similar rates of CUD to those who use cannabis for recreational purposes. Rigorous studies of the effects of cannabis use on clinical outcomes will be critical to inform patient and clinician decision-making.

This study describes a prospective, 9-month follow-up of participants enrolled in a randomized clinical trial (RCT; *NCT03224468*) in which adults seeking cannabis to alleviate pain, insomnia, anxiety, or depression were randomized to immediate card acquisition or 12 weeks delayed card acquisition groups. In the 12-week RCT, immediate cannabis card acquisition was associated with developing CUD, improved self-reported insomnia, and no change in pain, depression, or anxiety symptoms (29). Here, we report cannabis use frequency, CUD, pain, insomnia, anxiety, and depression symptoms over the 9 months following the 12-week randomized phase. Based on results of the RCT, we hypothesized that after 12 months of cannabis use, symptoms of insomnia would improve, but symptoms of CUD would increase. We did not hypothesize any changes in pain, depression, or anxiety symptoms.

2. Methods

This study was approved by the Massachusetts General Brigham Institutional Review Board. All participants provided informed consent. Participants were financially compensated for their time, but the study did not provide or pay for the medical cannabis cards or any cannabis products. Adults without CUD seeking to obtain a medical cannabis card for pain, insomnia, anxiety, or depressive symptoms participated in a 12-week, single-blind randomized pragmatic clinical trial (*NCT03224468*), described previously (29), in which they were assigned to either obtain a card immediately or to delay card acquisition by 12 weeks. Participants assigned to the immediate card acquisition group were required to obtain a card to participate in the study. All participants were then followed for a 9-month period in which all could obtain medical cannabis cards if they desired, and use the cannabis products of their choice, dose, and frequency following the randomized phase.

2.1. Design

Participants completed assessments of clinical symptoms (pain, insomnia, anxiety, depression), cannabis use and CUD at baseline and weeks 2, 4, and 12 of the randomized phase. During the follow-up period, participants completed assessments of clinical symptoms at months 6 and 12 and of cannabis use monthly.

2.2. Participants

Participants were men and women aged 18–65 (inclusive) who expressed an interest in using cannabis to alleviate symptoms of pain, insomnia, anxiety, or depression and were recruited through community advertising; a full description of the sample is reported elsewhere (29). Exclusion criteria included daily or near-daily cannabis use in the prior 3 months, diagnosis of current CUD, other substance use disorder, or serious unstable medical condition at screening or baseline assessments.

2.3. Measurements and outcomes

Cannabis use frequency was collected monthly *via* REDCap using a 7-point ordinal rating scale. Due to low cell counts, we collapsed the scale down to four ratings: (a) 5–7 days per week, (b) 1–4 days per week, (c) less than once a week, and (d) less than once a month.

We report results for five clinical outcomes. Pain in the past 24 h was assessed by the Pain Severity subscale of the Brief Pain Inventory Short Form (BPI-PS) (39) on a 0–10 point scale (0 = no pain, 10 = worst pain imaginable). Insomnia in the past

month was assessed by the Athens Insomnia Scale (AIS) (40) on a 0–24 point scale, with higher scores indicating more severe sleep difficulties. Anxiety and depressive symptoms in the past week were assessed using the corresponding subscales of the Hospital Anxiety and Depression Scale (HADS) (41), each on a 0–21 point scale, with scores of 8–10 indicating borderline abnormal and a score of 11 or greater indicating abnormal levels of anxiety or depression for a given subscale. Cannabis use disorder (CUD) symptoms were assessed in interviews by doctoral-level or registered nurse investigators blinded to group assignment using the CUD Checklist of the Diagnostic and Statistical Manual of Mental Disorders (42), with scores ranging from 0 to 11 (with 2 or more symptoms indicating a CUD diagnosis, and higher scores indicated more severe CUD).

2.4. Analytic plan

All analyses examined how clinical outcomes (cannabis use frequency, symptoms of pain, insomnia, anxiety, depression, and CUD) changed from the end of the RCT to the end of the follow-up period (month 12). Time was assessed *via* a linear trend, using the number of months since enrollment per participant (accounting for individual variation in the timing of study visits). All analyses included a participant-varying intercept and slope for the time trend. Analyses also included a covariate for a participant's symptom levels at baseline. We used a dummy-coded variable for randomization group (immediate = 1, delayed = 0).

We first assessed change in cannabis use over time, testing for differences by randomization group and for a group by time interaction. We fit the ordinal cannabis use outcome (the 4-point rating scale) using a multi-level cumulative probit regression (43). Analyzing the ordinal ratings using the cumulative probit model avoided systematic errors caused by analyzing ordinal ratings using linear regression (44).

We next assessed change in symptom levels for the five clinical outcomes (symptoms of pain, insomnia, anxiety, depression, and CUD) over time, again testing for differences by randomization group and for a group by time interaction. We fit the clinical inventory scores and CUD symptom counts using a multi-level beta-binomial regression model.

Finally, we reassessed change in symptom levels for the five clinical outcomes over time based on cannabis use frequency, regardless of randomization group. Here, we used an approach based on projective inference (45), fitting as a reference model a cumulative probit regression with subject-varying intercepts and slopes for change over time (expanded to capture linear, quadratic, and cubic trends) applied to participants' full set of 10 monthly cannabis use ratings. We used this reference model to interpolate continuous estimates of cannabis use at months 3, 6, and 12 (when clinical outcomes were collected).

All analyses were conducted in a Bayesian framework, allowing implementation of complex statistical models and intuitive interpretations of uncertainty intervals and p-values as the probability of a test statistic given the data and prior assumptions (46). To address the potential for an inflated risk of false positives (47), we used a model-averaging approach (48), in which results across nested models [i.e., models for (1) a main effect of time, (2) main effects of both time and group/cannabis use, or (3) their interaction] are averaged together based on their predictive utility [e.g., stacking weights based on leave-one-out cross-validation; (49)]. We report estimated standardized effect sizes (ES, mean differences scaled by baseline standard deviations), 95% credible intervals, and posterior p-values. All results are from the model-averaged adjusted estimates. Effects were deemed statistically significant if adjusted posterior $p < 0.05$.

3. Results

Among the 186 participants enrolled in the original clinical trial, 163 had at least one follow-up assessment (at either 6 or 12 months) with complete data for all five clinical outcomes and for cannabis use. The analytic sample was 68.1% female, 82.2% white, and had an average age of 37.3 (SD = 14.4) years. See Table 1 for additional descriptive characteristics measured at baseline. Participants in the immediate acquisition group were required to obtain a medical cannabis card to be eligible for the clinical trial, thus all (100%) obtained a card. In contrast, only 36.5% of participants assigned to delayed acquisition obtained a card by the 12-month timepoint. Although the majority of participants in the delayed acquisition group did not obtain a card, 74.6% reported using cannabis 1 or more days per week for at least a month during the follow-up period (months 3–12).

As previously reported (29), at the end of the clinical trial (month 3) the immediate acquisition group had higher rates of cannabis use compared to the delayed acquisition group (β = 1.49, CI = 0.99–2.00, post. $p < 0.001$). However, by month 12 the immediate acquisition group had reduced cannabis use (β = −0.50, CI = −0.88 to −0.08, post. $p = 0.020$), while the delayed acquisition group had a slight increase in cannabis use frequency (β = 0.38, CI = −0.15–0.86, post. $p = 0.132$). The immediate acquisition group still had greater use than the delayed group at month 12 (β = 0.61, CI = 0.01–1.31, post. $p = 0.046$) (Figure 1, Supplementary Table 1).

At month 12, 11.7% ($n = 19$) of participants, and 17.1% of those using cannabis daily or near-daily ($n = 6$) met DSM-V diagnostic criteria for CUD, defined as 2 or more symptoms of CUD; most had mild ($n = 15$), defined as 2–3 symptoms, two participants had moderate, defined as 4–5 symptoms, and two participants had severe CUD, defined as 6 or more symptoms. For those with a CUD diagnosis, the most frequently reported CUD symptoms were tolerance (58%), using despite experiencing problems (44%), spending a lot of time using (31%), and craving (31%). The most common combinations of symptoms were tolerance combined with either craving (10%), using more than intended (8%), or wanting to cut back (6%) (Supplementary Figure 1). There was no statistically significant effect of group on number of CUD symptoms by the 12-month timepoint (ES = 0.63, 95% CI = 0.00–1.31, post. $p = 0.185$).

Averaging over time points, the immediate acquisition group had lower AIS scores (ES = 0.30, −0.53 to −0.08, $p = 0.008$) and higher BPI scores (ES = 0.15, 0.03–0.27, $p = 0.012$) compared to the delayed acquisition group. There were, however, no statistically significant time by group interactions on any outcome (Supplementary Table 2, Supplementary Figure 2), indicating that

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TABLE 1 Participant characteristics at baseline.

Measure	Overall	Immediate	Delayed	*p*-value
Sample size	163	96	67	
Finished only 1 follow-up visit	11.7% (19)	9.4% (9)	14.9% (10)	$p = 0.667$
Age; M (SD)	37.3 (14.4)	38.4 (14.4)	35.7 (14.4)	$p = 0.930$
Biological sex at birth; % (*n*)				
Female	68.1% (111)	68.8% (66)	67.2% (45)	$p = 0.904$
Male	31.9% (52)	31.2% (30)	32.8% (22)	
Race; % (*n*)				
Asian	6.1% (10)	6.2% (6)	6% (4)	$p = 0.787$
Black or African American	6.7% (11)	6.2% (6)	7.5% (5)	$p = 0.716$
Multi-racial	2.5% (4)	3.1% (3)	1.5% (1)	$p = 0.870$
Not listed	2.5% (4)	1% (1)	4.5% (3)	
White	82.2% (134)	83.3% (80)	80.6% (54)	$p = 0.910$
Hispanic or Latino; % (*n*)	4.9% (8)	4.2% (4)	6% (4)	$p = 0.624$
Education level; % (*n*)				$p = 0.600$
High school	3.7% (6)	3.1% (3)	4.5% (3)	
Part college	19.6% (32)	15.6% (15)	25.4% (17)	$p = 0.674$
College 2–4 years	35.6% (58)	36.5% (35)	34.3% (23)	$p = 0.911$
Part grad school	40.5% (66)	44.8% (43)	34.3% (23)	$p = 0.978$
Unknown	0.6% (1)	0% (0)	1.5% (1)	
Education years; M (SD)	16.5 (2.3)	16.6 (2.3)	16.3 (2.3)	$p = 0.989$

although there was a main effect of group, the groups did not differ in how their clinical symptoms changed over time. Depression scores improved from month 3 to month 12, regardless of randomization group or frequency of cannabis use (ES = −0.13, 95% CI = −0.26 to −0.01, post. $p = 0.032$). Pain, insomnia, and anxiety symptoms did not change significantly over the follow up period (Table 2).

More frequent cannabis use was associated with greater pain (ES = 0.07, 95% CI = 0.02–0.12, post. $p = 0.006$) and more CUD symptoms (ES = 0.55, 95% CI = 0.31–0.86, post. $p < 0.001$). More frequent cannabis use was not associated with improvement in insomnia, depression, or anxiety. Those who used cannabis 3 or more days per week were 2.69 times more likely to develop CUD, with disorder rates of 15.4% for those who used 3 or more days compared to disorder rates of 5.6% for those who used <3 days. We found no statistically significant time by cannabis use interactions across any outcome (Table 3).

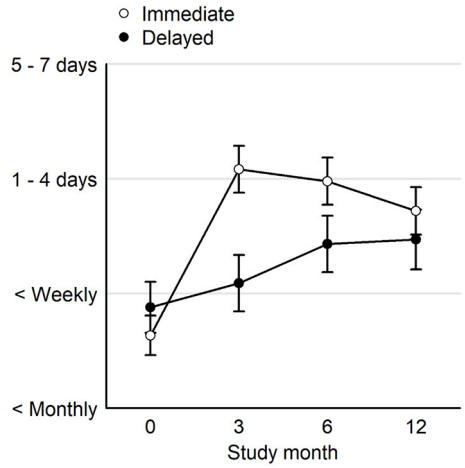

FIGURE 1
Averages and 95% uncertainty intervals over the 4-point ordinal rating for cannabis use at the start of the clinical trial (Month 0), the end of the clinical trial (Month 3), and the follow up period (Months 6 and 12). Immediate, immediate card acquisition group; Delayed, delayed card acquisition group.

TABLE 2 Symptoms of insomnia, pain, depression, anxiety, and CUD during the 9-month post-randomization period.

Outcome	Study month	Mean (SD); *N*
HADS [Anxiety]	3	6.6 (4.1); 163
	6	6.8 (4.3); 163
	12	6.2 (4.2); 149
Main effect of time		$p = 0.109$
HADS [Depression]	3	4.3 (3.8); 163
	6	4.0 (3.6); 163
	12	3.8 (3.5); 149
Main effect of time		$\mathbf{p = 0.032}$
AIS	3	7.9 (4.9); 163
	6	7.5 (4.8); 163
	12	7.3 (4.6); 149
Main effect of time		$p = 0.182$
BPI [Severity]	3	1.58 (2.18); 163
	6	1.30 (2.03); 163
	12	1.57 (2.16); 149
Main effect of time		$p = 0.891$
CUD symptoms	3	0.40 (0.83); 163
	6	0.48 (0.91); 163
	12	0.48 (1.02); 149
Main effect of time		$p = 0.695$

HADS, Hospital Anxiety and Depression Scale; AIS, Athens Insomnia Scale; BPI, Brief Pain Inventory; CUD, Cannabis Use Disorder, bolded p-values indicate a statistically significant change in symptoms over the 9-month follow-up period.

TABLE 3 Main effects of time and cannabis use frequency and their interaction for each clinical outcome.

Outcome	Effect	Cohen's D Mean; 95% CI	Post. *p*-value
HADS [Anxiety]	Main effect of time	−0.11; −0.24–0.03	$p = 0.111$
	Main effect of cannabis use	−0.07; −0.18–0.00	$p = 0.301$
	Time x cannabis use interaction	0.08; 0.00–0.24	$p = 0.338$
HADS [Depression]	**Main effect of time**	**−0.14; −0.26- −0.01**	$\mathbf{p = 0.030}$
	Main effect of cannabis use	0.00; 0.00–0.00	$p = 0.990$
	Time x cannabis use interaction	0.00; 0.00 to 0.00	p = 0.990
AIS	Main effect of time	−0.11; −0.26–0.04	$p = 0.149$
	Main effect of cannabis use	−0.08; −0.23–0.00	$p = 0.454$
	Time x cannabis use interaction	0.00; 0.00–0.02	$p = 0.530$
BPI [Severity]	Main effect of time	0.00; −0.08–0.08	$p = 0.952$
	Main effect of cannabis use	**0.07; 0.02-0.12**	$\mathbf{p = 0.006}$
	Time x cannabis use interaction	0.00; −0.03–0.02	$p = 0.951$
CUD symptoms	Main effect of time	0.07; −0.35–0.50	$p = 0.733$
	Main effect of cannabis use	**0.55; 0.31-0.86**	$\mathbf{p < 0.001}$
	Time x cannabis use interaction	0.04; −0.21–0.27	$p = 0.736$

HADS, Hospital Anxiety and Depression Scale; AIS, Athens Insomnia Scale; BPI, Brief Pain Inventory; CUD, Cannabis Use Disorder. Bolded p-values indicate a statistically significant effect.

4. Discussion

In this 9-month prospective follow-up analysis of a 12-week RCT of immediate or delayed medical cannabis card acquisition, greater cannabis use frequency was positively associated with more CUD symptoms and greater pain severity and not significantly associated with changes in insomnia, depression, or anxiety symptom severity.

Few studies assess the development of CUD in individuals using cannabis for medical purposes. The current study found that after 1 year of cannabis use, 11.7% of all participants and 17.1% of the daily or near-daily cannabis users had a CUD diagnosis, with 2 participants meeting criteria for severe CUD (6 symptoms). CUD at screening or baseline was exclusionary, so these were all new onset courses of CUD. Epidemiologic surveys of recreational cannabis use have indicated 3 in 10 adults who use cannabis develop CUD (36). Though prevalence in the current study is lower than the 30% 12-month incidence of CUD reported in Hasin et al. (36), it nonetheless indicates that individuals using cannabis for medical reasons may be at risk for CUD. Most current medical cannabis card regulations do not require a follow-up appointment with a certified physician after obtaining a medical cannabis card. This lack of follow-up differs from standard medical practice when prescribing other medications for these conditions such as antidepressants, opioids, and benzodiazepines. Due to the risk for CUD among individuals who use cannabis for medical concerns, a follow-up appointment with the prescribing physician may be warranted to assess balance between symptom improvement and emergence of CUD symptoms.

For those with a CUD diagnosis, the most frequently reported CUD symptoms were tolerance, using despite experiencing problems, spending a lot of time using, and craving. We recognize that there remains controversy in the field about whether a CUD diagnosis is appropriate for patients using cannabis for medical symptoms, rather than recreational purposes alone. For those taking *prescription* medications in the context of appropriate medical treatment, tolerance and withdrawal do not count as criteria for a substance use disorder. We note, however, that cannabis is not obtained *via* a prescription, but rather, through a recommendation. Thus, the system created for the regulation and distribution of cannabis for medical purposes is unique; unlike FDA-approved medications, the physician recommending cannabis has no authority over amounts, concentration, doses, or frequency of cannabis use for the patient and often no clinical guidance. Further, for many cannabis users, there is a blurred line between medical and recreational motives (e.g., in those using cannabis for "relaxation" purposes). Therefore, we did not discount tolerance or withdrawal as CUD symptoms in study participants.

The association between more frequent cannabis use and increased pain should be interpreted with caution, as it is unlikely that cannabis use caused or exacerbated pain. Instead, it is possible that individuals experiencing more pain used cannabis more frequently to treat their pain. The association between greater cannabis use and greater pain likely indicates that cannabis is not adequately treating pain symptoms. This viewpoint is supported by a recent position paper from the International Association for the Study of Pain (IASP) that found, after a comprehensive review of research on the use of cannabinoids to treat pain, there was a lack of sufficient evidence to endorse the general use of cannabinoids for the treatment of pain (50). Further, lack of improvement in symptoms of anxiety after 12 months of cannabis use adds to a growing body of literature that does not endorse cannabis as a treatment for these conditions (51). Though there was no significant worsening of symptoms, additional work suggests

heavy cannabis use may increase risk for depression (52) and other psychiatric illnesses (53), particularly among adolescents and young adults (54–56). The lack of benefit from cannabis indicates that individuals with these chronic conditions should consider evidence-based treatments. Additionally, because there was no placebo cannabis, and because all participants were seeking cannabis as a potential therapeutic, the trial design created bias toward finding a treatment effect attributable to expectancy. This strengthens our confidence in the null findings for improvement in pain, anxiety, and depression symptoms as a function of frequency of cannabis use. We do note that depression symptoms improved in all participants over time; though there was no significant effect of cannabis frequency, future studies should include non-using control participants in order to tease apart the effects of any cannabis use from the effect of time or study procedures that involve reflecting on and discussing symptoms, which may itself lead to reduction in symptoms (57).

Although we hypothesized improvements in insomnia symptoms, increased frequency of cannabis use did not predict greater improvement in insomnia. There was a main effect of group on insomnia symptoms, driven by improvement in the RCT phase in the immediate card acquisition group (29), but no additional benefit over the 9-month post-randomized period. Interestingly, though participants in the immediate card acquisition group experienced a short-term benefit of cannabis for sleep, their sleep did not continually improve during the 9-month post-randomized period (Supplementary Figure 2). This is in line with prior work on sleep and cannabis use which suggests an initial benefit to insomnia but disruptions in sleep quality if cannabis is used long term (32, 33).

This study should be interpreted in light of its limitations. First, the sample was predominantly female and white which may limit the generalizability of our findings. We used a pragmatic design, meaning that participants chose which cannabis products and how much they used; therefore, this study cannot determine the effect of specific cannabinoids on symptoms of these disorders. It will be important for future studies to quantify which doses and constituents of cannabinoids may be therapeutic. Further, though most participants received a medical cannabis card from a doctor, few received adequate advice on product choice and dosing, largely because the evidence for specific products and doses is lacking. Therefore, it is possible participants were not using cannabis at therapeutic doses. Even so, current regulations state that after receiving a medical cannabis card, individuals may choose their products and dosing, lending ecological validity to this study. We did not assess quality-of-life measures such as stress levels, activity levels, or positive affect. Other studies suggest that even if symptoms themselves do not improve, cannabis may improve these quality-of-life measures (58, 59). Finally, past CUD (>1 year before enrollment) was not exclusionary for this study, though we note that rates of past CUD were low (8.0% of participants) and the time between any CUD diagnosis and trial enrollment was often long (M = 23, SD = 20 years prior to study enrollment).

In conclusion, in this 9-month follow-up study of a 12-week randomized clinical trial of medical cannabis card ownership, we found an association between more frequent cannabis use and increased CUD risk, with no significant improvement in pain, anxiety, insomnia, or depression symptom severity as a function of cannabis use. The current findings call into question the long-term utility of cannabis as an effective tool in relieving clinical symptoms.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Massachusetts General Brigham Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JG, RS, and AE contributed to the conceptualization and design of the original study. JG, MC, KP, BT-C, and BH designed the current research question and data analyses. JJ, MP, GP, and MC assisted with data collection. KP and MP organized and cleaned the data. KP performed the statistical analyses. MC, KP, and JJ wrote the first draft of the manuscript. JG and AE provided funding for data collection and salary support. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

AE reports consulting income in the past 3 years from Charles River Analytics and Karuna Pharmaceuticals and editorial support through Pfizer.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Impacts of recreational cannabis legalization on use and harms: A narrative review of sex/gender differences

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Legalization of cannabis use for non-medical (recreational) purposes is changing the global cannabis landscape. As attitudes toward cannabis use become more positive and prevalence of use increases in complex ways, concerns emerge about the potential for increased cannabis-attributable harms. Understanding the who, why, and when of this likely increase in cannabis-attributable harms is thus an important public health priority. Both sex and gender contribute to variability in the use, effects, and harms of cannabis and thus sex/gender considerations are important when evaluating the impacts of cannabis legalization. The goal of this narrative review is to broadly discuss sex/gender differences in attitudes toward and prevalence of cannabis use, whether there are sex/gender differences in the impacts of cannabis legalization, and why these sex/gender differences might exist. One of our strongest conclusions is that men have always been more likely to use cannabis than women, yet the sex/gender gap in prevalence of cannabis use has narrowed over time, and this might be partly due to cannabis legalization. The existing evidence suggests that there have also been sex/gender differences in the impacts of legalization on cannabis-attributable harms such as cannabis-involved motor vehicle collisions and hospitalizations, though these results are more variable. The body of literature reviewed has focused almost exclusively on samples of cisgender research participants, and thus future research should encourage inclusion of transgender and gender-diverse participants. More consideration of sex- and gender-based analysis in research evaluating long-term impacts of cannabis legalization is a clear research priority.

KEYWORDS

sex, gender, cannabis, legalization, attitudes, prevalence, harms

1. Introduction

Cannabis continues to be one of the most commonly used psychoactive drugs worldwide. The most recent data from the United Nations Office on Drugs and Crime (UNODC) estimate that 209 million people used cannabis in 2020, which represents roughly 4% of the global population (1). The legal status of cannabis has been controversial since the late 1930s, and the

past two decades have seen dramatic changes in individual state- and country-level regulation of cannabis worldwide (2, 3). As of November 2022, commercial sale of non-medical (recreational) cannabis is legal at the national level in three countries (Uruguay, Canada, and most recently, Thailand), while an additional four countries have legalized possession and consumption of cannabis for non-medical purposes, with restrictions on sale and distribution (Georgia, Malta, Mexico, and South Africa). In the United States, cannabis is still illegal for any purpose at the federal level, but 21 states, two territories, and the District of Columbia have legalized non-medical cannabis use.

Legalization of non-medical cannabis use has had mixed effects on changes in prevalence of use. For example, one recent systematic review that identified 32 relevant studies found that legalization was associated with an increase in past-month cannabis use among young adults, but may not have had an impact on other cannabis use metrics or in other age groups such as adolescents (4). Data from the most recent National Surveys on Drug use and Health (NSDUH) in the US suggest that daily cannabis use may have increased significantly more than overall use; daily use rose from 0.65 to 2.31% from 2002 to 2020 (a nearly four-fold increase), while past-year prevalence increased from 11.03 to 17.47% over the same time period (5). Similarly, data from the Centre for Addiction and Mental Health (CAMH) Monitor Surveys in the Canadian province of Ontario found that past-year prevalence of cannabis use increased from 11% in 2011 to 26% in 2019, whereas daily use increased from 1 to 6% over the same time period (6). However, data from Monitoring the Future in the US has not seen much of an increase in prevalence of daily cannabis use, which has remained around 5–6% among 12th graders from 2002 to 2022 (7). The evidence is similarly mixed on the extent to which legalization has impacted cannabis-related harms such as prevalence of cannabis use disorder (CUD), cannabis-involved motor vehicle collisions, and cannabis-involved hospitalizations (8–10). Significant heterogeneity in the relationship between cannabis legalization and specific metrics of cannabis use and related harms suggests that legalization has not had a uniform impact across the population in countries that have legal access to non-medical cannabis use.

Sex and gender both have significant impacts on the use and effects of psychoactive drugs, including cannabis. Sex refers to biological attributes and functions of bodies, whereas gender refers to the socially and culturally constructed aspects of self-perception and social organization that shape identity, expression, roles, norms, behaviors, and relations. Both sex and gender are complex, multifaceted constructs, and neither are adequately described by binary frameworks, despite historical emphasis on sex (male, female) and gender (man, woman) as binary traits. While sex and gender are two distinct concepts, in reality, there is an intricate and dynamic relationship between sex and gender and it is challenging to draw a clear line between them; thus, the term "sex/gender" can be used to recognize this entanglement (11). The term "sex/gender" is not meant to conflate the concepts of sex and gender, but rather to acknowledge that we typically lack sufficient information to accurately attribute an observed difference to either sex or gender. For example, if a study finds that prevalence of past-year use of a drug differs between cisgender women and cisgender men (with no potential explanatory variables considered), there is not enough information to label this finding either a "sex difference" or a "gender difference," as the likelihood of using a psychoactive drug is dependent on both sex-related biological factors and gender-related sociocultural factors. In this case, we would use the term "sex/gender difference." For the purposes of this review, we will use the term "sex/gender" in cases where we are summarizing data and where there is insufficient evidence to attribute trends in the data to either sex or gender. In order to accurately reflect the evidence that we are reviewing, we will clearly identify whether an individual study analyzed their data with consideration of sex or gender and, where possible, provide details on how sex and/or gender were defined.

Sex/gender differences have been observed in cannabis use prevalence, routes of administration, acute effects, prevalence and severity of cannabis use disorder, and actions of the endocannabinoid system that mediates the effects of cannabis (12, 13). One of the most robust findings is the higher prevalence of cannabis use and cannabis use disorder (CUD) among men, compared to women (to be discussed in more detail in the body of this review). Nearly all of this research has involved cisgender men and women and used a binary man–woman, boy–girl, or male–female comparative framework, though there is a small and growing literature documenting cannabis use attitudes and harms among gender minorities (i.e., transgender and non-binary or gender-diverse individuals). As this manuscript will focus primarily on potential gendered mechanisms driving differences in cannabis-related outcomes, here we present a brief overview of sex differences in responses to cannabis to provide some context to the interested reader. There is a robust literature in animal models demonstrating that female rodents are more sensitive to the effects (e.g., motor, analgesic, and reinforcing effects) of cannabinoid drugs such as Δ-9-tetrahydrocannabinol (THC), the primary intoxication component of cannabis (13). These sex differences in rodents are often attributed to the actions of gonadal hormones such as estradiol; for example, estradiol influences analgesic effects of THC (14) and density of cannabinoid receptors in the mammalian brain (15). Importantly, in rodent models, there is a notable sex difference in metabolism of THC, where females metabolize THC primarily to a psychoactive metabolite, while males metabolize to a variety of mainly non-psychoactive metabolites (16). However, this evidence has not translated so clearly to humans; while multiple studies have found evidence of human sex differences in some cannabis-related outcomes using experimental designs, there is considerable heterogeneity in results, and human sex differences appear to be heavily dependent on factor such as THC dose, route of administration (e.g., smoked vs. oral), and participants' past experience with cannabis (13, 17).

Given the significant heterogeneity in the impact of cannabis legalization and the robust evidence demonstrating an impact of both sex and gender on cannabis use and related harms, the present narrative review aimed to do four things: (1) describe sex/gender differences in cannabis-related attitudes/perceptions and cannabis legalization support; (2) describe sex/gender differences in cannabis use prevalence and how cannabis legalization impacted cannabis use; (3) present an overview of how cannabis legalization may have impacted cannabis use during pregnancy and parenthood, which are particularly salient gendered life course factors; and (4) present an overview of the scope of evidence that suggests sex/gender may have impacted the effects of cannabis legalization on changes in cannabis-related harms. We took a narrative approach with this review in order to focus more on understanding why these sex/gender differences exist.

2. Sex/gender differences in attitudes toward cannabis use and support for cannabis legalization

2.1. Sex/gender differences in cannabis use attitudes and risk perceptions

Women tend to have more negative attitudes toward cannabis use than men. For example, in a sample of 1,713 Canadian undergraduate students, women had lower odds (odd ratio [OR] = 0.66) of having favorable attitudes toward cannabis acceptability compared to men (note that sex was used as a proxy variable for gender in this study) (18). Similarly, in a survey of 507 adolescents in Ireland that investigated gender differences, boys were more likely than girls to perceive cannabis as a safe substance (OR = 2.02) and less likely to perceive that cannabis use was a big problem for Irish teenagers (OR = 0.53) (19). In a large national survey of Norwegian university and college students (n = 49,688), a gender difference was found among respondents not reporting cannabis use: 40.9% of men perceived cannabis as no/low risk compared to only 16.4% of women (20). An analysis of 2002–2018 data from the National Surveys on Drug Use and Health (NSDUH) in the US (n = 949,285) suggested that gender differences in cannabis perceptions may be age-dependent (21). In adolescents aged 12–17 years, there was little evidence of a gender difference in cannabis perceptions, but among adults aged 18+ years, perceiving cannabis as low-risk was more common among men and perceiving cannabis as high-risk was more common among women (21).

One interesting note from the analysis of 2002–2018 NSDUH data in the US is that the gender gap in cannabis risk perceptions did not seem to change over time. While the prevalence of risk perception of cannabis varied by gender when data were aggregated or viewed cross-sectionally, time trend analysis found that the gender gap in risk perception did not change over time, with the exception of a greater decline over time in high-risk perception of cannabis in men in the 50+ age group (21).

2.2. Sex/gender differences in support of cannabis legalization and intentions to use cannabis if legalized

Men tend to have greater support for cannabis legalization, whereas women are less likely to support legalization. For example, a survey of 2,190 adults (aged 18+ years) in Michigan found that female gender was associated with lower odds of supporting cannabis legalization (OR = 0.46) (22). The authors of this survey explored reasons for supporting or opposing legalization using qualitative methods and found some gendered differences—women tended to cite potential medical benefits or increasing product safety as reasons for supporting legalization, while men tended to cite personal freedom (23). Other US studies have similarly found an association between male sex or gender and greater support for cannabis legalization (24, 25). The same trend has been observed in Norway (20), Ireland (19), New Zealand (26), and Malaysia (specific to decriminalization of medical cannabis) (27), while another study found that women in the Caribbean were more likely to support full prohibition of cannabis (28).

One study evaluated gender differences in trends in cannabis legalization support over time. The authors found that, while the overall proportion of US adults in favor of cannabis legalization has increased steadily over time (from just over 10% in 1969 to nearly 60% in 2016), gender did not have a significant impact on this trend (29). In this analysis (General Social Survey data spanning the years 1974 to 2016), women were consistently less likely to support legalization than men, though the difference was of small magnitude for most years and did not meaningfully change over the four decades (29). This seems to align with the previously discussed finding that temporal trends in cannabis risk perception over time were not impacted by gender, even though risk perceptions varied by gender when viewed cross-sectionally.

One study was identified that included gender minority respondents. In a survey of young adults who identified as sexual or gender minorities in Chicago (n = 1,114), there was a marginally significant effect of gender identity on perception of cannabis legalization, where cisgender men and gender minorities had slightly higher agreement with cannabis legalization than cisgender women (30).

Men are generally more likely to indicate intent to try cannabis if it becomes legal, compared to women. For example, an analysis of sex differences in data from five cohorts (2007 to 2011) of high school seniors in Monitoring the Future (a US national survey) found that, among adolescents not currently using cannabis (n = 6,116), female participants were less likely to indicate intention to try cannabis if legalized, compared to male participants (adjusted OR = 0.61) (31). In a study of Norwegian university and college students (n = 49,688), among respondents not reporting cannabis use, 13.2% of men intended to try cannabis if legalized, compared to just 5.4% of women (20). Data from multiple cycles of the Australian National Drug Strategy Household Survey (n = 23,855 in 2013, 23,749 in 2016, and n = 22,015 in 2019) found that male sex was associated with significantly increased odds (adjusted OR = 1.64) of willingness to try cannabis if it were legal (32). One study using data from the 2018 National Cannabis Survey (NCS) in Canada (n = 17,089) did not find a significant effect of sex on the odds to try or increase use of cannabis after legalization (after adjusting for province/territory and survey wave), though male sex was significantly associated with increased willingness to try or increase use in the unadjusted model (OR = 1.3) (33). Note that this study used gender as a proxy variable for sex (i.e., the survey variable was gender, but the authors interpreted this as participant sex).

2.3. Why are there sex/gender differences in attitudes toward cannabis use and legalization?

An understanding of why sex/gender differences in attitudes toward cannabis use and legalization exist is helpful to contextualize these findings and speculate how things may change over time. A study of 1,820 adolescents (aged 10 to 19 years) in the US suggested that there may be gender differences in determinants of cannabis risk perceptions: peer norms were more strongly related to risk perception in boys, whereas parental norms were more strongly related to risk perception in girls (34). Another study of 1,002 registered US voters (aged 18 to 95 years) suggested that the perceived lack of adequate regulations to prevent cannabis-related harms may play a role; a gender difference in support of cannabis legalization (support initially

lower in women) was no longer statistically significant if a reliable roadside test for cannabis-related driving impairment was available (25). In one of the most informative studies on this topic, Elder & Greene (2019) used data from the March 2013 Pew Research Center Political Survey (in the US) to test a series of hypotheses for the gender gap in support of cannabis legalization (35). In contrast to their hypotheses, parenthood was not a significant factor in predicting the gender gap in cannabis legalization support and increased religiosity among women did not fully account for the gender gap, despite being a significant predictor of cannabis legalization attitudes. Instead, the results of this study found that lifetime cannabis use was a highly significant predictor of favorable attitudes toward cannabis legalization, and this did explain the gender gap in attitudes (35). This is in line with other literature demonstrating that prior use of cannabis is one of the most robust predictors of legalization support (22, 31, 36, 37). As we will discuss in the next section, cannabis use is significantly more prevalent among men than women, which is likely at least in part due to stigmatization of women's cannabis use and sex/gender differences in opportunities to use cannabis.

2.4. Interim summary

Taken together, women appear to have more negative attitudes toward cannabis use, greater perception that cannabis use is harmful, and less support for cannabis legalization, and this appears to be true across multiple countries in North America, the Caribbean, Europe, and Asia. The negative association between female gender and support of cannabis use and legalization is likely due to a complex set of sociocultural factors, including adherence to traditional feminine gender roles, sex/gender differences in determinants of risk perceptions, and sex/gender differences in cannabis use. Though the data are still very limited, it appears that there have not been dramatic changes in the sex/gender gap in cannabis risk perception or support of cannabis legalization over time. However, to the best of our knowledge, no study has directly tested for an effect of cannabis legalization on sex/gender parity in cannabis-related attitudes or perceptions. This kind of effect might be expected if the gender differences in attitudes toward cannabis legalization are related to differences in socialization of girls and boys. For example, since girls have historically been socialized to worry more about moralistic social issues, one could predict that adult women who were socialized during periods of heightened concern toward illicit drug use might have much more negative attitudes toward cannabis use and legalization than younger women who were socialized during periods of increased societal acceptance of cannabis use, whereas this effect might not be observed in men (35).

3. Sex/gender differences in cannabis use prevalence and the impact of cannabis legalization on cannabis use

3.1. The sex/gender gap in cannabis use prevalence: Historical trends

Cannabis use has historically been significantly more prevalent among men than women, yet the sex/gender gap in prevalence has changed over time. Early data from the US National Alcohol Surveys suggested a gender convergence of past-year cannabis use from 1984 to 2000, which was largely driven by a greater decline in use among men overall, and a notably steep increase in past-year cannabis use in women aged 18 to 25 years between 1995 and 2000 (38). Data from the National Youth Risk Behavior Survey (school-based surveys of high school students in the US) from 1999 to 2013 similarly found evidence of sex converge in prevalence of past 30-day cannabis use over that time period (39). In contrast, one study using data from the National Survey on Drug Use and Health (2002–2014) actually found a widening of the gender gap in prevalence of past-year cannabis use, which was primarily due to an increase in use among men of lower income from 2007 to 2014 (40).

Chapman et al. conducted a systematic review and meta-analysis of studies examining birth cohort changes in the sex/gender gap in cannabis use prevalence in North America, Europe, and Oceania (41). Note that the authors did not specify whether the reviewed studies analyzed data with respect to sex or gender, and the authors use the terms sex and gender interchangeably in this article, so we retain the term "sex/gender" when discussing these findings here. Of the 22 studies included in the systematic review, 10 found evidence of sex/gender convergence in at least one indicator of cannabis use (e.g., past-month, past-year, or lifetime cannabis use), with the majority (7/10) finding that the convergence was due to a greater increase in use among women compared to men (41). Eleven studies found no evidence of changes in sex/gender differences in cannabis use over time, while a single study found that there was evidence of sex/gender divergence in prevalence of use driven by increased use among men (41). In the quantitative synthesis and meta-analysis, the pooled cannabis use sex/gender ratio varied from a high of 2.0 (men to women) in the 1941–1945 birth cohort to a low of 1.3 in the most recent birth cohort (1991–1995), and the meta-regression indicated that the decline in the cannabis use sex/gender ratio over time was linear and statistically significant (41).

The most recent data available, as reported in the 2022 UNODC World Drug Report, found that the gender gap in past-month prevalence of cannabis use in the US declined from 2002 to 2020, from a high of approximately 2.125 men to women reporting past-month use in 2007 to a low of approximately 1.25 men to women reporting past-month use in 2020 (1).

3.2. Sex/gender differences in cannabis use prevalence: Recent data

Cannabis use prevalence data from the Canadian Cannabis Survey (CCS; yearly data available from 2017 to 2022, available disaggregated by sex) and the US NSDUH (yearly data from 2017 to 2020, available disaggregated by gender) are presented in **Table 1** (past-year prevalence) and **Table 2** (prevalence of daily use). The CCS is an annual online cross-sectional survey of Canadians aged 16 years or older that has been administered since 2017, with the goal of evaluating the impact of the *Cannabis Act* on cannabis-related metrics in Canada (42–47). The NSDUH is a much longer-standing annual cross-sectional survey in the US, which has been running since 1971 and includes Americans aged 12 years or older (5). Overall, the past-year data (**Table 1**) show similar prevalence in Canada and the US that seems to be rising over the past 4–5 years,

TABLE 1 Past-year prevalence of cannabis use from the Canadian Cannabis Survey [data available from (42–47)] and the US National Surveys on Drug Use and Health [data available from (5)].

	2017	2018	2019	2020	2021	2022
CCS						
Males	26.1 [24.7–27.5]	26.5 [25.3–27.7]	28.6 [27.4–29.9]	30.7 [29.3–32.1]	28.6 [27.3–30.0]	29.7 [28.3–31.2]
Females	17.5 [16.3–18.8]	17.6 [16.7–18.7]	20.7 [19.6–21.8]	23.4 [22.2–24.6]	22.1 [20.9–23.3]	24.7 [23.5–26.1]
NSDUH						
Men	17.66 [16.90–18.44]	18.50 [17.80–19.23]	20.48 [19.81–21.17]	19.51 [18.26–20.84]	-	-
Women	12.49 [11.99–13.01]	13.56 [12.93–14.22%]	14.86 [14.25–15.49]	15.54 [14.47–16.67]	-	-

Data are presented as percentages (percent of total respondents endorsing past-year use) [95% CI]. Note that the terms "males" and "females" are used here to be consistent with CCS language.

TABLE 2 Prevalence of daily cannabis use from the Canadian Cannabis Survey [data available from (42–47)] and the US National Surveys on Drug Use and Health [data available from (5)].

	2017	2018	2019	2020	2021	2022
CCS						
Males	19.4 [17.2–21.9]	20.2 [18.2–22.4]	18.6 [16.8–20.6]	21.0 [18.9–23.2]	21.1 [18.9–23.4]	20.8 [18.6–23.2]
Females	16.8 [14.0–20.1]	16.3 [14.1–18.7]	16.1 [14.1–18.3]	13.7 [11.8–15.8]	16.2 [14.2–18.5]	15.6 [13.6–17.8]
NSDUH						
Men	2.00 [1.76–2.26]	2.26 [2.06–2.48]	2.52 [2.27–2.80]	2.78 [2.39–3.24]	-	-
Women	1.11 [0.96–1.28]	1.23 [1.07–1.40]	1.50 [1.35–1.67]	1.86 [1.60–2.16]	-	-

Data are presented as percentages [95% CI]. Note that CCS data represent percentage of daily use among respondents reporting past-year use of cannabis, whereas NSDUH data represent percentage daily cannabis use among all respondents.

with slightly higher prevalence each year in Canada and prevalence consistently higher in male respondents compared to female respondents. Daily use data are not comparable between Canada and the US because the weekly frequency data are restricted to respondents reporting past-year use in the CCS, whereas the NSDUH asks weekly frequency of all respondents. Nevertheless, trends in the data support increasing daily use of cannabis in both male and female respondents over time in the US, with less consistent trends in Canada.

While research on cannabis use among gender minorities is more limited, some evidence suggests higher use among transgender men compared to transgender women, paralleling the findings observed in cisgender adults. For example, in a US study of transgender adults ($n = 1,210$), 31.3% of transgender men reported past 3-month cannabis use compared to 19.0% of transgender women (48).

3.3. Sex/gender differences in the impact of cannabis legalization on cannabis use

A recent systematic review of post-legalization changes in adolescent and young adult cannabis use found mixed evidence for an impact of sex/gender, but overall, the results suggested that increase in post-legalization consumption was higher in girls and young women (4). This review identified eight studies that examined sex/gender influences on change in cannabis use; five found evidence that the increase was greater in girls/women. One large study of US undergraduate students in states that did enact non-medical cannabis legalization ($n = 234,669$ in seven states) or did not ($n = 599,605$ in 41 states) found that past 30-day cannabis use increased more among students in states with legal non-medical cannabis, and when data were disaggregated by gender, this effect was larger among young women (OR = 1.29 for women, 1.12 for men) (49). A longitudinal study of 563 young adults (aged 18 to 24 years) followed from 2015–2016 to 2019 found complex sex by time and sex by legalization interactions for changes in cannabis use over the study period—male participants' cannabis use decreased over time, but with a slight (non-significant) increase in use following legalization, whereas female participants' cannabis use increased over time, with a slight (non-significant) decrease in use following legalization (50). An analysis of sex differences in data from a repeated cross-sectional survey of Colorado high school students ($n = 26,019$ in 2013 to $n = 15,970$ in 2015) found a slightly (non-significant) decrease in male participants' past 30-day cannabis use, whereas there was a (marginally significant) increase in female participants' cannabis use (51). A similar analysis of sex differences in data from a repeated cross-sectional survey of undergraduate students at Washington State University (total $n = 13,335$ spanning 2005 to 2015) found that female participants had a greater increase in cannabis use following non-medical cannabis legalization than male participants (52). Another similar study of sex differences using repeated cross-sectional survey data (the California Healthy Kids Survey from 2010–2011 to 2018–2019, total $n = 3,330,912$) found that non-medical cannabis legalization was associated with a greater increase in both lifetime (OR = 1.17) and past 30-day (OR = 1.18) cannabis use in female participants compared to male participants (53). In contrast, one study of gender differences using data from the National Cannabis Survey in Canada found a statistically significant increase in cannabis use in men, but not women, in the year following legalization (2018 to 2019) (54). Finally, two studies using US data did not find a significant impact of sex/gender on changes in cannabis use related to legalization (55, 56).

One study was identified that explored the relationship between cannabis legalization and odds of using cannabis among sexual and gender minority youth. Data from the 2017 LGBTQ National Teen Survey ($n = 10,027$ youth in the US) found that residing in a state where cannabis is legal for non-medical purposes was associated with significantly increased odds (OR = 1.50) of current cannabis use, compared to residing in states with no legal access (57). Furthermore, experiences of sexual or gender minority victimization were associated

with greater odds of both lifetime (OR = 1.98) and current (OR = 1.99) cannabis use.

3.4. Why are there sex/gender differences in cannabis use prevalence?

There are numerous potential explanations for the observation of greater cannabis use among men, mostly rooted in gender norms, roles, and relations (58). One of the most likely explanations for sex/gender differences in cannabis use relates to early opportunities to use cannabis—in general, boys tend to have more opportunities to use cannabis than girls (59–62). Boys may be less supervised by parents, more likely to engage in outdoor activities that put them at increased exposure to drug use opportunities, or more likely to affiliate with older peers who have access to cannabis (59). It should be noted that this finding is not necessarily uniformly true across cultures (61), and since gender as a construct changes over time, changes in gender roles, norms, and relations may reduce this apparent gender difference in opportunities to use cannabis. Quantitative studies have found that cannabis use is positively associated with adherence to traditional masculine gender norms (63, 64), whereas adherence to traditional feminine gender norms tends to have a negative association with cannabis use (65, 66), and these relationships seem to be true for both boys and girls. For both boys and girls expressing masculinity, using cannabis might be a way to demonstrate masculine "toughness" (67, 68). In support of this idea, a handful of qualitative studies have found that adolescents and adults may "do gender" by engaging in cannabis use, i.e., using cannabis to reinforce masculinity or to resist femininity (69–72). On the other hand, qualitative work has demonstrated how gender norms might shape cannabis use, e.g., in a study of Canadian youth, regular use of cannabis by girls was perceived as inappropriate, whereas use by boys was perceived as cool (70). Taken together, these findings suggest that sex/gender differences in cannabis use prevalence are likely driven by a complex interplay of gender influences on initial opportunities to use cannabis (typically higher in boys), the use of cannabis to assert or reinforce masculinity (which would especially increase use among men and boys), and the stigma and negative attitudes toward women and girls using cannabis (which would reduce the likelihood of use among women/girls).

3.5. Interim summary

Cannabis use has historically been and continues to be more common among men than women, yet the sex/gender gap in use prevalence has clearly narrowed over time. Based on the available evidence, it seems that legalization of non-medical cannabis has contributed to a narrowing of the sex/gender gap, where the association between legalization and increased cannabis use is observed more consistently among women and girls. However, it is clear that sex/gender influences on cannabis use prevalence are complex and legalization is likely just one of many factors that influences the relationship. Changes in gender norms, roles, and relations over time will likely continue to shift the sex/gender gap in prevalence of cannabis use, independently of legalization.

4. The impact of cannabis legalization on cannabis use during pregnancy and parenthood

4.1. Cannabis use during pregnancy

Use of cannabis during pregnancy is a particularly salient gendered issue that is associated with significant medical and sociocultural stigma. Pregnant people who use cannabis may continue to do so during pregnancy for perceived health benefits (e.g., anti-nausea effects, pain and stress relief, sleep) and lack of clear information about the harms of gestational cannabis exposure (73, 74). As noted earlier, women's drug use is already stigmatized, and the increased stigma faced by pregnant people who use cannabis is a likely barrier to seeking information about prenatal cannabis use from healthcare providers, especially since cannabis use during pregnancy may be associated with legal repercussions such as interactions with child protective services (73, 75).

To date, evidence is mixed with regard to effects of gestational exposure to cannabis. While there is currently no direct evidence of cannabis as a teratogen (a compound that causes disturbance of fetal development) (76), observational human studies have raised concerns about long-term effects of cannabis exposure *in utero* (77). Lower mean birth weight in infants seems to be the most consistent effect of gestational cannabis exposure (76, 78, 79), as demonstrated in a recent meta-analysis (OR = 1.77) which also found a mean difference of 109 grams less in infants exposed gestationally to cannabis (76). Other studies have found potential neurobehavioral consequences of gestational exposure, including effects on cognition and aggression, though these studies have been criticized for not adequately controlling for relevant confounds such as co-use of other psychoactive drugs (e.g., alcohol, nicotine, opioids), maternal mental health disorders, and environmental factors such as poverty (75, 79, 80).

Wilson & Rhee recently systematically reviewed literature that evaluated the impact of cannabis legalization in the US on cannabis use during pregnancy and perinatal outcomes (81). Based on 16 identified studies, the authors concluded there was sufficient evidence to suggest that cannabis legalization caused an increase in cannabis use, CUD, and CUD treatment admissions during the preconception, pregnancy, and postpartum periods (81). Furthermore, based on six studies, there was some mixed evidence regarding cannabis legalization effects on perinatal and postnatal outcomes such as low birth weight and preterm birth (81). Data from one study in British Columbia suggest similar results in Canada. Legalization of cannabis in Canada was associated with significantly greater odds (adjusted OR = 1.71) of cannabis use during the preconception period, though the OR associated with the pregnancy period was not significant (82).

4.2. Cannabis use during parenthood

Cannabis use during parenthood is another salient gendered issue, where cisgender women/mothers experience greater stigma than cisgender men/fathers. Despite the stigma toward cannabis use by parents, some evidence suggests that cannabis may actually help to improve parent–child relationships by reducing parental stress, substituting for other drugs, or positively influencing parenting style (75).

The systematic review by Wilson & Rhee found some evidence of an increase in parental cannabis use associated with cannabis legalization, based on five studies (81). This may be at least partly due to increases in parental approval of cannabis use and decreases in perceived harms of adult cannabis use among parents (83, 84). Despite the increased use of cannabis by parents and decreased perceptions of harm of adult cannabis use, findings suggested that parents generally remained concerned about and disapproving of adolescent use of cannabis, regardless of legalization (81). Based on two studies reviewed, Wilson & Rhee (2022) concluded that there was insufficient evidence to determine whether cannabis legalization has had any impact on child abuse or neglect (81).

4.3. Interim summary

Taken together, the evidence suggest that cannabis legalization has led to increases in cannabis use before, during, and after pregnancy and during parenthood, which is likely related to general increases in adult cannabis use associated with legalization and increased approval of adult cannabis use among parents. However, so far, the evidence suggests a mixed relationship between cannabis legalization and adverse pregnancy outcomes, and no evidence that legalization has led to an increase in child abuse or neglect. Further longitudinal work is needed to disentangle the relationships between cannabis legalization, increased use of cannabis among pregnant people and parents, and potential adverse postnatal outcomes. At the same time, counseling of pregnant people and parents who use cannabis should shift to a harm reduction approach to avoid reinforcing barriers to disclosing personal cannabis use and encourage evidence-based discussions of potential harms and benefits of cannabis use during pregnancy and parenthood (75).

5. Sex/gender differences in the impact of cannabis legalization on cannabis-related harms

5.1. Cannabis use disorder

Men are more likely than women to meet criteria for CUD and typically have greater severity of CUD symptoms (85–88). For example, in the 2020 NSDUH, 6.03% of male respondents were estimated to have a CUD, compared to 4.08% of female respondents (5). Yet, women may escalate their use of cannabis faster than men (e.g., fewer years between age of first use and age of first CUD symptom) (85, 87, 89, 90), an observation that has been termed the "telescoping phenomenon." It should be noted that telescoping research has been criticized for the significant male bias in foundational research (which was overwhelmingly based on data from cisgender men) and interpretation of results (which employed a framework that implicitly positioned men's substance use as normative and women's substance use as deviant or more pathological) (91). Nevertheless, a significant body of literature has documented sex/gender differences in CUD presentation, such as more frequent or severe mood symptoms (including suicidality and general psychological distress) in women with CUD (92–95) and greater "hazardous" or higher-risk cannabis use (e.g., larger quantities or longer episodes of use, use prior to engaging in activities like driving) in men with CUD (85, 96, 97).

In addition to the previously discussed gendered factors that influence attitudes toward and prevalence of cannabis use, there are likely significant biological factors that influence CUD prevalence and severity. For example, a significant body of literature in animal models has found that female rodents are more sensitive to the reinforcing and rewarding effects of cannabinoids like THC than male rodents (13). Sex differences work from our group at the Centre for Addiction and Mental Health (CAMH) has found that, compared to male participants, female participants tend to smoke less cannabis under placebo-controlled laboratory conditions and have lower concentrations of THC in blood, yet experience similar subjective cannabis high, suggesting that women may need lower doses of cannabis to experience the same high as men (98, 99). Other human laboratory studies have found that, at the same dose of THC, female participants may experience greater subjective effects of cannabis than male participants, including some positive subjective effects associated with addiction liability (100, 101). Interestingly, some studies in rodent models have found that females develop tolerance to certain effects of THC faster than males (102, 103). Taken together, the available animal and human evidence suggests that female sex may be associated with reinforcing and/or rewarding effects of cannabis at lower doses than male sex, which in combination with faster tolerance, could lead to faster escalation of use in addiction-vulnerable individuals assigned female at birth. While these findings are intriguing and may, in part, explain why women tend to escalate use of cannabis faster than men, it is important to recognize that sex-related biological influences on responses to cannabis are still not fully understood and that sociocultural factors still play a significant role in determining trajectories of cannabis use.

Limited evidence of cannabis legalization effects on CUD prevalence or severity exists, let alone evidence that considers sex/gender. For example, a recent systematic review including articles up to March 2022 (with a focus on youth and young adults) identified only one relevant study that examined the impact of cannabis legalization on CUD (104). An analysis of US data from the National Survey on Drug Use and Health (2008 to 2016) found an increase in past-year CUD associated with legalization in adolescents aged 12–17 years and adults aged 26+ years, but not young adults aged 18–25 years (105). Data in Canada found a statistically significant increase in prevalence of CUD in young adults aged 18 to 24 years (106). Neither study considered sex/gender differences.

5.2. Cannabis-related motor vehicle collisions and other injury

Driving under the influence of cannabis (DUIC) is a behavior that is more common in men than women (107–111). For example, among respondents who reported past-year cannabis use in the 2021 CCS, 26.2% of male respondents reported driving within 2 hours of smoking or vaping cannabis, compared to 13.8% of female respondents (45). This is likely due to a number of factors, including the increased prevalence of cannabis use among men (as previously described), reduced perception of risk of DUIC among men (112, 113), or other characteristics that tend to more common among men than women, such as increased risk-taking (114, 115).

The results are very limited with regard to sex/gender differences in changes in DUIC and collision risk associated with cannabis legalization. One study in the Canadian province of British Columbia used data from drivers treated after motor vehicle collisions at four trauma centers (spanning January 2013 through March 2020) and included sex in their analysis. The authors found that the increased prevalence of moderately injured drivers with a level of THC in blood of at least 2 ng/ml associated with legalization was greatest among male participants (adjusted prevalence ratio = 2.44) (116). An analysis of gender differences in data from the National Cannabis Survey in Canada found that men were more likely than women to report driving within 2 h of using cannabis in the past 3 months both before and after legalization, though the gender difference did not change appreciably from pre- to post-legalization (117). In contrast, a recent systematic review (64 observational studies included) found that legalization of medical cannabis was associated with greater decline in motor vehicle fatalities among male participant than female participants, though they did not identify any studies that examined sex differences in the impact of non-medical cannabis legalization on DUIC or collision risk (118). The lack of consideration of sex in studies of cannabis legalization and DUIC is a significant limitation of this literature.

One study was identified that evaluated the impact of state cannabis laws on self-harm and assault, using US data on commercial and Medicare Advantage health plan beneficiaries from January 1, 2003, to December 31, 2017, and considered sex (119). While no overall effects of cannabis legalization on rates of self-harm or assault were found, there was a significant effect of legalization on self-harm in male participants under 40 years old (119).

Taken together, the limited available evidence suggests that legalization of non-medical cannabis may drive further increases in prevalence of DUIC and collision risk among men. A recent study in the US found that perceived safety of DUIC, but not perceived legality, was significantly associated with DUIC, and that perceived safety mediated the relationship between cannabis legalization and DUIC (120). This speaks to the need for cannabis and driving educational campaigns targeted specifically to young men, who are by the far the most likely demographic to engage in DUIC and be involved in motor vehicle collisions.

5.3. Cannabis-attributable hospitalizations

Acute, transient effects of cannabis such as cognitive impairment, psychotomimetic (i.e., psychosis-like) effects, and psychological distress can lead to emergency department (ED) visits, especially in situations of accidental exposure to cannabis or unexpected highs from high-dose cannabis products (3, 8). Data in the US (especially from Colorado and Washington states, which have the longest history of legal access to non-medical cannabis) have identified associations between cannabis legalization and ED visits related to CUD, motor vehicle accidents and other accidental injury associated with cannabis use, head injuries, cyclic vomiting (likely representing an increased incidence of cannabis hyperemesis syndrome), childhood poisonings and accidental pediatric exposures, psychological distress in adults, and burns related to unsafe handling of butane during attempts to isolate THC from cannabis oil (10). Pre-legalization research has general found that more men than women present with cannabis-related ED visits and hospitalizations (94, 121).

Studies assessing the impact of cannabis legalization on cannabis-related ED visits, hospitalizations, and reports to poison control centers have had mixed findings with regard to sex/gender differences. For example, a study using ICD-10 codes from academic medical centers in Boston, Massachusetts (data from January 2012 to December 2019) found evidence of a gender difference; i.e., that legalization was associated with an increase in the ratio of women to men testing positive for cannabinoids upon ED presentation (122). Another study in the province of Ontario that considered gender found that cannabis legalization was associated with significant increases in cannabis-related ED visits, especially among women (123). Some further interesting trends emerged in this study. For example, the initial legalization of cannabis use in October 2018 was associated with an increase in cannabis-related ED visits especially among women aged 45–64 years, whereas the legalization of cannabis edibles in 2020 was most strongly associated with increased cannabis-related ED visits among women aged 18–44 years (123). The authors proposed that the initial legalization effect was due to older adults (especially women) trying cannabis for the first time, whereas the effect of cannabis edible legalization may be related to the increased preference for edible products among younger adults (123). A repeated cross-sectional study in Ontario, Canada, found that legalization of cannabis edibles and commercialization of new cannabis products in February 2020 was associated with a significant increase in ED presentations of cannabis hyperemesis syndrome, which seemed to be a sex-related effect driven by a statistically significant increase in female participants but not male participants (124). In contrast to the previous studies, data from Colorado found that cyclic vomiting presentations to the ED increased in parallel to increases in cannabis use associated with non-medical legalization, and that men who presented to the ED with cyclic vomiting had significantly greater odds (OR = 2.4) of cannabis-related codes than women (note that this study used sex and gender interchangeably) (125). An analysis of sex differences in data from the Canadian province of Quebec found a significant increase in the percentage of substance-related hospitalizations involving cannabis from pre- to post-legalization in male participants aged 10 to 14 years, but not female participants of any age or older male participants (126). Similarly, an analysis of data from the US National Poison Data System that considered sex found that the commercialization of non-medical cannabis was associated with increases in cannabis exposures reported, and the increase was greater among male participants than female participants (127).

Taken together, there appears to be mixed evidence for sex/gender differences in cannabis legalization impacts on cannabis-attributable hospitalizations. A very tentative conclusion is that legalization may have increased cannabis-attributable hospitalizations to a greater extent in women, especially older women, which would be in line with prevalence data showing greater increases in cannabis use among women in the past several years. However, a few studies have found that legalization led to even greater increases among men and boys. Given the Ontario findings of gender by age interactions in the impact of legalization (123), it will be imperative for future studies to monitor trends using an intersectional approach.

6. Conclusion

Legalization of non-medical cannabis use has clearly led to changes in the global cannabis landscape, including changes in attitudes toward use, prevalence and patterns of use, the demographics of individuals using cannabis, and in cannabis-attributable harms. There are broad and robust sex/gender differences in the use, effects, and harms of cannabis, and there are likely sex/gender differences in the impacts of cannabis legalization. Women tend to have more negative attitudes toward cannabis use and legalization than men, and this is likely due to a complex interplay of gender roles and norms. While overall attitudes toward cannabis use have become more positive over time and support for cannabis legalization has increased, the sex/gender gap in legalization support may not have changed to a significant extent, suggesting that the underlying gender constructs that influence legalization support have not changed meaningfully. However, there have been significant changes in the sex/gender gap in cannabis use prevalence over time: while men have historically been much more likely than women to use cannabis, this gap has narrowed. The narrowing of the sex/gender gap in cannabis use prevalence is presumably due to changing gender norms and roles, though there is significant evidence that cannabis legalization has played a role in narrowing the gap. There seems to be a significant effect of cannabis legalization on increased use of cannabis before, during, and after pregnancy, and during parenthood, though this (so far) does not seem to be associated with a corresponding increase in adverse pregnancy or early childhood outcomes. Legalization may have further increased the likelihood of cannabis-related motor vehicle collisions, and there seem to be complex sex/gender influences on the impact of legalization on cannabis-attributable hospitalizations.

One important take-away of this review is the need for more robust data on sex/gender differences in cannabis legalizations impacts. Despite a broad body of literature evaluating impacts of legalization, few studies have considered sex or gender. Further, the existing research has focused almost exclusively on cisgender adults, and more work is needed to understand how legalization may have impacted transgender and gender-diverse youth and adults. More consideration of sex and gender in cannabis legalization research will be imperative to fully understand the scope of legalizations impacts worldwide.

Author contributions

JM conceptualized the manuscript and wrote the first draft. BLF provided guidance and contributed to reviewing and editing the manuscript. All authors contributed to the article and approved the submitted version.

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Publisher's note

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Mental health adverse events with cannabis use diagnosed in the Emergency Department: what are we finding now and are our findings accurate?

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We have previously reviewed the types and numbers of cannabis-associated adverse events that have mental health presentations that are encountered in the Emergency Department. A particular challenge in examining these events is disentangling cannabis use adverse events from adverse events associated with use of multiple recreational substances. Since that review was published, cannabis legalization for recreational use has greatly expanded world-wide and with these changes in the legal climate has come clearer information around the frequency of adverse events seen in the Emergency Department. However, as we examined the current state of the literature, we also examined some of research designs and the biases that may be impacting the validity of the data in this field. The biases both of clinicians and researchers as well as research approaches to studying these events may be impacting our ability to assess the interaction between cannabis and mental health. For example, many of the studies performed examining cannabis-related admissions to the Emergency Department were administrative studies that relied on front line clinicians to identify and attribute that cannabis use was associated with any particular admission. This narrative review provides an overview on what we currently know about mental health adverse events in the Emergency Department with a focus on the mental health impacts both for those with and without a history of mental illness. The evidence that cannabis use can adversely impact genders and sexes differently is also discussed. This review outlines what the most common adverse events related to mental health with cannabis use are; as well as noting the most concerning but much rarer events that have been reported. Additionally, this review suggests a framework for critical evaluation of this field of study going forward.

KEYWORDS

mental health, adverse event, cannabis (marijuana), Emergency Department use, cannabis legalization

1. Introduction

Cannabis was legalized for recreational use in Canada on 17 October 2018. The reactions to this legislative action appear to be primarily split between two quite divergent viewpoints: positive from the groups who campaigned for cannabis legalization and disappointment from groups involved in treating individuals who experience the negative outcomes of cannabis use. Use of cannabis has quietly increased since legalization in Canada but the enormous business potential expected by the proponents of legalization have also failed to materialize (1). Cannabis use overall in Canada has increased each year since legalization from an estimated 15% of all adults over age 15 in 2017 (pre-legalization) to 25.2% of all adults over 15 in 2021 (2, 3). This increase is similar to what has been seen in other countries that have legalized (as opposed to decriminalized) cannabis use (4). The onset of the COVID-19 pandemic and opioid crisis have stalled what efforts were being made to attempt to inform the general public of the potential harms that cannabis use can pose for some individuals. While it is generally agreed that cannabis adverse events are not common, with increasing tetrahydrocannabinol (THC) concentration coupled with increased frequency of use, this may become a more common issue. For example, the rate of cannabis use disorder, the DSM-5 diagnosis for cannabis dependence or abuse, has increased from an estimated 10% of cannabis users to 22% (5, 6). The need to communicate the risks of cannabis use is ever increasing as there are now 38 states in the United States that have legalized medical cannabis use with 19 legalizing recreational use (4). South Africa, the Seychelles and Ghana have decriminalized cannabis for personal use (7). Other countries such as Canada and Uruguay have fully legalized cannabis use for both recreational and medical use (4). One comprehensive study examined the use of cannabis pre-post legalization in 587 4 year colleges in the United States (US) from 2008 to 2018 comparing cannabis use in college students in states with legalized recreational cannabis to those in states with restricted cannabis approaches and found that past 30 day use increased more in colleges where recreational cannabis was legal (OR = 1.23; 95% CI 1.19–1.28) (8). Here we aggregate the common and uncommon psychiatric adverse events that can be experienced with cannabis use with the hope that this will serve as a resource for Emergency Department (ED) personnel in discussing cannabis use in relation to ED visits for those who have experienced an adverse event related to mental health.

Since publishing our previous paper (9), further studies have examined adverse events related to cannabis use that can be experienced and result in an Emergency Department visit primarily based on administrative data. Papers examining cannabinoid hyperemesis syndrome (CHS) are probably the most common and the most frequently picked up by the media as this is clearly a dramatic adverse event and the related paradoxical effect of increased nausea that can be associated with use of cannabis during pregnancy. An article on the topic in relation to ED impacts was conducted by Andrews and colleagues but like all the cannabis related side effects, this side effect only affects a small proportion of users. However, from pre-post legalization in Canada, the number of ED visits per 100,000 increased from 15 to 21 to 32 in 2020 (10). This still represents a small number of cannabis users. If we frame this as a response to a pharmaceutical that is under consideration for government licensing; this frequency would mean it was considered a rare side effect. If we extend this analysis to examine cannabis adverse events in the same manner as a standard government approved pharmaceutical then the more serious adverse events would be the risk of stroke and some of the lung associated injuries such as hemoptysis which are all more clearly associated with heavy use (11–14). These are what we could consider medical side effects of cannabis use with clear quantitative measures of imaging to show the damage from the event with still more research needing to be done regarding dose relationships and temporal association; but this is outside the scope of this review. What is even more complex to examine and disentangle are the mental health adverse events which we try to address here. Additionally, we examine some of the factors that we believe are potentially complicating analysis of data in this area.

2. Methodological approach to this review

This is a narrative review around Emergency Department presentations related to mental health and cannabis use, and it is not a systematic review. We do aim for a balanced approach to show the uncertainties in the literature and indicate areas where we encourage researchers to focus further efforts. The approach we have taken is briefly outlined here. Searches of Pubmed/Medline, Web of Science, and Google scholar were conducted from June 2022 to August 2022 with a focus on papers after October 2020 as this was the end date for our last review on the topic though some prior papers are included to give further context (9). The search terms employed included cannabis or marijuana and Emergency Department and adverse events or mental health or prevalence. Another series of searches was conducted to examine emergency transport, ambulance, and emergency mobile units in conjunction with the term cannabis. We employed the medical subject heading terms for each of the previous terms. This review is focused on effects of cannabis use that result in a need for urgent care and, in particular legal recreational cannabis use on mental health ED presentations. Hence, presentations due to synthetic cannabinoids are not included in this article. Papers located by searching the databases were hand searched for other studies examining mental health impacts associated with confirmed cannabis use in the Emergency Department and emergency transport setting. Published studies from case series to systematic reviews were included in this manuscript. Abstracts were not included.

3. Literature update

The research in this field has become more and more defined into two categories. The first is one that examines outcomes is mental health presentations to the ED in individuals who prior to the presentation had no history of a diagnosed mental health disorder. These presentations are often referred to as acute mental health presentations to the ED, although many studies examining acute effects do not record the previous mental health status of the individuals who presented. The other category examines individuals with a previously diagnosed mental health disorder who used cannabis, either acutely or more commonly chronically, and presented to the ED requiring assistance.

3.1. Potential impacts of cannabis related ED visits on ED resources

Cannabis related ED visits are not as numerous as visits related to alcohol misuse. However, there is a concern that cannabis related visits may pose a larger resource burden to the health care system. This is a significant concern in today's healthcare resourcing. One study from Oregon showed only 1.8% of visits to the ED were cannabis-related but for one ED site alone this represented $5.6 million in hospital charges. Cannabis adverse events may represent an all or nothing approach to healthcare needs, if the adverse event reached the level of requiring an ED visit, it was a "significant burden" on hospital resources (15). Another example of how intensive care can be for cannabis intoxicated patients relates to a trauma patient study performed in Los Angeles, California which was not focused on mental health impacts of cannabis, but showed that cannabis use was associated with increased use of mechanical ventilation in trauma patients who had used cannabis (16). This study again represents patient presentations that would pose a significant burden on the healthcare system. A case–control cohort study examining individuals in Ontario, Canada from 2014 to 2017 found that cannabis users had a significantly higher odd of an all-cause ED visit (OR 1.22, 95% CI 1.13 to 1.31) but odds of mortality were not affected (17).

As previously mentioned, since our last examination of this topic there have been considerably more administrative studies conducted on ED visits and cannabis use (9). Earlier administrative reports such as the period of 2012–2016 reported statistically significant increases in the number of ED visits for each year examined; of cannabis related ED visits, with 24.8% were for psychiatric reasons (18). These frequencies seem to be increasing in jurisdictions with cannabis with higher THC content (19, 20). Interestingly, as noted in media interviews product below 24% THC is not of current market interest (1). Increased cannabis use world-wide where cannabis has been legalized may also be contributing to this trend of increasing visits (4). One study actually examined not only the impact of legalization on ED visits related to cannabis use, but also the period of commercialization that occurred about 6 months after legalization in Canada when provincial governments enacted their frameworks for commercial sale of cannabis by a larger retail community. This study by Myran et al. showed that pre-legalization ED visits were increasing but immediate post-legalization the rate leveled off, only to increase again once more commercial outlets were in the marketplace (21). This analysis framework would warn against examining the immediate 6 months pre-and 6 months post-legalization for examining impacts of legalization on ED visits. Another innovative approach to measuring the impact of cannabis legalization on ED service is a study examining the impact of the lottery system for dispensary licenses in Arizona. This study found that Emergency Department visits acutely related to cannabis use rose 45% in the zip codes where a dispensary license was awarded though the visits were not broken out into medical vs. physical health (22).

3.2. Studies considering "Cannabis only" ED presentations

Cannabis is often one of several recreational/illicit substances that may be found in an individual patient's system upon presentation to the Emergency Department. Some studies have attempted to tease apart "cannabis only" clinical presentations. One such study examined cannabis only presentations at an Emergency Department in Switzerland. The study noted that cannabis only presentations overall could be classed as mild but that the group of 186 patients only positive for cannabis had more palpitations (25.3%), anxiety (22.6%), panic attacks (7.5%), and chest pain (14.5%) which was interesting to our group as in our experience the categories of palpitations can overlap with anxiety and panic attacks (23). The classification of psychosis was found in 6.5% of the sample (23). Similarly another retrospective chart review from Michigan covering the time period of November 2018 to October 2020, 39.8% of the individuals presented with an adverse event related to cannabis use that was neuropsychiatric (24). Within this sample of 452 individuals, severe anxiety was the most common presentation at 36.1% followed by altered mental status at 22.3%, suicidal ideation at 14.4%, and hallucinations at 12.8% and psychosis was the presenting complaint in 4.2% of the presentations. This study also showed a longer length of ED stay for neuropsychiatric presentations and not surprisingly, greater odds of a psychiatric admission (24). A similar research design of ICD administrative data but with chart review included, showed visits related to cannabis use increasing year over year in Colorado for psychiatric related chief complaints from 2012 to 2016 with psychiatric codes for both chronic and acute type presentations comprising 63.0% of the visits (18). 75% of the mental health related visits were acute with anxiety being 13.4% of the presentations ($n = 85$) and concerningly, suicide attempt as the next most common at 11.9% ($n = 75$) (18). The discrepancies between these two studies with and without chart review may reflect issues in methodology of one study only using ICD code data where without the "chart check," the cannabis association is missed.

There is a body of literature not only examining cannabis related ED visits but specifically examining what impact cannabis legalization had on mental health visits to the Emergency Department. The results from these studies vary widely and this may be due to differences in methodological approaches. One administrative database study from an Alberta, Canada ED found a decrease in psychotic diagnoses in the ED over time comparing pre-legalization (2013) to post-legalization (2019). However, there was a significant increase in individuals leaving the ED against medical advice/prior to treatment which could call this result into question (25). An electronic surveillance reporting system used for 19 selected Emergency Departments across Canada showed an annual percent change of 30.1% for all cause cannabis related ED visits for both children and adults between 2015 and 2018 (26). 31.3% were cannabis only presentations (26). A study from a single ED in Ontario, Canada did not show an increase in their cannabis related ED visits comparing the 6 months before and the 6 months after legalization though the age of presentation did vary with individuals between 18 and 29 years showing a 56% increase in cannabis related ED visits over the study periods. The sample size for this study was quite small with 79 cases in the pre-legalization cohort and 94 cases in the post-legalization cohort (27). Pertinent to this discussion, the chief complaint overall for both cohorts was substance abuse (29%), with bizarre behavior next at 16%, hallucinations/delusions were at 6% but unusually, anxiety was the lowest of the mental health codes at 4% of the sample (27). Electronic records from Alberta and Ontario, Canada from 1 April 2015 to 31 December 2019 were used to examine occurrence of psychotic illness associated with cannabis use pre and post-recreational cannabis legalization and found that ED encounters

doubled for cannabis-induced psychosis during the time period examined. Using the National Ambulatory Care Reporting System (NACRS), this group found no impact of legalization on occurrence of ED related visits for psychosis in this study with a larger number of encounters examined than some other studies cited here (greater than 200,000 visits) (28). However, this study had a couple of differences from some other administrative studies, only the ICD-10 code for F12.5 cannabis induced psychosis and the ICD-10 related codes for schizophrenia and related disorders were used without inclusion of the hallucinations or delusions codes. This study would likely have a mix of acute psychosis and previously diagnosed with a psychotic disorder and as noted by the authors, studies are lacking to assess the validity of the approach (28). Altogether these studies show that there are measurable numbers of cannabis-associated mental health encounters in the ED but whether legalization was a factor in the increasing rate over time seems unclear.

3.2.1. ED visits related to cannabis use and sex or gender

The increase in cannabis use from 2017 to 2021 in Canada is largely attributable to a significant increase in use by women (2). The UN drug report 2022 also demonstrates that the gender gap in cannabis use is closing world-wide (4). This closing gender gap is also reflected in the results of studies examining the EURO-DEN database of drug involved ED encounters from 36 centers in 24 European countries and in individuals 20 years of age or less, there was no difference in representation of cannabis-related encounters between males and females (29). This cohort has 9.8% of the drug related presentations being cannabis related with only co-ingestion of alcohol allowed for inclusion. An interesting observation from the EURO-DEN cohort, which for all ages is 70% male, was that anxiety was the top clinical feature associated with cannabis intoxication presenting to the ED at 28% of the presentations. However, when broken out by sex, 32.3% of females presented in this manner as compared to 25.4% of males (30). Agitation was classified separately and comprised 23% of the ED presentations with acute psychosis at 9% of the cohort of 4,268 presentations. Patients older than 49 years were less likely to present with anxiety (30). For comparison, the nationwide Emergency Department sample (NEDS) database in the US was examined for cases of cannabis poisoning and for the year 2016, 0.014% of the total ED admissions were cannabis related but these admissions were more likely to meet criteria for various mental illnesses including psychosis, anxiety and mood disorders with females having an association between cannabis toxicity and anxiety (AOR of 2.30) or mood disorder (AOR 2.30) that was significantly higher than the associations seen for males with the same conditions (31). Reasons for difference in the cannabis related presentations between males and females are under study by various approaches with one group examining partnered ED patients showing adverse childhood events being associated with a greater odds of problematic substance use in females (32).

3.2.2. Cannabis presentations and route of administration

There is also evidence that route of exposure may impact what the character of the presentation to the ED will be. The evidence base for this point is not extensive, but it is instructive to consider the issues around the different routes of cannabis administration. One older case series showed hospitalization for cannabis-induced psychosis due to edibles was the outcome in a population of daily cannabis smokers. These individuals reported consuming more than 100 mg of THC prior to the admission and no other substance use reported with only two of the 5 patients having had a previous episode of cannabis induced psychosis (33). This paper highlights that even experienced cannabis users may need further information on the possible dangers of edible cannabis products. In a retrospective chart review done on ED visits in Colorado between 2012 and 2016, among visits attributable to cannabis, encounters associated with inhaled cannabis were more likely to be cannabinoid hyperemesis syndrome (18%) as the top presentation as opposed to oral ingestion which had acute psychiatric symptoms (18%) or intoxication (48%) with edibles accounting for a greater number of ED visits than their sales numbers would suggest (34). A recent retrospective cohort study from seven EDs in Western Michigan, where cannabis was legalized in December 2018, covering the period of November 2018 to July 2020, found 17.1% of ED admissions were related to edibles and that admissions related to edibles increased over the study period post-legalization (35). The consideration of a divergence for medical vs. psychiatric symptomology based on route of ingestion is an area for further study.

The reason for this discrepancy between inhaled and ingested cannabis effects may be two-fold. The first may relate to pharmacokinetics, and a point that many readers will be familiar with, that inhaled cannabis is absorbed with a peak plasma concentration within minutes and has intoxication effects within 15 to 30 min as compared to oral consumption that affects the user's system within 1–2 h (36). The second point may be a pharmacodynamic one. The inhalation of cannabis bypasses first pass metabolism by the liver whereas oral administration does not. This results in different metabolite levels with different affinities for the cannabinoid receptors as the predominant metabolites in the user's body. 11-hydroxy-THC, which is also psychoactive, is the predominant metabolite but is seen at higher concentrations after oral ingestion and it has a higher affinity for the CB1 receptor than Delta-9 THC (37, 38). Another point made by Lewis et al., is that cannabis edibles are generally made from cannabis extracts, further increasing the likelihood that the dosing information is not correct on the package, or that the THC content is not homogeneous in the product (35).

3.2.3. ED visits related to cannabis use in individuals with medical authorization or undergoing substance treatment

While the focus is on recreational cannabis, there are also studies examining ED presentations in those with medical cannabis usage. An interesting side note to this topic are two recent surveys of emergency physicians that showed 68.3% of respondents believed that cannabis is medically beneficial (39) and 70.7% agreed that cannabis has medical value (40). ED physicians in the surveys also showed an awareness of the evidence for medical cannabis use for pain and post-chemotherapy vomiting (40). A cohort study from Alberta, Canada examined the short term outcomes for 29,153 individuals with medical authorization to use cannabis and found that within a median time frame of 240 days, 14 patients visited the ED or had cannabis poisoning that resulted in hospitalization and a further 26 individuals visited the ED or were hospitalized for mental health concerns (41). Clearly, this is not a significant rate of adverse events but the study did develop seven predictors of a mental health ED visit for medical

cannabis users which included prior poisoning by psychoactive drugs, mental and behavioral disorders due to psychoactive drugs or alcohol, other previous mental health disorders and younger age (41). This suggests factors that could be used to determine who is suitable for a medical cannabis authorization and prior mental health concerns would be a contraindication to medical use.

3.2.4. Cannabis related presentations in those with a diagnosed substance use disorder

The assessment of ED use by individuals with cannabis use can also be examined from the approach of looking at how many ED visits individuals who are in treatment for a cannabis use or related disorder had. One study looked at healthcare utilization overall by individuals in a substance use disorder treatment program and looked at ED utilization by SUD category in Belgium. Individuals with a cannabis use disorder (CUD) had a rate ratio of 2.8 when comparing cases and controls for use of the ED (42). Another study looked at cannabis use disorders which can be associated with chronic cannabis use such as mental illness, addiction, anxiety, or suicidal behaviors as well as chronic physical illnesses such as lung and cardiovascular conditions. This is broader than examining individuals undergoing cessation therapy but as expected multimorbidity associated with cannabis use predicted more ED use (43). However, when compared relatively in another study, ED service use for individuals seeking treatment for a cannabis use disorder was less than that of alcohol use disorder patients and polysubstance users (44).

3.2.5. Cannabis use and suicidality

The role of cannabis-associated adverse events in suicides is still unclear; however, this issue is now more often being addressed in research studies. One example from a retrospective chart review from Michigan from November 2018 to October 2020 found that of the 452 individuals presenting with an adverse event related to cannabis use that was neuropsychiatric in nature, suicidal ideation was seen in 14.4%, and hallucinations at 12.8% (24). In another study, 299 acute psychiatric presentations to the ED from 2012 to 2016 in Colorado were examined, as previously mentioned, and suicide attempts were 75 of the presentations (11.9% of the overall ED presentations related to cannabis) (18). This compiled data, while lacking currently in depth, is concerning not only for the immediate outcome of harm or mortality but also for the work in the field of psychotic disorders that has shown substance-induced psychosis (including cannabis) with self-harm as a feature of the presentation is a predictor for future conversion to psychotic or bipolar disorder (45).

3.3. Cannabis use and homicidal or violent presentations to the ED

The most overlooked by the public and quite concerning mental health presentation with cannabis use is individuals who have a severe aggressive adverse reaction to their cannabis intoxication. One study from Switzerland examined cases of violent ED presentations and found 103 cases of violence in 164,846 ED encounters so this can be considered a very rare presentation. However, half of these cases involved cannabis use and overall cannabis was associated with more of the violent cases than was cocaine (46). Also of note, 14 of the cases were associated with domestic violence and 39% of those were cannabis related (46). However, co-use of alcohol was not an exclusion criteria for this study. Another study from Victoria, Australia examined 548 violent events in a regional ED and found that 2% of them were related to cannabis use. The authors of this paper also note that violence was more likely to be associated with cannabis withdrawal than intoxication (47). Homicidal ideation was reported in 3.1% of another study from Michigan (24). Another study from Spain looked at the role of age in cannabis related presentations to the ED and found that agitation, aggression and psychosis were more common in patients over 40 years of age (48). Another study looking at point of care saliva testing for illicit substance use among individuals who required a security response for an unarmed threat in the ED found that 8% of their prospective sample was positive for cannabis and among the entire sample, only 22% reported past 24 h illicit drug use but point of care testing for illicit substances found positive tests were 40.2% of the sample (49). This study illustrates another confound in this body of research of the reliance in many cases of the patient self-reporting their cannabis use.

3.4. Mental health issues with intoxication in children

Mental health symptoms, and the potential for permanent changes in brain structure in developing brains with repeated exposures to cannabis, have been well-described in adolescents. However, Emergency Department presentations for cannabis intoxication or poisoning in children tend to include more physical symptoms such as ataxia, lethargy, and tachycardia, and not symptoms related to mental health. We do have evidence that these adverse events are increasing in frequency with one study reporting cannabis-related visits rose from 3.8 per 100,000 in a cohort with an upper age limit of 24 in 2003 to 17.9 per 100,000 in 2017 (50). While the upper age limit of 24 is a classification more of emerging adult than youth or children, it may be instructive to note that the setting for this study was in Canada where medical cannabis, but not recreational cannabis, was legal at the time. However, as has been reported, going through a medical approval phase affects population attitudes toward perception of risk for cannabis use (51). Poisonings in children can be severe though are rarely fatal. The concern is that the long-term impact on the developing brain of having a cannabis poisoning at a young age is not currently known. While it is known that repeated cannabis exposure in youth under 18 years of age is a risk factor for the development of psychosis and may have lasting impact on cognition, it is not clear what the impact of a single large dose of THC might be (52–54). Studies to date have been focused on the immediate outcomes of childhood poisoning with most studies reporting an average age of 3 years for accidental ingestion (21). This is an area for future research.

There are more studies on the impact of cannabis on mental health in the adolescent population since our last review. One recent study using sentinel surveillance of self-harm using the electronic Canadian Hospitals Injury Reporting and Prevention Program from 2011 to 2019 showed an increase of 15.9% per year in self harm with intentional substance-related injuries exceeding unintentional injury cases and 92.3% of the cannabis-related self-harm being in the 10–19 years of age group (55).

3.5. Limitations of ICD based studies

Many of these studies were conducted on administrative databases and based on the exclusive use of ICD codes to retrospectively identify cannabis attributable cases. Several groups, ours included, have begun to wonder if this approach is sufficient to accurately identify and track these encounters. ED clinicians may not explicitly use the drug related code, instead opting to use a more symptom related code either as a preference or in the busy atmosphere of an ED use the first code that "fits" the presentation in front of them. One study from Oregon used ICD codes and the electronic medical record with an embedded question asking the clinician to consider if this presentation was cannabis related. This gave 1.6% of classified visits that were cannabis attributable for adults and 0.66% of pediatric visits with cannabis relation but the authors noted that among the charts classified by the question as being cannabis related, only 22% for adults and 17% for pediatric cases had a cannabis related ICD code in the record (15). This suggests there was a disconnect between the entry of a cannabis related ICD code and the association of the presentation with cannabis use. Our work which is in the preliminary analysis stage examining 52, 427 presentations to our three local EDs using ICD-9 codes for the period between October 2018 and June 2020 show 1.7% of presentations being related to cannabis by ICD code but when the charts were hand searched 4.8% were found to be related to cannabis use by the ED encounter chart notes (Crocker, pers. comm). While there are few studies to examine this point, it does raise the question of are we approaching the impacts of cannabis on the ED in the most comprehensive way?

3.6. How accurate is our approach to examining ED visits related to cannabis use

How we gauge the impact of recreational and medical cannabis use presenting in the ED may benefit from a bit of re-thinking. High workload demands, a need to address the most immediate health concern and implicit bias may all be playing a role in the quality of the data that is used for much of the research in this field. A recent study in the ED for example examined rates of mistriage and found that roughly 30% of encounters were mistriaged across over 5 million encounters in the United States with groups such as Black Americans more likely to be mistriaged suggesting bias may play a role in the mistriage rates (56). There is a body of literature examining bias in healthcare delivery, with healthcare bias usually being reflected in poorer quality mental healthcare. Individuals with mental illness and addictions experience lower quality of care overall, with these diagnoses identified as a key factor in these negative outcomes (57). There are also studies showing health professionals have an implicit stigma against individuals with mental illness that can lead to poor outcomes for these patients (57–59). However, there is more than one type of stigma and some work has shown that implicit bias predicted over-diagnosis in individuals with mental health training and explicit bias predicted more negative outcomes for patients compared to providers with less mental health experience (60). Bias has been studied in ED personnel primarily with a socioeconomic lens (61). The ED is an environment that is high stress and highly physically demanding at times. While studies that focus on quality of care have examined possible errors to clinical practice with exhaustion in the ED environment, there is also a component of emotional exhaustion which can affect executive function and potentially allow a greater influence of personal bias as a result (62). There may also be, as noted by another group, biases in assigning cannabis use codes to certain racial and ethnic groups which might be related to the frequency of cannabis attributable visits (15). All of this discussion leaves aside the complication that not every patient will report cannabis use in the Emergency possibly due to stigma and given the long half-life of THC in the body, toxicological tests are not always informative. Combined, these factors suggest an examination of the impact of potential bias on ED encounters is required, particularly as it relates to cannabis associated physical and mental health ED presentations.

Further evidence that we may not be accurately tracking use of cannabis in the Emergency Department can be made by inference from the fatality information seen in motor vehicle collisions. The percentage of fatally injured drivers in the United States that had cannabis in their system in 2000 was 9.0%, but by 2018 it had risen to 21.8% in comparison to alcohol involvement which had remained stable (63). Additionally, when trauma patients were assessed, one study found 43% of these patients in 2016 had at least cannabis in their system and that injuries associated with the presence of cannabis were more likely to require mechanical ventilation (16). Another study done in Georgia showed that the odds of dying with cannabis were greater than those of cocaine if presentation to the ED was required (64). This information logically implies that cannabis use is more widely associated with trauma and fatalities and ED presentations than our current ICD code-based studies would suggest.

ED clinicians logically enter the codes for the trauma or symptoms to be urgently dealt with and entering a note on the role of cannabis may not be a priority in that moment. Additionally, the ED is commonly a very busy hospital unit and if triage codes are subject to error then by extension one might consider how accurate ICD code entry may be (56) Further not every clinical case in the ED is simple. For example, the situation with mental health presentations can complicated by an initial uncertainty of whether an anxiety presentation is a reflection of an acute adverse event or a longer standing diagnosis. However, if a drug–drug interaction between cannabis and a psychiatric medication has reduced the effectiveness of that psychiatric medications and this is the underlying cause of the ED presentation, how do we code this case? Many studies being done in the realm of the ED are subject to these complications but these weaknesses and how to address them to improve the accuracy of our findings are rarely discussed. This is why we suggest the new approach that groups such as (18) and our own group are taking of both using ICD codes and searching the electronic medical record are so important (18). Interestingly, Shelton found that ICD codes related to cannabis use were not necessarily attributed to cannabis use whereas our work suggests that the ICD codes are missing the cannabis association and merely representing the symptomatic presentation. These approaches demonstrate the weakness of a strictly administrative code approach for considering the role of substance use such as cannabis in ED visits but also may suggest differences in culture between American and Canadian Emergency Departments. In either case, the wider adoption of electronic charting, and technology to allow searching within these charts, will improve access to visit notes and hopefully add depth to findings in this field.

4. Where do we go from here?

Cannabis-associated ED presentations are not numerous, but as the literature base is expanding for this topic, if the cannabis-related presentation reaches the level of requiring urgent care, it is likely to be more complex and costly than alcohol related ones (15). We continue to espouse a view that, like alcohol, cannabis is best used in moderation and it not suitable for everyone. We would encourage public health campaigns to echo this message.

There are several possible approaches being tried to address the problem of increasing cannabis associated ED visits. One approach is brief interventions for cannabis use in the ED which may work for an acute presentation by an occasional user; however, cannabis use disorder has shown to be quite intractable to treatment, and thus these interventions may not be of value for chronic users (65, 66). Another approach is to address planning capacity for mental health and addictions services in the ED setting (67). This would include embedding consultation liaison services in the ED or an adjacent psychiatric emergency service in the ED which is occurring in some locations. Further work is also needed to address the question of whether legalization of cannabis use affects the opioid crisis by reducing opioid-related emergency visits. Overall, the appearance of cannabis related ED visits appears to be continuing to rise and with increased use of edibles and higher THC content, this seems unlikely to change. The total number of these visits may not comprise a high volume of ED presentations but as noted in this review, these presentations may be complex and costly resulting in a greater burden to the healthcare system than the number of encounters might suggest.

There are also concerns noted here that we may be underestimating the extent of the problem due to a variety of possible reasons related to entering ICD codes not reflecting the involvement of cannabis use in the encounter. Future research should address this potential problem through methods such as ICD study validation by cross-checking the medical record for ED encounter notes to ensure cannabis related encounters are not being overlooked. While we work directly in a team of both emergency room clinicians and psychiatry clinicians and researcher, this is not always the case. It would benefit this research field if more researchers worked directly with ED staff to educate or explain the importance of the use of these codes to accurately reflect drug involvement if we are to base our healthcare planning on these approaches.

We hope this review provides information to ED clinicians on the likely impacts of cannabis on their practice and serves as a reference when addressing a patient's contentions that their cannabis use is harmless. There is an argument to be made that this is the case for the majority of occasional cannabis users but like any drug, cannabis will have adverse effects on some individuals who take it.

Author contributions

CC wrote the first draft and compiled the edits. PT and JE edited drafts. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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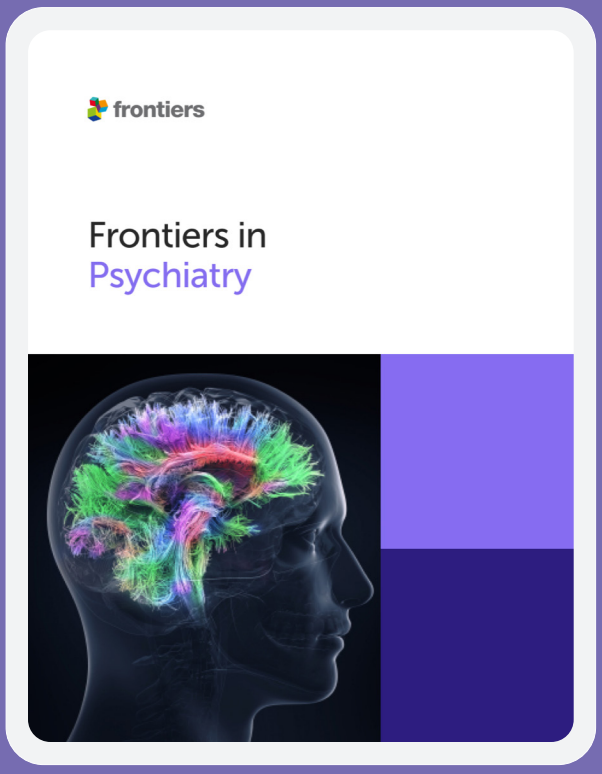

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