Exploring medical cannabis use in individuals with a traumatic brain injury

Elizabeth N. R. Schjelderup[1], Caroline A. MacCallum[2,3] , Lindsay A. Lo[4] , Jessie Dhillon[1], April Christiansen[5], Carly Pistawka[6] , Kathryn Rintoul[1], William J. Panenka[7,8] , Alasdair M. Barr[1,8]*

[1]Department of Anesthesiology, Pharmacology & Therapeutics, Faculty of Medicine, University of British Columbia (UBC), Vancouver, BC V6T 1Z3, Canada

[2]Department of Medicine, Faculty of Medicine, University of British Columbia (UBC), Vancouver, BC V5Z 1M9, Canada

[3]Faculty of Pharmaceutical Sciences, University of British Columbia (UBC), Vancouver, BC V6T 1Z3, Canada

[4]Department of Public Health Sciences, Dalla Lana School of Public Health, University of Toronto, Toronto, ON M5T 3M7, Canada

[5]Centre for Neuroscience Studies, Queen's University, Kingston, ON K7L 3N6, Canada

[6]Department of Microbiology & Immunology, Faculty of Science, University of British Columbia (UBC), Vancouver, BC V6T 1Z3, Canada

[7]Department of Psychiatry, Faculty of Medicine, University of British Columbia (UBC), Vancouver, BC V6T 2A1, Canada

[8]British Columbia Mental Health and Substance Use Services Research Institute, Vancouver, BC V5Z 4H4, Canada

*Correspondence: Alasdair M. Barr, Department of Anesthesiology, Pharmacology & Therapeutics, Faculty of Medicine, University of British Columbia (UBC), 2176 Health Sciences Mall, Vancouver, BC V6T 1Z3, Canada. al.barr@ubc.ca

Abstract

Aim: Traumatic brain injury (TBI) is a common neurological condition, which can present with a wide range of neuropsychological symptoms. Treating this broad spectrum of symptoms represents a significant medical challenge. In part because of this, there is growing interest in the use of medical cannabis to treat the sequelae of TBI, as medical cannabis has been used to treat multiple associated conditions, such as pain. However, medical cannabis represents a heterogeneous collection of therapies, and relatively little is known about their effectiveness in treating TBI symptoms. The aim of the present study was therefore to assess medical cannabis use in patients with TBI.

Methods: In the present study, a retrospective chart review was conducted of patterns of cannabis use and TBI symptoms in individuals who used medical cannabis to treat TBI-related symptoms. All subjects were recruited from a medical cannabis clinic, where cannabis was authorized by physicians, using licensed cannabis products. A total of 53 subjects provided written consent to have their charts reviewed.

Results: Neuropsychiatric conditions, including depression, pain, and anxiety were frequent in this group. The most common forms of medical cannabis consumption at intake included smoking, vaping, and oral ingestion. Patients used a combination of high tetrahydrocannabinol (THC)/low cannabidiol (CBD) and low THC/high CBD products, typically 1–3 times per day. Medical cannabis appeared to be relatively well-tolerated in subjects, with few serious side effects. At follow-up, subjects self-reported improvements

in TBI symptoms, although these were not statistically significant when assessed using validated questionnaires.

Conclusions: Overall findings indicate modest potential benefits of medical cannabis for TBI, but further research will be required to validate these results.

Keywords

Introduction

Traumatic brain injuries (TBIs) pose a serious burden on the healthcare system, yet there is currently no approved pharmacological agent specifically for TBI recovery [1]. Over the last three decades, the prevalence of TBIs in the USA has remained high: nearly half of all adults in the USA have experienced at least one TBI during their lifetime [2], representing 3–4 million new cases a year in the USA [3]. Falls represent the most common cause of TBI cases, followed by assaults, motor vehicle or traffic accidents, and sport-related injuries [4]. For those with more severe TBI, there are significant associated costs for those requiring hospitalization [5, 6]. Brain-related injuries range in severity, with an estimated 70–90% of TBIs designated as "mild" [7]. Injuries can be either focal or diffuse and include primary brain damage from mechanical trauma, as well as secondary pathology from excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, neuroinflammation, axon degeneration, and apoptotic cell death [8]. While most symptoms from mild TBIs resolve within 1–3 months, some individuals experience long-term effects including fatigue, insomnia, anxiety, and depression, collectively known as post-concussion syndrome (PCS) [9].

Recently, interest in using medical cannabis as a treatment modality for TBIs has grown due to its potential to treat a wide range of physical symptoms directly related to the TBI or other injuries sustained from the associated incident [10]. Typical burdensome symptoms following TBI such as fatigue, sleep disturbance, anxiety, depression, migraine, and pain align with the commonly reported reasons for medical cannabis use, suggesting the potential utility of medical cannabis for TBI [11–13]. Preclinical studies in animal models have investigated the link between cannabinoids and endocannabinoids on symptoms such as pain and depression [14–16] which are commonly seen following TBI, although confirmation of the benefits of medical cannabis for pain remains ongoing [17]. Animal models of TBI which have administered cannabinoids have reported reduced allodynia and neuroinflammation, improved functional recovery, as well as alleviation of behaviors homologous to anxiety and depression [18–20]. Experimental data suggest that cannabinoids facilitate these improvements by mediating several underlying physiological mechanisms of TBI, including prevention of neuronal cell death, reduction in excitotoxicity, and activation of cell remodeling processes [21]. Despite the promising results from pre-clinical studies, human studies of medical cannabis and TBI are limited. A phase II clinical trial in severe TBI patients demonstrated a significant reduction in intracranial pressure and improved neurological functioning following synthetic cannabidiol (CBD) treatment [22]. However, no clinical markers were considered significant in a phase III trial, despite the treatment being well tolerated [23]. On the other hand, an observational study examining cannabis use during the post-concussion period showed that those using cannabis had a marginally significantly lower symptom severity at the 3- and 4-week follow-up compared to the other unrecovered individuals [24], while cannabis use was more common in a prison population with prior TBI than those prisoners without TBI [25].

Due to the limited and varied evidence in human studies, more research is needed to understand the therapeutic potential of medical cannabis in TBI. To date, most studies of cannabis use in those with TBI have focused on recreational use [21]. However, there are distinct differences between medical and recreational cannabis users with respect to the intent of use, dose, method of administration, and frequency of use [26, 27]. Furthermore, recreational cannabis users may not be familiar with the best treatment strategies [28, 29]. This may result in suboptimal control of symptoms and unwanted adverse effects.

Medical cannabis clinics can provide specialized knowledge and treatment plans by trained healthcare workers, who ensure that safe and regulated cannabis-based products are used [30]. Medical cannabis products are ideally manufactured using "good practice" guidelines, to ensure purity and stability of compounds, in a standardized manner, and a variety of different formulations are available [31], although a concerning number of violations of these rules have been noted in many countries. Through a retrospective chart review, this study aimed to provide an exploratory description of the demographics, user profiles, and symptom improvements of patients who have experienced a brain injury when using medical cannabis under an established medical cannabis clinic in Canada.

Materials and methods

Patients

Participants (*n* = 53) were recruited from Greenleaf Medical Clinic (GLMC), a specialized medical cannabis clinic in Langley, British Columbia, Canada. The clinical model at GLMC is patient-centered and in concordance with the College of Physicians and Surgeons of British Columbia's medical cannabis standard of practice [32]. Referrals to GLMC are submitted by licensed physicians or nurse practitioners. Patients then fill in a customized intake form gathering information related to their specific condition and complete validated questionnaires, including the Generalized Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), Brief Pain Inventory (BPI), and Opioid Risk Tool (ORT). Patient medical records and medication history are used to confirm diagnoses and to assess risk factors and potential contraindications. This clinical data is used to determine medical cannabis treatment eligibility and baseline symptom severity and to monitor for treatment success with medical cannabis.

Following the referral process, patients receive patient education on the benefits and risks associated with medical cannabis, as well as guidance on safe administration and dosing. Afterwards, patients have a one-on-one consultation with a physician at GLMC that involves discussing their treatment expectations and objectives, a careful explanation of the individualized treatment plan, and titration instructions [33]. Dosing and titration recommendations take into consideration the patients' diagnosis, symptoms, contraindications, and risk factors [33]. The GLMC physician then provides a cannabis authorization, written in accordance with Canadian federal regulations, akin to a prescription. Following the appointment, a consultation report is sent to referring physicians including the detailed treatment plan, follow-up frequency, and any specific recommendations such as monitoring for potential risk factors, adverse events, or the supervised tapering of pharmaceutical medication.

Potential study subjects were identified through the clinical medical health record database, which was used to identify anyone who had indicated they had a brain injury in their medical history on the GLMC intake form. This was a retrospective chart review of patients enrolled in an ongoing data registry study. Inclusion criteria in the study required individuals to be 19 years of age or older, and able to provide informed consent. There were no exclusion criteria. All potential subjects were required to provide informed written consent to release their medical records for research purposes. Anyone who was unreachable through their file contact information was not included. A total of 395 patients met eligibility criteria, 180 individuals responded to recruitment communications, and 53 patients consented and were included in the final analysis. Many eligible patients had only filled out the intake form but never saw a GLMC doctor or initiated medical cannabis treatment, which likely contributed to the low response rate. An honorarium gift card of 10 Canadian dollars was provided to patients for their time.

Measures

In the retrospective chart review, information was collected from electronic medical records, as we have performed previously [34, 35], including physician and cannabis counselor notes and forms filled out by patients at intake and follow-up appointments. Intake forms contained demographics, medical reason for seeking cannabis authorization, medical and psychiatric history, current and previous prescription and over-the-counter medications, previous or current therapies (e.g., physical therapy), substance use history

(e.g., alcohol, recreational drugs), and current cannabis use. Sufficient follow-up information was available for 28 patients (53%) who had returned to the clinic for repeat appointments.

During a standard follow-up appointment, information was collected on symptoms and side effects, product specifics, dosage, and prescription medication use. Patients self-reported any noticeable changes in symptoms, in addition to any side effects they had experienced. Product information collected included the product name, route of administration, and licensed producer. For each product, dosage in mg was determined by patient reporting of frequency, concentration (% mg/g for dried flower, or number of mg/g for oil), and consumption per dose (number of inhalations or volume in mL). All values were available on product labels, as this is a requirement for medical products in Canada. The mg amount of daily and individual doses, therefore, was calculated using these values.

Indicators of mental health were collected using validated scales at both intake and subsequent follow-up appointments. For this investigation, we examined results from the GAD-7, PHQ-9, and BPI. The GAD-7 is a commonly used 7-item questionnaire with good clinical validity that is used to screen for and assess the severity of anxiety symptoms [36]. The PHQ-9 is a well-validated 9-item questionnaire used to measure the existence and severity of depressive symptoms [37]. Finally, the BPI is a standard pain questionnaire used in both research and clinic to measure pain symptoms and their interference in an individual's day-to-day life function [38].

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of continuous variables. Descriptive statistics were run for all variables, and compared between intake and follow-up. Differences between continuous variables at intake and follow-up appointments were assessed with a paired sample *t*-test or Mann-Whitney *U* tests, if non-parametric. Analyses were done using the Statistical Package for the Social Sciences (SPSS) software version 27 (IBM, Armonk, USA).

Results

Participant demographics

The participants consisted of 53 patients recruited from GLMC. The majority of patients were female (32, 60.4%, Table 1). The age of patients when assessed at intake ranged from 19 years old to 72 years old [mean = 47.1, standard deviation (SD) = 13.01].

Table 1. Participant demographics and medical history

Parameters	Outcome [*n* = 53 (%)]
Participant demographics	
Male	21 (39.6)
Female	32 (60.4)
Age (year, mean ± SD)	47.1 ± 13.0
Low income	30 (56.6)
On disability insurance	26 (49.1)
Works outside home	13 (24.5)
Medical history	
History of depression	37 (69.8)
Current or prior suicidal ideation	17 (32.0)
Back and neck pain	42 (81.1)
Anxiety	40 (75.5)
Chronic pain/neuropathy	38 (71.7)
Migraines	30 (56.6)
Sleep disorder	28 (52.8)
Post-traumatic stress disorder	20 (37.7)

Medical history

A history of depression and previous or current suicidal ideations were reported in many patients. Patients self-reported between 2 and 19 (mean = 9.2, SD = 4.2) medical reasons for using cannabis. In addition to brain/head injury/concussion, the most common medical reasons for using cannabis were largely due to pain and other neuropsychiatric conditions (Table 1). The most commonly reported cause of TBI was motor vehicle accidents (19, 35.8%), while over half did not report the cause of injury; other causes included falls, bicycle accidents, and assault.

Cannabis use patterns at intake

At the first appointment, it was found that 15 patients (28.3%) had previously been evaluated by a physician for medical cannabis; 26 (49.1%) were already using cannabis. Of these subjects, 18 (34.0%) reported everyday usage, 2 (4%) reported every other day, 3 (6%) reported 1–2 times per week, and 3 subjects (6%) used more than once a month but less than 1–2 times per week. Within patients already using cannabis at the time of intake, methods of administration included smoking (24, 92.3%), vaporization (20, 76.9%), oral ingestion (oils or capsules; 17, 65.4%), edibles (18, 69.2%), and topical (11, 42.3%). Of those who were able to provide a value of the amount of cannabis consumed per day by self-report, 14 (26%) reported less than 1 g, 8 (15%) reported 1–2 g, 2 (4%) reported 3–4 g, and 2 subjects (4%) reported using 5 g or more than 5 g a day. The most common reasons reported for using cannabis at intake in the 26 subjects were to reduce the use of other medications (20, 38%) and to reduce the use of opioids (5, 9%).

Cannabis use patterns at follow-up

Data on cannabis use patterns were available for 26 patients at follow-up (Tables 2 and 3); the median time to follow up after baseline visit was 6.5 months [interquartile range (IQR) = 2.5 months]. A total of 13 patients (50.0%) were consuming their cannabis through oral ingestion and/or edibles, 8 (31.0%) were using both oral ingestion/edibles and inhalation methods of administration (e.g., vaporization or smoking dried flower), and 5 (19.0%) were using inhalation only.

Table 2. Cannabis use patterns at first follow-up appointment: strain and frequency of use

Parameters	Inhalation only [*n* = 5 (%)]	Oral ingestion only [*n* = 13 (%)]	Both [*n* = 8 (%)]
Strain			
High THC/low CBD	3 (60.0)	3 (23.1)	2 (25.0)
Balance 1:1	0 (0)	0 (0)	0 (0)
Low THC/high CBD	1 (20.0)	3 (23.1)	0 (0)
High THC/low CBD and low THC/high CBD	0 (0)	7 (53.8)	5 (62.5)
Unknown	1 (20.0)	0 (0)	1 (12.5)
Frequency			
As needed	1 (20.0)	0 (0)	0 (0)
Once per day	1 (20.0)	3 (23.1)	0 (0)
Twice per day	0 (0)	3 (23.1)	0 (0)
Three times per day	0 (0)	7 (53.8)	5 (62.5)
Four times per day	3 (60.0)	0 (0)	1 (12.5)
Unknown	0 (0)	0 (0)	2 (25.0)

Quantity of dried cannabis per use was not discernible from available data. THC: tetrahydrocannabinol

Table 3. Cannabis use patterns at first follow-up appointment: THC and CBD dosages

Cannabinoid	Cannabis oil dosage*	Oral ingestion only [*n* = 13 (%)]	Both [*n* = 8 (%)]
THC	< 10 mg	5 (38.5)	3 (37.5)
	≥ 10 mg	2 (15.4)	2 (25.0)
	≥ 25 mg	0 (0)	0 (0)
	≥ 50 mg	1 (7.7)	0 (0)
	Unknown	2 (15.4)	2 (25.0)

Table 3. Cannabis use patterns at first follow-up appointment: THC and CBD dosages (*continued*)

Cannabinoid	Cannabis oil dosage*	Oral ingestion only [*n* = 13 (%)]	Both [*n* = 8 (%)]
CBD	< 10 mg	3 (23.1)	0 (0)
	≥ 10 mg	4 (30.8)	2 (25.0)
	≥ 25 mg	1 (7.7)	3 (37.5)
	Unknown	2 (15.4)	2 (25.0)

*: some patients reported using multiple oil products

In patients who utilized both oral ingestion and inhalation methods of administration, 5 (62.5%) reported the combined use of high THC/low CBD and low THC/high CBD products and 2 (25%) reported the use of high THC/low CBD products only. Higher doses of CBD were reported in these patients compared to those in the oral ingestion-only group, with 3 patients (37.5%) using ≥ 25 mg of CBD per dose and none using less than 10 mg of CBD per dose.

At the first follow-up, 22 patients were authorized the same daily quantity as intake. In the 4 patients that had their authorized daily amount increased, 3 of them (75%) were from 1 g to 2 g, and 1 (25%) was from 2 g to 2.5 g. Of the 17 patients who reported cost, most (58.8%) were spending 100–300 dollars per month on cannabis products.

At the follow-up appointment, 40.7% of patients reported having experienced side effects at some point during treatment, while 59.3% did not report any. Of the 11 patients reporting side effects, 5 participants (45.5%) had dizziness, 2 (18.2%) had intoxication, 2 (18.2%) had anxiety, and 2 (18.2%) had fatigue. 6 patients experienced less commonly reported side effects, 1 patient (9.1%) reported dissociation and lethargy, 1 patient (9.1%) reported brain fog and dry mouth, 1 patient (9.1%) reported jitters, 1 patient (9.1%) reported depression, 1 patient (9.1%) reported headache, and 1 patient (9.1%) reported weight gain. No patients reported discontinuation of cannabis due to side effects.

Symptom changes

Out of the 28 participants with follow-up data, 26 had filled out the GAD-7, PHQ-9, and BPI questionnaires at intake and follow-up. Average scores decreased, signifying improvement, for all of the questionnaires. However, a statistically significant difference in GAD-7, PHQ-9, and BPI scores was not found between intake and follow-up (Table 4).

Table 4. Symptom changes

Test	Intake mean [*n* = 26 (SD)]	Follow-up mean [*n* = 26 (SD)]	Change score mean (SD)	*t*-value (25)	*P* value
PHQ-9	12.9 (6.5)	10.9 (6.1)	–2.0 (6.4)	1.6	0.128
GAD-7	10.7 (7.3)	9.2 (6.0)	–1.5 (6.3)	1.3	0.222
BPI	74.1 (16.6)	70.2 (14.7)	–4.0 (15.0)	1.3	0.191

Within the subgroup of patients that had follow-up data (*n* = 26), the number of patients with moderate to severe anxiety (GAD-7 of from 10 to 21) decreased from 13 (50%) to 10 (38%) between intake and follow-up. Similarly, the number of patients with moderate to severe depressive symptoms (PHQ-9 of from 10 to 27) decreased from 17 (65%) to 14 (54%) between intake and follow-up.

Perceived symptom improvement

At the time of follow-up, patients were asked about their symptom improvement on a percentage scale. The mean percentage and median percentage improvement in sleep, pain, depression, and anxiety was reported (Table 5).

Table 5. Perceived symptom improvement*

Symptom	Mean [*n* = 28 (%, SD)]	Median [*n* = 28 (%, IQR)]
Sleep	41.3 (46.3)	37.5 (78.8)

Table 5. Perceived symptom improvement* (*continued*)

Symptom	Mean [*n* = 28 (%, SD)]	Median [*n* = 28 (%, IQR)]
Pain	32.1 (41.5)	30.0 (56.3)
Anxiety	22.1 (37.0)	12.5 (50)
Depression	22.7 (40.0)	2.5 (57.5)

*: symptom improvement measured on a percentage scale with 100% being complete improvement

Improvements in daily life function

When asked to name a daily function or activity that patients were able to partake in since starting medical cannabis treatment (recorded at the first follow-up meeting, using an open-form field question), 6 patients (21.4%) reported an improved ability to exercise. A total of 5 patients (17.9%) reported an improved ability to partake in household chores and attend appointments, while 2 (7.1%) reported improved social engagement.

Concomitant medication reduction

At follow-up, of the 15 patients asked, 8 (53.3%) reported a reduction in medication since starting medical cannabis treatment. Of the patients that reported a reduction in medications, 2 (25%) reported a stimulant reduction, 2 (25%) reported nonsteroidal anti-inflammatory drugs (NSAIDs) reduction, 1 (12.5%) reported an opioid reduction, 1 (12.5%) reported a sedatives reduction and 2 patients (25%) did not specify the medication that was reduced.

Discussion

This study, using retrospective chart review, examined the demographics, health conditions, and cannabis use patterns of post-TBI patients at GLMC using medical cannabis under the care of an experienced medical cannabis physician. Medical cannabis did not appear to worsen, and may have marginally improved depression, anxiety, and pain symptoms in patients with TBI, although these effects may have also improved independently with time or due to placebo effects from seeing a doctor and receiving care. Notably, self-reported improvements in sleep and reduced medication were also found. Most patients primarily ingested medical cannabis (e.g., oral oil), with fewer inhaling dried cannabis flowers. This study provides preliminary evidence of the limited efficacy and patterns of use of medical cannabis in patients who have previously sustained a brain injury.

Demographics

This study consisted of a majority of female patients, providing valuable insight into an understudied demographic. Sex-based and gender-based differences in response to medical cannabis have been observed previously [39, 40], reiterating the need for more female and women-focused studies. The sex ratio seen within this study may be related to differences in symptom sequelae following TBI. Although men are more likely to sustain a TBI in their lifetime, women often have higher symptom loads and longer duration symptoms and are more likely to seek medical help following the injury [41–43]. It is therefore possible that women may be more likely to seek alternative care, such as medical cannabis, following a TBI. The median age of patients at intake was 47.1 years old, which is slightly higher than reports on other medical cannabis users. Rosenthal and Pipitone [44] reported a median age of 46, while Bonn-Miller et al. [11] observed a median age of 41.2. The majority of the patients reported an income below 30,000 dollars per year. Notably, this sample has a high rate of patients on disability, which is consistent with the finding that individuals who have experienced a TBI in their lifetime are more likely to claim disability or welfare [45]. Finding suitable treatments for symptoms following a TBI may help to reduce the rate of long-term disability claims.

Symptom management

While all subjects in the study had previously experienced a brain injury, the second most common indication for medical cannabis use was pain. Additionally, migraines, anxiety, and depression were also commonly reported as reasons for pursuing medical cannabis authorization. These findings are consistent with other studies which document pain, anxiety, and depression as some of the most common reasons for patients using cannabis [44, 46–49]. Recreationally, cannabis has been reported to be used for managing PCS including anxiety and headache [50]. While it could not be confirmed if these additional indications were a result of a TBI or pre-existing conditions, it may indicate individuals are seeking medical cannabis to control some symptoms associated with a TBI.

Modest subjective and measurable improvements, as quantified by validated questionnaires, in mental health, quality of life, and pain were reported in patients with persistent, burdensome symptoms following a TBI. However, because of the absence of a control group not receiving cannabis, it is not possible to determine how much these symptoms may have naturally declined over time. While our findings report a decrease in all validated questionnaire scores between intake and follow-up, indicating a decrease in symptoms, the findings were not statistically significant. However, given the modest sample size, there may not have been enough statistical power to detect small to medium effect sizes. Despite this, an important finding was that patients were not experiencing a clear worsening of symptoms following cannabis initiation. While some side effects were reported, most were mild and well-known cannabis-associated side effects. In clinical practice, it is typically observed that these subside within 24–48 h as tolerance builds [51]. Furthermore, at follow-up, patients reported subjective improvements in sleep (mean = 41.3%) and pain (mean = 32.1%), with improvements in depression and anxiety also noted. The discrepancy between the validated questionnaire and self-reported improvements could potentially be explained by participant bias in reporting their own experience. Cushman et al. [52] found that the percentage reduction in pain can be overestimated in comparison to the change in scores of the 11-point numerical pain rating scale. This could suggest that patients may overestimate their percentage of improvements in symptoms following treatment. Perceived improvements in sleep, pain, anxiety, and depression may therefore be informative in indicating the perceived value of medical cannabis treatments for patients experiencing long-term symptoms from a TBI. Finally, although the PHQ-9 and GAD-7 are recommended screening tools following a mild TBI [53], we acknowledge the validated questionnaires used in this study were not designed to measure the complete array of symptoms associated with TBI. For example, headache and cognitive dysfunction (such as impaired attention, memory, and executive functioning) were not formally assessed, yet the use of medical cannabis has been associated with improvements in both of these symptoms [54, 55]. As such, the full scope of benefit may not have been captured.

Cannabis use patterns

In this sample, 26 patients (49.1%) were already using cannabis at the time of their first clinic appointment, with 18 (34%) already using it every day, thereby suggesting that patients may have been using cannabis to self-manage their symptoms prior to seeking medical treatment at GLMC. Most patients using cannabis at intake were smoking cannabis cigarettes as their method of use. This aligns with current literature, in which smoked cannabis is the most commonly preferred method of consumption, particularly in participants using cannabis recreationally [56, 57]. It has been well-studied that smoking cannabis can have a negative effect on respiratory functioning and cause other health concerns, so it is generally not recommended by physicians [58–60]. At follow-up, the most common method of administration was only ingesting cannabis oil, which suggests that seeking medical authorization not only encourages patients to use products from certified licensed producers but also to use a method of administration that is considered safer due to accurate dosing and no respiratory risk [33]. The ideal route of administration for a patient will depend on whether they are seeking to treat acute or chronic symptoms [51]. Inhalation methods (e.g., vaporization and smoking) are best suited for acute symptoms due to a quicker onset of action [61], and vaping is seeing increased use in the community [62]. Ingestion methods (e.g., cannabis oils) are best suited for chronic symptoms due to a longer duration of action [61]. The switch to using

cannabis oils seen within this sample suggests that most patients are likely seeking the use of medical cannabis for the treatment of chronic symptoms. This is aligned with other studies evaluating reasons for medical cannabis use [12, 63]. Some studies on medical cannabis patients still report smoking as a popular route of administration [46, 64]. This may reflect differences in medical cannabis patients who are self-treating or under the care of a healthcare provider and highlights the importance of education on how to best utilize medical cannabis.

The majority of patients inhaling cannabis reported the use of high THC concentrated products. This may be due to THC generally being more efficacious for acute symptoms (e.g., nausea or breakthrough pain) compared to CBD [65, 66]. In contrast, patients using ingestion and those using ingestion with inhalation often reported using both high THC and high CBD concentrated products. This likely reflects the treatment approach used at GLMC for chronic conditions, in which patients use CBD to control daytime symptoms, in order to limit the risk of impairment, and THC to control nighttime symptoms (e.g., sleep) [33].

The majority of patients reported no side effects associated with cannabis use (17 patients, 59.3%), while mild side effects were reported in 11 patients (40.7%), indicating that treatment was generally well tolerated. Reported side effects were consistent with common cannabis-related side effects including dizziness, fatigue, and anxiety [51]. It is important to note that these reported side effects do not suggest that cannabis exacerbates neurocognitive deficits following a TBI including loss of concentration and memory [9]. With regards to this latter point, although the neurocognitive function was not specifically assessed in the present study, a number of important recent studies have shown that initiation of medical cannabis either has no harmful effect or actually improves neurocognitive function in users [67–69], in domains such as executive function. Additionally, no patients reported that side effects caused discontinuation of medical cannabis, which is in accordance with a previously published abstract that determined that mild cannabis-related adverse events did not discourage use in individuals with TBI [70]. However, it is possible that the clinic lost patients who experienced side effects to follow-up, and therefore this information was not captured. There is a great need for more prospective research to better assess this relationship.

Mental health

The high prevalence of depression within this sample is consistent with many studies [11, 12, 26–28] which indicate that mental health is an important indicator of patients seeking medical cannabis. A total of 37 patients (69.8%) reported depression in our sample, much higher than the estimated lifetime prevalence in community samples [71]. A history of depression has been found to be an important indicator of long-term symptoms following a TBI, which could explain the high proportion of patients who have experienced depression seeking alternative treatments [43, 72]. Alternately, only 28 patients (52.8%) reported specifically using medical cannabis to help with their depression symptoms, which is similar to the prevalence in other medical cannabis studies [11, 44, 48]. Anxiety was reported as a reason for medical cannabis use in 40 patients (75.5%). Anxiety is commonly reported as a reason for initiating medical cannabis use [44, 48, 73]. Mental health issues following a TBI are common [74] and medical cannabis might help to alleviate these symptoms.

A large portion of patients reported experiencing pain, potentially indicating an increased risk for the use of opioids and other pain-relieving medications. At the time of follow-up, patients reported that they had reduced other medications, including opioids, pain relievers, and stimulants, since starting treatment at GLMC. Cannabis has been reported to aid in harm reduction and reduce prescription medication and alcohol use in multiple studies [75–77]. It has also been reported as a mediator to control distress in those with prior trauma [78]. Cannabis should continue to be investigated as a modality to prevent misuse of other substances in patients who have experienced a TBI [76, 79].

To our knowledge, this is the first full retrospective chart analysis on medical cannabis use in individuals who have experienced a brain injury. In the future, prospective studies with larger sample sizes

are important in understanding the safety and potential benefits of medical cannabis for patients who have experienced a TBI.

Limitations

In addition to limitations associated with performing a retrospective chart analysis, the modest sample size of this study (n = 53 baseline assessments and n = 26 follow-up assessments) could affect the generalizability of data and the ability to detect significant associations. This limitation is extended further by the manner in which nearly half the sample was already using cannabis at entry, which would be likely to significantly reduce the size of any therapeutic effect (as subjects may already have been benefitting from suboptimal use of recreational cannabis). It could be predicted that those who were already using cannabis at the start of treatment might already have gained significant clinical benefits from the drug, even if the use was not clinically optimized; if so, this might have reduced the clinical impact compared to "new starts" who began using medical cannabis *de novo* and resulted in an underestimation of treatment efficacy. Thus, the high heterogenicity and low number of subjects, combined with pre-existing cannabis use, make substantial conclusions difficult. However, this is inherent to the TBI population. While the information was found in the physician's notes, the questionnaires within the intake and follow-up forms relied on self-reported data, which may have led to less precision. Some charts were incomplete, or patients did not return for follow-up, which may affect the completeness of data extracted, although this is a common concern in chart reviews. The exact statistical nature of missing data values for different variables was not determined (i.e. missing at random *versus* not missing at random) as to do so would require follow-up with subjects to obtain some of this data which was beyond the scope of the research ethics board (REB) approval. Thus, future studies should design their protocols in such a way to make this possible. Additionally, with the available information, it could not be determined if co-morbid symptoms were a result of the TBI or from pre-existing conditions. It will also need to be determined whether such studies are feasible in countries where attitudes towards medical cannabis in general may be less favorable than in the USA [80]. Nevertheless, there is a paucity in the literature on data for individuals with TBI who use medical cannabis. The present data offer a number of benefits, including that all clients were seen by a medically trained clinician, authorized to use legal and high-quality cannabis-based products (whose contents are known accurately), all clients were treated at a medical cannabis clinic where all staff have high levels of expertise, and all clients completed questionnaires that are routinely used for clinical research studies. Thus, the data provide exploratory information about the use of medical cannabis in TBI which will inform the design of other larger studies in the future.

Conclusion

This study contributes novel data on the use of medical cannabis in patients who previously sustained a brain injury. The heterogenous nature of this sample is representative of real-world diversity for this complex and chronic condition. Currently, very little evidence is available for this population, thus this study serves as important insight to guide future research.

In the present study, neuropsychiatric conditions, including depression, pain, and anxiety were common in this group who had experienced a TBI. The most frequent methods of medical cannabis ingestion included daily smoking, vaping and oral consumption, and included a combination of products with differing ratios of THC to CBD. While there was limited or inconclusive evidence of improvements in pain and mental health using validated scales, there were self-reported improvements in mental health, sleep, and reduction of polypharmacy. Importantly, medical cannabis did not appear to worsen patient symptoms including mental health and pain. Taken together, these findings indicate there may be some therapeutic potential for medical cannabis in patients with brain injury. Further investigations using larger, higher-powered trials are necessary to better evaluate the safety and efficacy of medical cannabis for this population.

Abbreviations

BPI: Brief Pain Inventory

CBD: cannabidiol

GAD-7: Generalized Anxiety Disorder-7

GLMC: Greenleaf Medical Clinic

PHQ-9: Patient Health Questionnaire-9

SD: standard deviation

TBIs: traumatic brain injuries

THC: tetrahydrocannabinol

Declarations

Acknowledgements

We thank all patients and staff who were involved in the project. We acknowledge Fonda Betts, Tanya Adams, and Greenleaf Medical Clinic.

Author contributions

ENRS: Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—original draft. CAM: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Validation, Writing—review & editing. LAL: Formal analysis, Investigation, Methodology, Validation, Writing—review & editing. JD: Data curation, Project administration, Supervision, Writing—review & editing. AC and KR: Data curation, Investigation, Validation, Writing—review & editing. CP: Writing—review & editing. WJP: Conceptualization, Funding acquisition, Resources, Writing—review & editing. AMB: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing—original draft.

Conflicts of interest

CAM has received consulting fees or honoraria from Andira, Active Patch Technologies, Dosist, Strainprint, Emerald Health Therapeutics, Sapphire Clinics, Aleafia, Spectrum, Tilray, Numinus, Aurora and MD Briefcase. She is on the Board of Directors for the Green Organic Dutchmen. The other authors report no potential conflicts.

Ethical approval

Study ethics for this chart review were approved by the Clinical Research Ethics Board of the University of British Columbia (H17-03359) and complies with Declaration of Helsinki.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

Data cannot be shared due to the stipulations of the ethics approval to ensure privacy of the patients involved.

Copyright

References

1. Galgano M, Toshkezi G, Qiu X, Russell T, Chin L, Zhao LR. Traumatic brain injury: current treatment strategies and future endeavors. Cell Transplant. 2017;26:1118–30.

2. Whiteneck GG, Cuthbert JP, Corrigan JD, Bogner JA. Risk of negative outcomes after traumatic brain injury: a statewide population-based survey. J Head Trauma Rehabil. 2016;31:E43–54.

3. Coronado VG, McGuire LC, Sarmiento K, Bell J, Lionbarger MR, Jones CD, et al. Trends in traumatic brain injury in the U.S. and the public health response: 1995–2009. J Safety Res. 2012;43:299–307. Erratum in: J Safety Res. 2014;48:117.

4. Gardner AJ, Zafonte R. Chapter 12 - Neuroepidemiology of traumatic brain injury. Handb Clin Neurol. 2016;138:207–23.

5. Public Health Agency of Canada. Injury in review, 2020 edition: spotlight on traumatic brain injuries across the life course [Internet]. Ottawa: Public Health Agency of Canada; [cited 2021 Oct 10]. Available from: https://www.canada.ca/en/public-health/services/injury-prevention/canadian-hospitals-injury-reporting-prevention-program/injury-reports/2020-spotlight-traumatic-brain-injuries-life-course.html

6. Chen A, Bushmeneva K, Zagorski B, Colantonio A, Parsons D, Wodchis WP. Direct cost associated with acquired brain injury in Ontario. BMC Neurol. 2012;12:76.

7. Cassidy JD, Carroll LJ, Peloso PM, Borg J, von Holst H, Holm L, et al.; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO collaborating centre task force on mild traumatic brain injury. J Rehabil Med. 2004;36:28–60.

8. Ng SY, Lee AYW. Traumatic brain injuries: pathophysiology and potential therapeutic targets. Front Cell Neurosci. 2019;13:528.

9. Daneshvar DH, Riley DO, Nowinski CJ, McKee AC, Stern RA, Cantu RC. Long-term consequences: effects on normal development profile after concussion. Phys Med Rehabil Clin N Am. 2011;22:683–700.

10. Saulino PA, Greenwald BD, Gordon DJ. The changing landscape of the use of medical marijuana after traumatic brain injury: a narrative review. Brain Inj. 2021;35:1510–20.

11. Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. Am J Drug Alcohol Abuse. 2014;40:23–30.

12. Kosiba JD, Maisto SA, Ditre JW. Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: systematic review and meta-analysis. Soc Sci Med. 2019;233:181–92.

13. Hawley LA, Ketchum JM, Morey C, Collins K, Charlifue S. Cannabis use in individuals with spinal cord injury or moderate to severe traumatic brain injury in Colorado. Arch Phys Med Rehabil. 2018;99:1584–90.

14. Hill MN, Barr AM, Ho WS, Carrier EJ, Gorzalka BB, Hillard CJ. Electroconvulsive shock treatment differentially modulates cortical and subcortical endocannabinoid activity. J Neurochem. 2007;103:47–56.

15. Rouhollahi E, MacLeod BA, Barr AM, Puil E. Cannabis extract CT-921 has a high efficacy-adverse effect profile in a neuropathic pain model. Drug Des Devel Ther. 2020;14:3351–61.

16. Barr AM, Phillips AG. Increased successive negative contrast in rats withdrawn from an escalating-dose schedule of D-amphetamine. Pharmacol Biochem Behav. 2002;71:293–9.

17. Henderson LA, Kotsirilos V, Cairns EA, Ramachandran A, Peck CC, McGregor IS. Medicinal cannabis in the treatment of chronic pain. Aust J Gen Pract. 2021;50:724–32.

18. Belardo C, Iannotta M, Boccella S, Rubino RC, Ricciardi F, Infantino R, et al. Oral cannabidiol prevents allodynia and neurological dysfunctions in a mouse model of mild traumatic brain injury. Front Pharmacol. 2019;10:352.

19. Alalawi A, Dodu JC, Woolley-Roberts M, Brodie J, Di Marzo V, Soderstrom K. Cannabidiol improves vocal learning-dependent recovery from, and reduces magnitude of deficits following, damage to a cortical-like brain region in a songbird pre-clinical animal model. Neuropharmacology. 2019;158:107716.

20. Braun M, Khan ZT, Khan MB, Kumar M, Ward A, Achyut BR, et al. Selective activation of cannabinoid receptor-2 reduces neuroinflammation after traumatic brain injury via alternative macrophage polarization. Brain Behav Immun. 2018;68:224–37.

21. Hergert DC, Robertson-Benta C, Sicard V, Schwotzer D, Hutchison K, Covey DP, et al. Use of medical cannabis to treat traumatic brain injury. J Neurotrauma. 2021;38:1904–17.

22. Knoller N, Levi L, Shoshan I, Reichenthal E, Razon N, Rappaport ZH, et al. Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial[*]. Crit Care Med. 2002;30:548–54.

23. Maas AI, Murray G, Henney H 3rd, Kassem N, Legrand V, Mangelus M, et al.; Pharmos TBI investigators. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. Lancet Neurol. 2006;5:38–45.

24. Lawrence DW, Foster E, Comper P, Langer L, Hutchison MG, Chandra T, et al. Cannabis, alcohol and cigarette use during the acute post-concussion period. Brain Inj. 2020;34:42–51.

25. Durand E, Chevignard M, Watier L, Fix M, Weiss JJ, Pradat-Diehl P. Traumatic brain injury among young offenders in France based on the results of the Fleury TBI study. Cogent Soc Sci. 2017;3:1398125.

26. Turna J, Balodis I, Munn C, Van Ameringen M, Busse J, MacKillop J. Overlapping patterns of recreational and medical cannabis use in a large community sample of cannabis users. Compr Psychiatry. 2020;102:152188.

27. Lo LA, MacCallum CA, Yau JC, Panenka WJ, Barr AM. Factors associated with problematic cannabis use in a sample of medical cannabis dispensary users. Psychiatr Clin Psychopharmacol. 2022;32:262–7.

28. Berey BL, Aston ER, Gebru NM, Merrill JE. Differences in cannabis use characteristics, routines, and reasons for use among individuals with and without a medical cannabis card. Exp Clin Psychopharmacol. 2023;31:14–22.

29. Gottschling S, Ayonrinde O, Bhaskar A, Blockman M, D'Agnone O, Schecter D, et al. Safety considerations in cannabinoid-based medicine. Int J Gen Med. 2020;13:1317–33.

30. MacCallum CA, Lo LA, Pistawka CA, Boivin M. A clinical framework for evaluating cannabis product quality and safety. Cannabis Cannabinoid Res. 2023;8:567–74.

31. Brunetti P, Pichini S, Pacifici R, Busardò FP, Del Rio A. Herbal preparations of medical cannabis: a vademecum for prescribing doctors. Medicina (Kaunas). 2020;56:237.

32. Practice standard: cannabis for medical purposes [Internet]. Vancouver: College of Physicians and Surgeons of British Columbia; [cited 2021 Oct 10]. Available from: https://www.cpsbc.ca/files/pdf/PSG-Cannabis-for-Medical-Purposes.pdf

33. MacCallum CA, Lo LA, Boivin M. "*Is medical cannabis safe for my patients*?" A practical review of cannabis safety considerations. Eur J Intern Med. 2021;89:10–8.

34. Tse L, Schwarz SK, Bowering JB, Moore RL, Barr AM. Incidence of and risk factors for delirium after cardiac surgery at a quaternary care center: a retrospective cohort study. J Cardiothorac Vasc Anesth. 2015;29:1472–9.

35. Tse L, Bowering JB, Schwarz SK, Moore RL, Burns KD, Barr AM. Postoperative delirium following transcatheter aortic valve implantation: a historical cohort study. Can J Anaesth. 2015;62:22–30.

36. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166:1092–7.

37. Kroenke K, Spitzer RL, Williams JB. The PHQ-9. J Gen Intern Med. 2001;16:606–13.

38. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain. 2004;20:309–18.

39. Cuttler C, Mischley LK, Sexton M. Sex differences in cannabis use and effects: a cross-sectional survey of cannabis users. Cannabis Cannabinoid Res. 2016;1:166–75.

40. Cooper ZD, Craft RM. Sex-dependent effects of cannabis and cannabinoids: a translational perspective. Neuropsychopharmacology. 2018;43:34–51.

41. Munivenkatappa A, Agrawal A, Shukla DP, Kumaraswamy D, Devi BI. Traumatic brain injury: does gender influence outcomes? Int J Crit Illn Inj Sci. 2016;6:70–3.

42. Gupte R, Brooks W, Vukas R, Pierce J, Harris J. Sex differences in traumatic brain injury: what we know and what we should know. J Neurotrauma. 2019;36:3063–91.

43. Silverberg ND, Gardner AJ, Brubacher JR, Panenka WJ, Li JJ, Iverson GL. Systematic review of multivariable prognostic models for mild traumatic brain injury. J Neurotrauma. 2015;32:517–26.

44. Rosenthal MS, Pipitone RN. Demographics, perceptions, and use of medical marijuana among patients in Florida. Med Cannabis Cannabinoids. 2021;4:13–20.

45. Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. Arch Phys Med Rehabil. 2014;95:986–95.E1.

46. Troutt WD, DiDonato MD. Medical cannabis in Arizona: patient characteristics, perceptions, and impressions of medical cannabis legalization. J Psychoactive Drugs. 2015;47:259–66.

47. Mahabir VK, Merchant JJ, Smith C, Garibaldi A. Medical cannabis use in the United States: a retrospective database study. J Cannabis Res. 2020;2:32.

48. Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. Harm Reduct J. 2005;2:18.

49. Stubbs JL, Thornton AE, Gicas KM, O'Connor TA, Livingston EM, Lu HY, et al. Characterizing traumatic brain injury and its association with losing stable housing in a community-based sample. Can J Psychiatry. 2022;67:207–15.

50. Gallant C, Luczon R, Ryan D, Good D. Investigating cannabis use and associated symptoms among university students with and without a history of concussion. Neuropsychol Rehabil. 2022;32:967–91.

51. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12–9.

52. Cushman D, McCormick Z, Casey E, Plastaras CT. Discrepancies in describing pain: is there agreement between numeric rating scale scores and pain reduction percentage reported by patients with musculoskeletal pain after corticosteroid injection? Pain Med. 2015;16:870–6.

53. Silverberg ND, Iaccarino MA, Panenka WJ, Iverson GL, McCulloch KL, Dams-O'Connor K, et al.; American Congress of Rehabilitation Medicine Brain Injury Interdisciplinary Special Interest Group Mild TBI Task Force. Management of concussion and mild traumatic brain injury: a synthesis of practice guidelines. Arch Phys Med Rehabil. 2020;101:382–93.

54. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain. 2018;19:37.

55. Ware MA, Wang T, Shapiro S, Collet JP; COMPASS study team. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015;16:1233–42.

56. Russell C, Rueda S, Room R, Tyndall M, Fischer B. Routes of administration for cannabis use – basic prevalence and related health outcomes: a scoping review and synthesis. Int J Drug Policy. 2018;52:87–96.

57. Lo LA, MacCallum CA, Yau JC, Barr AM. Differences in those who prefer smoking cannabis to other consumption forms for mental health: what can be learned to promote safer methods of consumption? J Addict Dis. 2023;41:258–62.

58. Fischer B, Russell C, Sabioni P, van den Brink W, Le Foll B, Hall W, et al. Lower-risk cannabis use guidelines: a comprehensive update of evidence and recommendations. Am J Public Health. 2017;107:e1–12. Erratum in: Am J Public Health. 2018;108:e2.

59. Tashkin DP. Marijuana and lung disease. Chest. 2018;154:653–63.

60. Piano MR. Cannabis smoking and cardiovascular health: it's complicated. Clin Pharmacol Ther. 2017;102:191–3.

61. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. Br J Clin Pharmacol. 2018;84:2477–82.

62. Lim CCW, Chan GCK, Wadsworth E, Stjepanović D, Chiu V, Chung JYC, et al. Trends and socio-demographic differences of cannabis vaping in the USA and Canada. Int J Environ Res Public Health. 2022;19:14394.

63. Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. Eur J Intern Med. 2018;49:44–50.

64. Haug NA, Padula CB, Sottile JE, Vandrey R, Heinz AJ, Bonn-Miller MO. Cannabis use patterns and motives: a comparison of younger, middle-aged, and older medical cannabis dispensary patients. Addict Behav. 2017;72:14–20.

65. Stith SS, Li X, Orozco J, Lopez V, Brockelman F, Keeling K, et al. The effectiveness of common *Cannabis* products for treatment of nausea. J Clin Gastroenterol. 2022;56:331–8.

66. Musty RE, Rossi R. Effects of smoked cannabis and oral δ^9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy. J Cannabis Ther. 2001;1:29–56.

67. Sagar KA, Dahlgren MK, Lambros AM, Smith RT, El-Abboud C, Gruber SA. An observational, longitudinal study of cognition in medical cannabis patients over the course of 12 months of treatment: preliminary results. J Int Neuropsychol Soc. 2021;27:648–60.

68. Dahlgren MK, Lambros AM, Smith RT, Sagar KA, El-Abboud C, Gruber SA. Clinical and cognitive improvement following full-spectrum, high-cannabidiol treatment for anxiety: open-label data from a two-stage, phase 2 clinical trial. Commun Med (Lond). 2022;2:139.

69. Eadie L, Lo LA, Christiansen A, Brubacher JR, Barr AM, Panenka WJ, et al. Duration of neurocognitive impairment with medical cannabis use: a scoping review. Front Psychiatry. 2021;12:638962.

70. McVige J, Kaur D, Hart P, Lillis M, Mechtler L, Bargnes V, et al. Medical cannabis in the treatment of post-traumatic concussion (P3.9-027). Neurology. 2019;92:P3.9-027.

71. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of depression in the community from 30 countries between 1994 and 2014. Sci Rep. 2018;8:2861. Erratum in: Sci Rep. 2022;12:14856.

72. Langer LK, Alavinia SM, Lawrence DW, Munce SEP, Kam A, Tam A, et al. Prediction of risk of prolonged post-concussion symptoms: derivation and validation of the TRICORDRR (Toronto Rehabilitation Institute Concussion Outcome Determination and Rehab Recommendations) score. PLoS Med. 2021;18:e1003652.

73. Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. J Psychoactive Drugs. 2011;43:128–35.

74. O'Connor TA, Panenka WJ, Livingston EM, Stubbs JL, Askew J, Sahota CS, et al. Traumatic brain injury in precariously housed persons: incidence and risks. EClinicalMedicine. 2022;44:101277.

75. MacCallum CA, Eadie L, Barr AM, Boivin M, Lu S. Practical strategies using medical cannabis to reduce harms associated with long term opioid use in chronic pain. Front Pharmacol. 2021;12:633168.

76. Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. Cannabis Cannabinoid Res. 2017;2:160–6.

77. Corroon JM Jr, Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs – a cross-sectional study. J Pain Res. 2017;10:989–98.

78. Brammer WA, Conn BM, Iverson E, Lankenau SE, Dodson C, Wong CF. Coping motives mediate the association of trauma history with problematic cannabis use in young adult medical cannabis patients and non-patient cannabis users. Subst Use Misuse. 2022;57:684–97.

79. Adams RS, Corrigan JD, Dams-O'Connor K. Opioid use among individuals with traumatic brain injury: a perfect storm? J Neurotrauma. 2020;37:211–6.

80. Gritsenko V, Kogan M, Konstantinov V, Marinova T, Reznik A, Isralowitz R. Religion in Russia: its impact on university student medical cannabis attitudes and beliefs. Complement Ther Med. 2020;54:102546.