PURPLE HAZE: ISSUES ON CANNABIS LEGALIZATION

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PURPLE HAZE: ISSUES ON CANNABIS LEGALIZATION

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EDITORIAL
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Editorial: Purple Haze: Issues on Cannabis Legalization

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Editorial on the Research Topic

Purple Haze: Issues on Cannabis Legalization

Considering the progressive legalization of cannabis across jurisdictions, we prepared a special topic that addresses significant issues relevant for future legalization initiatives. This topic seeks to: (i) characterize the personal characteristics of individuals who support recreational and medical cannabis legalization; (ii) characterize the profiles of people who use cannabis and related compounds such as tetrahydrocannabinol (THC) and cannabidiol (CBD); (iii) document the psychiatric and cognitive consequences of cannabis products, used either for recreational or medical purposes; and (iii) define priority areas deserving more research.

Using data from the 2016 *National Drug Strategy Household Survey* completed by 21,729 participants in Australia, Chiu et al. investigated the relationship between personal characteristics and support for cannabis legalization. Forty percent and 77% of participants supported the legalization of recreational and medical cannabis use, respectively. Cannabis use and high-risk drinking were associated with increased support of recreational and medical cannabis legalization. Nicotine use was only associated with increased support of recreational cannabis legalization. Although younger age was associated with greater support for legalization of recreational cannabis use, there was more support for legalization of medical cannabis use in older individuals. Psychological distress was associated with a higher likelihood of supporting recreational cannabis legalization, whereas support for medical cannabis legalization was stronger amongst individuals with chronic pain. Nevertheless, cannabis-use status was the strongest statistical predictor of support for both recreational and medical cannabis legalization.

People who use cannabis and related products for recreational and medical purposes do not form a homogeneous group of individuals, raising the need to characterize user profiles. Using data from an online survey completed by 329 people with "regular" use of cannabis, Amiet et al. examined the relationship between cannabis-use motives, expectancies, and profiles and psychological symptoms. Latent class analyses revealed two groups: those endorsing multiple motivations (social, coping, etc.) and higher positive and negative expectations of cannabis

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use, and those with low motives and expectancies. Individuals with High Motives and High Expectancies were more likely to meet criteria for cannabis use disorder (CUD) and report higher levels of anxious, depressive, and psychotic symptoms. These results are consistent with previous studies, thus defining modifiable targets (e.g., motives and expectancies) for future psychological interventions for CUD. Leveraging data from an online survey completed by 533 people who use cannabis and drink alcohol, Karoly et al. categorized participants into those who use cannabis for medical vs. recreational purposes. They determined that the former subgroup reported drinking less frequently than the latter group. In secondary analyses, they found that the use of high-THC/CBD was associated with more drinks on cannabis-use days. Such results demonstrate that cannabis and alcohol co-use is influenced by the reasons for cannabis use and cannabis content. On a related topic, Vilches et al. examined the potential differences between people who use CBD with and without cannabis co-use. Based on a survey completed by 182 respondents who reported using CBD, the authors noted that those with cannabis co-use were younger, had lower educational attainment, were more likely to use nicotine and to misuse alcohol, used more varied methods of CBD consumption (e.g., vaping, smoking, edible), and were more likely to report medical ailments such as sleep disorders. The association between cannabis and other substance use is consistent with previous studies.

The association between cannabis use and psychotic symptoms has been one of the most rigorously examined (1, 2). For instance, for those with a diagnosed psychotic disorder, there is reliable evidence showing that cannabis use is associated with poorer prognoses (3). Given that the psychotomimetic effects of cannabis are attributed to THC, and that the pharmacological effects of THC can be (partially) reversed by CBD in rodents (4), it has been hypothesized that CBD may be considered as an antipsychotic treatment. As reviewed Ahmed et al. the evidence remains inconclusive despite promising results. Two clinical trials have produced positive outcomes, while another trial failed to do so.

Compared to the cannabis-psychosis association, the link between cannabis and depression is less firmly established. In their review paper, Langlois et al. observed a bidirectional relationship between cannabis use and depression; although most studies showed an association, the link was not always observed. The risk for depression is possibly higher in people with heavy use of cannabis and those having initiated their consumption in early adolescence. While cannabis use is associated with a worsened prognosis in individuals with major depressive disorder (MDD), the link to suicide remains controversial. Data are insufficient in some areas, including with respect to the psychological treatment of CUD in MDD patients, the antidepressant potential of CBD, and mechanisms underlying the cannabis-depression association. Regarding the latter issue, Blum et al. argue that this association is due to the development of cannabis-induced hypodopaminergic anhedonia, as evidenced by positron emission tomography studies. If cannabis use increases the risk of experiencing anxio-depressive symptoms, one might expect cannabis abstinence to be associated with improvements in these symptoms. To investigate this possibility, Cooke et al. performed a study in non-treatment seeking adolescents who were randomized to 4 weeks of abstinence (achieved through contingency management) or ongoing consumption. Both groups had lower levels of anxiety and depression at thprovide doi linke study endpoint, and there were no between-group differences. Among the several reasons that could explain these results, the authors note that the recruited sample was composed of people with recreational use of cannabis. The recruitment of CUD individuals may have produced different results. Finally, Dellazizzo et al. reviewed evidence regarding the potential link between cannabis use and violence. Their meta-analyses demonstrated that cannabis is a potential risk factor for violent behaviors in youths and in people with psychotic disorders. The limitations of the studies performed in the field are discussed, most particularly in the case of studies performed in individuals with psychotic disorders (e.g., cross-sectional studies failing to properly control for potentially confounding factors). Two main explanatory models are presented: a pharmacological model whereby violence results from the pharmacological effects of cannabis; and a social model, whereby violent behaviors are the result of the social habits associated with the use of an illegal substance.

Cannabis may impair cognition, which may in turn impact academic and work achievement, and increase the risk for car accidents. Bourque and Potvin summarize the evidence on both the acute and residual effects of cannabis on cognition. Based on a previous meta-analysis (5), they show that acute intoxication with cannabis/THC is associated with prominent impairments in verbal memory and working memory. Impairments in speed of processing and executive functioning have also been observed across studies. Regarding potential residual effects of cannabis on cognition, deficits are typically mild to moderate, and most probably reversible. These conclusions may be misleading, however, considering that cross-sectional studies on cannabis have mostly focused on use rather than CUD. High-quality longitudinal studies have shown that cannabis use is mostly associated with deficits in verbal learning and executive functioning. The effects of cannabis on cognition have led investigators to identify the neural mechanisms underlying harmful effects. As reviewed by Morie and Potenza functional magnetic resonance imaging studies on executive functions demonstrate that cannabis use is associated with alterations in activity in frontal and cingulate regions; however, results are heterogeneous, and it remains to be determined if alterations are primary or secondary to cannabis use. Compared to *recreational* cannabis use, much less is known about the cognitive effects of cannabis use for *medical* purposes. To address this issue, Eadie et al. performed a scoping review of trials involving patients with neuropathic pain who were treated with smoked, vaporized or sublingual THC. The evidence indicated a cognitive decline among THC patients, mostly in a dose-dependent manner. However, the cognitive differences between THC and placebo groups were no longer different after 4 h of recovery. In theory, several factors may influence this general trend, including THC dose, the route of THC administration, interactions of THC with other drugs, CBD content and tolerance to THC, genetic

factors and comorbidities. Their respective roles will need to be determined in future studies examining the cognitive effects of medical cannabinoids.

Among its acute effects, cannabis/THC impairs driving-relevant cognitive functions, including distance estimation, reaction time, vigilance, and processing speed. Likewise, most experimental studies reviewed Pearlson et al. show that acute cannabis/THC intoxication significantly impairs driving abilities, as measured in the laboratory. Meta-analyses have also shown that acute cannabis consumption increases the likelihood of motor vehicle accidents. The risk is not as elevated as in the case of alcohol; however, the combination of cannabis and alcohol seems to be particularly harmful. Increased frequencies of driving under the influence have been reported in some jurisdictions having legalized cannabis. As individuals consume cannabis products with higher potencies, it is reasonable to expect that more cannabis-related motor vehicle crashes will occur. The association between cannabis use and motor vehicle accidents is a major public health concern, since no reliable detection method of cannabis intoxication is available. THC is highly lipophilic, and as a result, serum or plasma THC levels do not predict well performance impairment. Current initiatives on new cannabis detection methods are discussed. Notwithstanding the growing diversification of cannabis forms and their routes of administration, the impact of these cannabis products on driving abilities has been understudied. This is the case, among others, of THC concentrates (e.g., dab, wax, shatter) which usually contain very high levels of THC. In an uncontrolled experimental study involving 65 individuals experienced in the use of concentrates, Hitchcock et al. sought to investigate this question. Using a mobile laboratory to measure motor abilities required for driving, participants were invited to use cannabis concentrates *ad-libitum*. Results showed that motor performance was impaired immediately after (e.g., arm speed and balance) and 1 h after (e.g., arm speed and leg speed) use of cannabis concentrates. These results highlight that cannabis concentrate use impairs driving-relevant motor abilities and raise significant issues regarding intoxication detection, particularly as THC plasma levels did not correlate with motor performance.

As observed by Matheson and Le Foll, there are scarce data on the harms of newer and/or more potent cannabis products, such as edibles, oils, concentrates, topicals and sprays. As legalization without restrictions may be as harmful to public health as prohibition, the authors propose to implement, in cannabis legalization models, (i) robust data collection to monitor harms associated with new cannabis products; (ii) early restrictions on cannabis edibles and high-potency products until safety data are gathered; and (iii) proper labeling of these cannabis products to clearly communicate dose information and health risks. As voiced by Crocker et al., another area requiring further research relates to the risk of emergency department (ED) visits. Although preliminary, an increase in cannabis-related ED visits has been described in Colorado, Nevada and Canada after cannabis legalization. Mental adverse events precipitating ED presentations include anxiety, agitation, suicidal thoughts and psychotic symptoms.

Together, the articles in this topic cover a broad range of considerations relating to the legalization of cannabis for recreational and medical purposes. As multiple jurisdictions progress with such legalization, appropriate support for research, prevention, treatment and policy initiatives should be made available to promote the public health.

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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REVIEW
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Violence and Cannabis Use: A Focused Review of a Forgotten Aspect in the Era of Liberalizing Cannabis

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There has been a shift surrounding societal and legal perspectives on cannabis reflecting changing public attitudes towards the perceived safety and social acceptability of cannabis use. With cannabis liberalization internationally, the focus of most cannabis-related harms has been on effects with users themselves. Harm-to-others including injuries from violence have nevertheless been unfortunately largely overlooked. While studies remain heterogeneous, there is meta-analytical evidence pointing towards an association. The aims of this focused review are two-fold: (I) review the evidence from meta-analyses on the association between cannabis and violence; and (II) provide an overview of possible mechanisms relating cannabis use to violence. First, evidence from meta-analytical studies in youths, intimate partners, and individuals with severe mental disorders have shown that there is a global moderate association between cannabis use and violence, which is stronger in the latter more at-risk population. Preliminary data has even highlighted a potential dose-response relationship with larger effects in more frequent users. Although of importance, this subject has remained essentially forgotten as a public health concern. While literature remains inconclusive, data has suggested potential increases in cannabis use following liberalization policies. This may increase violent outcomes if the effect is directly related to the use of cannabis by means of its psychophysiological modifications. However, for the moment, the mechanisms associating cannabis use and violence remain to be clearly resolved. Considering the recency of policy changes on cannabis, further methodologically sound research using longitudinal designs should examine the effects that cannabis use may have on different forms of violence and the trends that emerge, while evaluating the effects of possible confounding factors (e.g. other substance use). In addition, as evidence-based research from meta-analyses have shown that cannabis use is associated with violence, measures must be taken to mitigate the risks.

Keywords: cannabis use, violence, meta-analyses, legalization, public health

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INTRODUCTION

Worldwide populational data shows that roughly 200 million individuals have used cannabis in the past year (1) and 13 million have a cannabis use disorder (CUD) (2). In recent years, there has been a shift surrounding societal and legal perspectives on cannabis reflecting changing public attitudes towards the perceived safety and social acceptability of its use (3). There is thus a growing number of U.S. states (e.g. Washington, Colorado) and countries (e.g. Portugal, Canada, Netherlands) that have liberalized their cannabis laws by decriminalizing (i.e. lessening the penalties for cannabis offenses) or legalizing its use for medical or recreational purposes (3, 4). Following these policy changes, although literature remains inconclusive and very preliminary with some studies having found no effect, there is some evidence that has also suggested a certain increase of cannabis use in some age groups such as young adults and older adult populations (4–7). Some data likewise suggested changes in frequency of use following recreational cannabis legalization in the U.S. with findings showing a small increase in adolescent CUD and increases in past-month cannabis use, past-month frequent cannabis use, and past-year CUD among adults over 26 years (8). Of note, studies, furthermore, suggest that cannabis has grown more potent as measured by the proportion of Δ^9-tetrahydrocannabinol (THC) content in relation to cannabidiol (CBD) content (THC to CBD ratio) (9, 10). Accordingly, with policy changes, there has been increased attention into cannabis-related harms such as motor vehicle accidents, emergency medical attendances and hospitalizations, severe mental disorders (SMD) as well as suicides (1, 7). Harm-to-others including injuries from violence have nevertheless been unfortunately largely overlooked (11).

Violence is a complex and multifactorial issue that has serious health and social consequences (12). The association between cannabis and violence has created a range of debates. Although studies remain heterogeneous [i.e. (13–20)], there is meta-analytical evidence pointing towards an association. Particularly with liberalization policies aiming for public health and safety while using cannabis, harm-to-others should constitute an essential element for outcome monitoring (7, 11). The aims of this focused review are two-fold: (I) review evidence from meta-analyses on the association between cannabis and violence; and (II) provide an overview of possible mechanisms relating cannabis use to violence.

REVIEWING EVIDENCE ON THE CANNABIS-VIOLENCE ASSOCIATION

Meta-Analytical Evidence

Our team conducted a systematic search of literature in the online databases of PubMed, PsycINFO, Web of Science and Google Scholar to identify all relevant research reporting on the cannabis-violence relationship with no restriction as to the type of population being investigated. Additional records were identified through cross-referencing. Searches used key words that were inclusive for violence [e.g. (aggression, violent)] and cannabis use [e.g. (marijuana, cannabis)]. The search syntax was tailored for each database. No setting, date or geographical restrictions were applied. Searches were limited to English and French language sources and meta-analytical study designs. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for the inclusion of meta-analyses within this review is found in **Figure 1**.

Below is a description of findings from meta-analyses in (i) youths and emerging adults, (ii) intimate partners, and (iii) individuals with SMD. To ensure clarity, the following qualitative descriptions of the strength of reported effects were used for (i) Odds Ratio [OR (21); small = 1.0–1.5, moderate = 1.6–2.5, strong = 2.6–9.9, and very strong = ≥ 10.0] and (ii) Cohen's d [d (22); small = 0.2, medium = 0.5, and large = > 0.8].

Youths and Emerging Adults

Our team chose to conduct a meta-analysis to clarify the association between cannabis use and violence, more precisely, the perpetration of any type of physical violence by adolescents and young adults (23). Studies were included so long as the behaviors being reported comprised acts of physical violence (e.g. aggravated assault, sexual aggression, fighting, robbery). Studies were excluded if the definition of violence was unclear or included other types of behaviors (e.g. delinquency, verbal aggression, victimization, suicidality). As for cannabis use, all types of frequency measures (e.g. lifetime, occasional, frequent use) were extracted to examine a potential "*dose-response*" relationship in our sub-analyses. Based on this meta-analysis of 30 study arms, a moderate association between cannabis use and the perpetration of physical violence was observed [OR = 2.11, Confidence interval (CI) = 1.64–2.72]. This emerged from studies amounting from a large sample of 296,815 adolescents and young adults and showing no publication bias. It is, however, important to note that there was a high level of heterogeneity between studies, which may be due to the heterogeneous methods used in studies to measure and define physical violence. A challenge in the interpretation of findings is to rule out alternative explanations on the association itself and its direction, which this meta-analysis has attempted to do with the sub-analyses. First, preliminary findings on the effects of frequency do suggest a potential dose-response relationship, while mostly driven by two studies reporting high ORs (24, 25). More specifically, frequent, persistent and long-term users (i.e. early onset cannabis users) have been shown to experience more mental health and behavioral problems, such as aggression and delinquency (25–28). Beyond frequency of use, current studies did not conduct a detailed assessment of cannabis exposure/usage patterns (e.g. type of cannabis, number of joints, dosage, cannabis potency) (29), which may differentially be associated with violence. Second, the effect remained significant when considering studies additionally adjusting for several covariates including sociodemographic variables and other important confounding factors that may have better explained the relationship (e.g. other substance use such as alcohol, stimulants, conduct problems or psychopathic traits and prior violence) (30). Importantly, results showed that the effect size estimates did not differ substantially between studies that controlled for confounders versus those that did not (OR = 2.01 and OR = 2.62, respectively), meaning that the association is unlikely to be fully explained by

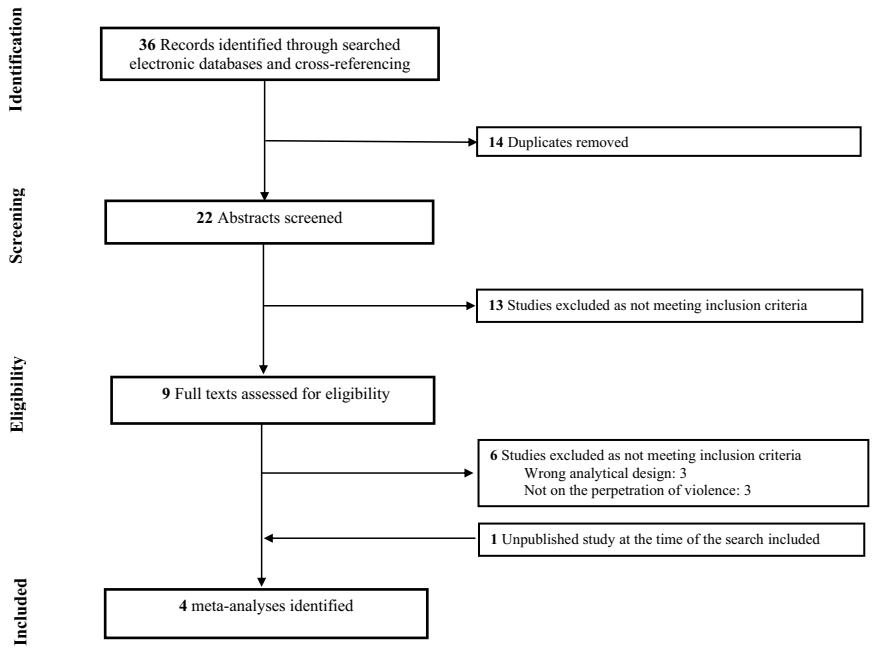

FIGURE 1 | Flow-chart depicting the search strategy employed to find the meta-analyses included in this review.

confounders. Third, concerning the directionality of the association, we performed a sub-analysis with available data specifically from longitudinal studies and findings showed that cannabis use during adolescence may indeed lead individuals to perpetrate physical violence in early adulthood (OR = 2.02). Of note, the results from longitudinal studies may also be attributed to reverse causality (31, 32). A limited number of authors have indeed reported findings consistent with reverse causality suggesting that physical violence in adolescents and young adults may increase the risk of initiating the use of cannabis later in life (27, 31–33). This still needs further investigation.

Intimate Partners

Physical dating violence perpetration is an example of a behavioral problem that could be influenced by cannabis use in youths as well as in adults. A meta-analysis by Johnson et al. (34) focused on U.S. adolescents and emerging adults aged 11 to 21 and defined physical dating violence as any non-sexual physically aggressive behavior among current or former romantic, sexual/intimate or dating partners. They retrieved 11 studies with six on adolescents and five on emerging adults, which provided evidence for an association between cannabis use and violence perpetration. Globally, there was a 45% increase in the odds of perpetration (OR = 1.45, CI = 1.20–1.76) in cannabis users. As observed in the meta-analysis above, there was minimal evidence of publication bias, but a substantial amount of heterogeneity between studies. As stated by the authors of the meta-analysis, this was mostly the case of five included studies with methodological differences focusing on emerging adults. In comparison to adolescent literature, these latter studies comprised heterogeneous samples (e.g. 60% on college students, at least 70% Caucasians), a variety of study designs (e.g. cross-sectional, longitudinal, daily diary) and most adjusted for alcohol use. Another review by Moore et al. (35) quantitatively evaluated the empirical evidence on the relationship between several types of drugs, including cannabis, and partner aggression perpetration (psychological aggression, physical abuse, sexual coercion/abuse, and mixed forms) in a variety of populations (e.g. substance abuse treatment facilities, community samples). In the 15 studies retrieved for cannabis use, a small effect size (d = 0.22, CI = 0.21–0.28) was found for all types of interpersonal violence including psychological, physical, sexual abuse, and mixed. Effect sizes were larger for psychological aggression broadly defined (d = 0.35, CI = 0.19–0.50), and physical aggression (d = 0.21, CI = 0.14–0.27) in comparison to other forms of aggression. Notably, men's use of cannabis was positively related to the perpetration of aggression. This study found that the relationship between cannabis use and intimate partner aggression was stable and reflected little variability in the effect sizes across studies. While both these meta-analyses found a positive association between cannabis use and violence, unfortunately, with the limited studies included, they did not conduct supplementary sub-analyses to further examine the direction of the association.

Individuals With Severe Mental Disorders

We conducted a meta-analysis to examine the association between cannabis use/misuse and the perpetration of violence in adult

individuals with SMD (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, bipolar disorder, and major depression) (36). Notably, these individuals are already at an elevated risk of violence in comparison to the general population (37, 38). To be as inclusive as possible, studies were not restricted so long as they evaluated any type of violence/aggression by any means such as clinical observation and self-reports. The meta-analysis included 12 final articles amounting to a total of 3,873 subjects. Results showed a moderate association between cannabis use and violence in individuals with SMD (OR = 3.02, CI = 2.01–4.54). As observed in the other meta-analyses, there was no publication bias, however, the database was characterized by high heterogeneity. This may partly be due to the studies displaying a variety of definitions for violence and assessment methods. Importantly, to determine whether other factors may have modified the effect, we also conducted sub-analyses. When considering adjusted studies only, the effect was slightly smaller, but remained significant (OR = 2.82, CI = 1.89–4.23). The four studies adjusted for several factors including sociodemographic variables and other confounding factors such as substance use and presence of psychiatric disorders. Of clinical interest, the association was significantly higher for cannabis misuse in comparison to cannabis use (OR = 5.8, CI = 3.27–10.28 versus OR = 2.04, CI = 1.36–3.05). In contrast to our meta-analysis in youths, this frequency association was not driven by any individual studies. Beyond frequency of use, it was not possible to examine other cannabis exposure patterns (e.g. type of cannabis, dosage, potency). Moreover, since most data was cross-sectional and retrospective, evidence was limited as a basis for concluding on the direction of the association. Longitudinal studies examining the association between cannabis use and violent behavior in patients with SMD are critically needed.

Summary: Public health significance of evidence

- There is a *moderate* association between cannabis use and physical violence in youths and emerging adults, with a potential *dose-response* association. Moreover, longitudinal evidence suggests that cannabis use may lead to future violent outbursts.
- There is a *small to moderate* association between cannabis use/misuse and intimate partner aggression perpetration.
- There is a *moderate* association between cannabis use and violence in populations with severe mental disorders, with a significant increase for frequent users or those with a cannabis use disorder.
- Evidence highlights that violence should be an *important indicator to monitor* considering recent cannabis liberalizations in several countries.

OVERVIEW OF POTENTIAL MECHANISMS EXPLAINING VIOLENT BEHAVIOR AND THE POTENTIAL IMPACT WITH CANNABIS LEGALIZATION

Harm-to-others such as violence constitutes an essential outcome to monitor in a public health perspective (7, 11). There are two main positions that have prevailed as to the consequence cannabis use policies might have on violence outcomes that depends chiefly on the impact these policies have on cannabis use as well as the mechanism by which cannabis and violence are associated (e.g. psychophysiological effects versus social context described below). Hence, although literature remains inconclusive, it has been hypothesized that there may be an increase in the number of cannabis users following the legalization of medical and recreational cannabis more particularly for adult samples (4–7, 39). Accordingly, for illustrative purposes, considering an expected increase of cannabis use:

i. A rise in the rate of violence may be observed if the mechanisms involved is psychophysiological (e.g. increase of aggression-related effects while intoxicated or during withdrawal) Or
ii. A reduction in the risk of violence may be observed if the mechanisms involved is social (e.g. reduction of black-market-, gang-related violence).

The following describes both these mechanisms and briefly explores the support for these mechanisms from literature on the legalization of recreational cannabis in the U.S. Markedly, the first four states to legalize cannabis for recreational use were Colorado and Washington in 2014 and Alaska and Oregon in 2015.

Psychophysiological Mechanisms

From a neurobiological perspective, cannabinoid receptors, CB-1 and CB-2, bind endogenous ligands, primarily anandamide and 2-arachidonoylglycerol to modulate neural activity (40). Amid receptors, CB-1 receptors are the predominant cannabinoid receptor type within the central nervous system and have been shown to mediate the effects of exogenous cannabinoids (41, 42). The main active ingredient in cannabis, THC, acts as a partial agonist for CB-1 receptors in the brain (43). With a lower efficacy than at CB-1 receptors, THC also demonstrates partial agonist properties for CB-2 receptors (44). CB-1 receptors are abundant in several cerebral regions, such as the cerebellum, basal ganglia, cingulate cortex, amygdala, hippocampus and frontal cortex that participate in several functions (e.g. executive, emotional, reward, and memory processing) (40, 45). Such brain function modulation occurs *via* direct interactions with the endocannabinoid system and indirect effects on neurotransmitter systems including the glutamatergic, GABAergic and dopaminergic systems (40, 45). Animal studies have shown that THC produces morphological changes (e.g. reductions in synapses, cell body size and dendritic length) in these brain regions with high CB-1 receptor expression (46–50).

Animal studies have found that THC produces complex effects on aggression. Indeed, animal studies have not produced clear-cut results, as both anti-aggressive as well as aggressive-inducing effects of THC have been documented [see (51–53) for reviews]. Discrepant results are likely related to several laboratory factors with the dose, delivery of administration and concurrent environmental manipulations being prominent aspects to consider. Based on a review of animal studies (52), it

has been generally found that studies using smaller doses of THC/cannabis have been less likely to report the emergence of aggression, whereas studies using higher doses and more chronic exposure have rather led to an increase in aggressiveness. Such dose-dependent effects on aggression have been stated to be due to the fact that CB-1 agonists at low doses may increase serotonin (a key neurotransmitter system derived mainly from dorsal and medial raphe involved in aggression control), while at higher doses, they may induce a decrease of serotonin, thereby increasing aggression (54). In addition, experiments with genetically modified animal models, such as mice, lacking CB-1 receptors (CB-1KO) have also revealed alterations in the regulation of emotion and aggressive behaviors (55). For instance, CB-1KO mice exhibited stronger aggressive responses than wild-type mice when exposed to social interaction tests (56, 57). This may be explained by differences in serotonin that were observed in CB-1KO mice. While they appeared to better metabolize serotonin due to an increase in catechol-O-methyltransferase levels in the raphe nucleus and amygdala, gene expression of monoamine oxidase-A was also augmented in the amygdala, which may have reduced serotonin levels leading to increased aggressiveness (57). This supports the role of CB-1 receptors in aggressive behaviors. In all, animal models are necessary since they allow to generate hypotheses and may provide some parallels to aggression in humans (53). Although such findings on animal studies in controlled laboratory environments do not necessarily translate to human studies, they provide evidence of a relationship between CB-1 receptor and aggressive states.

Similar to animal models, alterations in brain regions have been observed in human studies, particularly in CB-1 receptor rich areas mediating not only executive and cognitive functions, but also emotional and affective processing [see (58) for a review]. These alterations in humans may lead to aggressive tendencies. While functional imaging studies on aggression as an outcome per se in association to cannabis use are lacking in human literature, changes observed in key regions involved in emotional processing such as the amygdala and the anterior cingulate cortex may be relevant to the regulation of negative emotions such as anger and hostility. Several studies have indeed found that acute cannabis use may alter the activity of these regions when presented with stimuli of negative valence, notably threatening stimuli (e.g. fearful and angry valence) (59–65). For instance, it was found that inhaling 6 mg of THC impaired task performance for matching emotional faces with negative emotional content, but not those with positive content (59). While processing stimuli with a negative emotional content, there was a reduction in neural activity in a network of brain regions including the amygdala, orbitofrontal gyrus, hippocampus, and prefrontal cortex. A further study showed that THC reduced the functional coupling between the basolateral amygdala with the rostral anterior cingulate cortex and the superficial amygdala with the medial prefrontal cortex (62). It is worth noting that the net effects of orally administered THC and CBD on amygdala activation during the processing of fearful faces have shown to be in the opposite direction (64). Further evidence of emotion dysregulation after chronic cannabis use is provided in functional imaging studies (66–70). Reductions in response within the cingulate, frontal cortex, and the amygdala during the presentation of negative emotional stimuli have been observed in literature on chronic cannabis use (68, 70). While passively exposed to negative and neutral valence pictures, negative emotional stimuli produced hypoconnectivity between the amygdala and dorsolateral prefrontal cortex in active users and orbitofronto-striatal and amygdala hyper-connectivity following 28 days of abstinence (67). Overall, cannabis users appear to process emotional stimuli differently in comparison to non-users and this may explain their impairment in the recognition of affect (68). Therefore, neutral stimuli can attain emotional/affective salience during the use of cannabis (71). Deficits in emotion recognition have been associated with violence (72, 73) and thus cannabis use inducing such impairments may increase the risk of violent acts. At the moment, the potential association between cannabis-induced changes in neural functioning and violent behavior in humans remains speculative, and future fMRI studies will need to directly measure levels of irritability and/or aggressiveness in cannabis users to determine if there is an association or not.

Compared to the general adult population, youths are particularly vulnerable to the neural effects of cannabis that is worthy of discussion. Preclinical studies have evidenced that the endocannabinoid system matures slowly during development, with maximal CB-1 receptor abundance achieved during adolescence, and that this system plays a key role in neural refinement during adolescence (74). More precisely, it has been shown that the chronic activation of CB-1 receptors by exogenous cannabinoids during adolescence could disrupt the maturation of GABAergic interneurons in the prefrontal cortex and disrupts the GABA-glutamate balance (75, 76). As a result, youths may be more vulnerable to the adverse consequences of cannabis use. In human literature, reviews have concluded that frequent cannabis use in adolescents and young adults is associated with anomalies in brain structure, including alterations in the basal ganglia, hippocampus, amygdala, cerebellum, cingulate cortex, and prefrontal cortex (58, 77–79). The findings suggest that earlier initiation of cannabis use is associated with more prominent alterations (79). Thus far, the most consistent alterations produced by cannabis use, mostly its chronic use, during youth have been observed in the prefrontal cortex. Such alterations may potentially lead to a long-term disruption of cognitive and executive functions (80). Interestingly, early and frequent cannabis use in adolescence predicts poor cognition and even emotional processing in adulthood (81), which may increase the likelihood of aggressiveness later in life. There are indeed indications that continued exposure to cannabis in youths is associated with a higher risk of subsequent violent behavior in later adulthood (27).

At the behavioral level, both acute and chronic cannabis intoxication may (i) impair neurocognitive domains (e.g. executive functioning) and create perceptional distortions (e.g. interpreting neutral actions as aggressive), (ii) impair a user's ability to suppress aggressiveness, (iii) heighten physiological arousal making users feel paranoid, anxious or panicky (35). Withdrawal symptoms, which are reported by up to a third of regular users are of clinical significance as they can be impairing

and associated with trouble ceasing use (82). These symptoms typically onset within 24 to 48 h following abrupt cessation in frequent users and contribute to irritability, restlessness, and anxiety that may likewise be associated with aggression (35, 83). These effects apply to psychiatric samples such as those with SMD as well. Both the acute intoxication and chronic use, in addition to the effects stated above, may lead to poor clinical outcomes and interfere with treatment by worsening and promoting psychiatric symptoms (84–86). Early regular and frequent cannabis use has been shown to be associated with onset of psychosis and worsens the course of the disorders (87, 88). Moreover, cannabis use may exacerbate psychotic symptoms such as delusions, which, in combination with the intoxicating effects of cannabis, may increase the risk of violence (13, 35). It is essential to note that individuals with SMD are also more likely to use cannabis and have comorbid substance use disorders in comparison to the general population (5, 89–93). This may reflect an attempt to cope with psychological distress (e.g. negative affective symptoms) or relieve the side effects of medication (e.g. antipsychotics) through cannabis use (e.g. self-medication) (94). Given the risks of continued substance use, it is important to identify the emergence of problematic use even more so as this population is at an increased risk of exhibiting aggressive behavior (37, 38). Lastly, distal influences (e.g. psychiatric disorders, childhood abuse, history of substance use) in concurrence with proximal factors (e.g. acute intoxication, impulsivity, emotional reactivity, encounter setting) may help to explain the increase in the risk for aggression when in the context of a conflictual interaction (35, 95). For example, cannabis intoxication in individuals with stable personality traits such as hostility and callousness may lead them to act aggressively when triggered in a fight. Although, it is worth noting that it is not only the psychophysiological effects of cannabis use per se that might induce violence, but also factors associated with substance use in general. As an example, the use of substances and related environments may lead to relational frictions, thereby increasing the chances of violence in conflictual circumstances (35).

Support From Cannabis Legalization Literature

A few scholars have recently found results showing that legalizing recreational cannabis may increase violence. Hughes et al. (96) assessed the relationship between both medical as well as recreational cannabis dispensaries and yearly neighborhood crime in Denver between 2012 and 2015, including the two-year period immediately following commencement of legal retail sales in January 2014. This was examined by controlling for correlates of neighborhood crime, including socioeconomic disadvantage and the concentration of high-risk commercial establishments. The authors found that the presence of at least one medical/recreational cannabis dispensary was associated with a statistically significant increase in neighborhood crime (e.g. robbery and aggravated assault). At the state-level, Lu et al. (97), comparing rates of crime in Washington and Colorado to states not legalizing cannabis, found some immediate increases in crime at the point of recreational legalization. Moreover, Lin et al. (98) conducted a non-peer reviewed quasi-experimental difference-in-difference analysis to study the potential effect of cannabis use on domestic violence by exploiting municipal and temporal variations in the enactment of recreational cannabis laws in Denver-Aurora-Lakewood Metropolitan Statistical Area from 2011 to 2016. They found that the enactment of recreational cannabis laws in 2014 led to a substantial increase in domestic violence. Denver and Aurora experienced a 48.2% increase in domestic violence rate as compared to their two control cities. Since the legal age to procure recreational marijuana is 21 years old, they even observed that the effect was only significant for perpetrators over that age. The effect was significant across gender and ethnic groups. As for offence severity, the effect concentrated for categories of simple assault, intimidation, minor injury, and no injury. As alcohol interacts with cannabis use, the authors found that the main findings were not driven by co-use of alcohol and cannabis.

Social Mechanism

Supplementary explanations relate to the interaction between people and their social environments specifically. In jurisdictions where cannabis is illegal, users may obtain cannabis in the black market, thereby potentially exposing individuals to the risk of violence (99). The association between cannabis use and violence perpetration could be more broadly situational. For instance, selling or purchasing cannabis may promote criminal behavior for economic motives or to sustain substance use behaviors. While this may seem less relevant for intimate partners, relationships could be placed at risk of intimate partner aggression by supporting a habit related to use (e.g. stealing money) or by means of procuring a substance (e.g. forcing a partner to obtain a substance) (95). Aggressive tendencies may also occur within the broader system of drug use within the black-market (e.g. disputes over neglecting to pay debts) (95, 100). Legalizing recreational cannabis would ensure that citizens can procure the substance in places not governed by organized crime. Consequently, consumers would be less likely exposed to violent/criminal lifestyles.

Support From Cannabis Legalization Literature

Further analyses of recreational law reforms may best demonstrate whether eliminating the cannabis black-market might affect violent and property crime. Research has therefore also found support for the claim that legalizing recreational cannabis may reduce violent outcomes. Brinkman et al. (101) observed reductions on crime rates in geographical proximity to cannabis dispensaries in Colorado. There were no significant effects in crime on neighboring dispensary density. They found that a supplementary dispensary in a neighborhood led to a decline of 17 crimes per month per 10,000 citizens. This finding corresponded to a nearly 19% reduction in relation to the typical crime rate. The effect was generally stronger for nonviolent crimes (e.g. criminal trespassing, public-order crimes, criminal mischief, and simple assault). Dragone et al. (102) further examined crime rates from 2010 to 2014 in counties along the Washington-Oregon border before and after legalization in Washington. They used a quasi-experiment research design that combined a difference-in-difference design (where Washington acted as the treatment group, Oregon as the control group, 2010–2012 was the pre-legalization period and

2013–2014 was the post-legalization period) and spatial regression discontinuity designs (where the border marked a discontinuity in the legal status of cannabis in 2013–2014). The authors noted significant drops in rape and property crime in Washington side counties relative to Oregon-side counties. The study by Lin et al. (98) did find reductions in high gang-related crimes including aggravated assault and robbery, supporting the social mechanism as well. Moreover, Lu et al. (97) used a quasi-experimental, multi-group interrupted time-series design to examine crime rates in Colorado and Washington and determine if and how these rates were influenced by the legalization of recreational cannabis in 2012 and the beginning of retail sales in 2014. This study suggested that cannabis laws more broadly, and the legalization of recreational cannabis, have had minimal effects on major crime. While there were some short-term increases as stated in the section above, these did not result in long-term effects. They observed no statistically significant long-term effects apart from a significant decrease of burglary in Washington.

Summary of Findings

Overall, there is evidence demonstrating an increase as well as a decline in general criminality/violence following the legalization of recreational cannabis, thus supporting both mechanisms. Under the first paradigm, research reinforces that legalizing cannabis policies may be expected to show a potential increase in cannabis use (while literature remains inconclusive in this regard) and may alter some users' behavior, thereby increasing aggression. Under the second paradigm, the underground cannabis market intertwined with criminality is expected to diminish as the cannabis market becomes legalized. It may be possible that both a rise and reduction in different violent outcomes may emerge following cannabis legalization since both the psychophysiological and social effects can occur simultaneously as has been observed in the study by Lin et al. (98). The limited literature on policy changes have therefore not elucidated the mechanisms associating cannabis use and violence since the studies have been conducted in various settings and have used a variety of methodologies (i.e., quasi-experimental difference-in-difference analysis, quasi-experimental, multi-group interrupted time-series design). Globally, supporting studies for both paradigms have assessed how crime is related to the density of cannabis outlets or they have examined state-level changes. Using more rigorous methodologies, some authors have also considered pre-legalization trends in their analyses and controlled for confounding factors, providing better quality evidence for both mechanisms. More thorough investigations are still warranted.

DISCUSSION

Considering international cannabis policy changes, this focused review aimed to revise the evidence on the association between cannabis use and violence as well as to examine the potential mechanisms involved. Available evidence from meta-analytical studies in youths, intimate partners, and individuals with SMD have shown that there is a global moderate association between cannabis use and violence, which may be stronger in the latter more at-risk population. Though, not only is any type of use of cannabis associated with violence, but preliminary data has highlighted a potential dose-response relationship with larger effects in more frequent users. In this sense, the association between cannabis use and violence is not to be overlooked.

Of interest, positive associations between cannabis use and violence have also emerged in more recent studies following these meta-analyses. For instance, scholars have observed an association between cannabis and violence in intimate partners [e.g. (103–105)]. Our team conducted four additional studies to elucidate the association using more robust methodological strategies and well-known databases in youth populations from the Quebec Health Survey of High School Students (106) and Longitudinal Studies of Child Abuse and Neglect (107) as well as in samples with SMD from the MacArthur Violence Risk Assessment Study (108) and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (109). Beyond associational research, our studies using longitudinal designs were conducted in the aim to further understand the direction of the cannabis-violence association as solely few investigations have been carried out on the matter (27, 31, 33, 107–110). Our studies on psychiatric samples have supported the finding of a unidirectional association between cannabis use and violence (108, 109). In this regard, our research team has recently re-analyzed data from the NIHM-funded CATIE trial. In a sample of 965 patients followed for 12 months, a cross-lag model was implemented to examine the association between cannabis use and violent behavior. Results showed that persistent cannabis use predicted subsequent violent behavior, while the reverse relationship was not significant. Results remained significant after controlling for alcohol and stimulant use. As such, this analysis of longitudinal data showed a unidirectional association between cannabis and violence in schizophrenia (109). On the other hand, our study on adolescents also supported a reverse relationship, that is that externalizing behavior in youths may lead to the subsequent use of cannabis. Hence, using developmental joint trajectory models, it was found that higher levels of trait aggression at ages 10 to 16 were associated with cannabis use at 16–18 years old (107), which supported some scholars' claim that the association is bidirectional (27, 111). This highlights the importance of better understanding the direction of the association.

Although the mechanism associating cannabis and violence remains to be clearly resolved, a variety of strategies should be implemented in order to reduce the negative impacts of cannabis legalization (82). From a biological perspective, as CBD is more reliably associated to therapeutic properties (such as neuroleptic, relaxant and neuroprotective effects), increasing CBD content may prove to be a sustainable strategy to mitigate cannabis-induced harms (112). Nevertheless, the effects of CBD on violence remain unknown. From a social perspective, preventative measures and intervention programs on mental health and risk behavior should be implemented in school settings since youths remain predominantly susceptible to the detrimental effects of cannabis. They should be provided critical educational information for

decision-making and discouraged from initiating and adopting more chronic patterns of use (113). Awareness should be prioritized among professionals (e.g. social workers, educators, clinicians) who are in contact with more vulnerable or violence-prone populations. Professionals should take the necessary measures to further diffuse their knowledge through psychoeducation to their treating individuals. Markedly, efforts should be made to deter violence-prone populations from using cannabis. These at-risk populations include samples from forensic and carceral settings. Noteworthy, in comparison to other drugs, lifetime and regular cannabis use remains the highest drug of use in inmates and the highest drug at time of offence (114). In this sense, crime and substance misuse comprise public health issues for criminal offenders who are released from carceral settings. Interventions should ultimately aim to decrease post-release risky behavior (e.g. cannabis use) among inmates or forensic patients returning to the community (115). Mental health clinicians should screen their patients for cannabis use patterns and related adverse effects of aggression (82). Until a secure exposure pattern (e.g. quantity of cannabis, potency level) is determined by research, withholding from regularly using cannabis may be a better option in these at-risk and vulnerable populations. Moreover, evidence-based treatments and interventions, such as contingency management, relapse prevention, motivational interviewing, and cognitive behavioral therapy showing promising results (116), should be offered to those with problematic cannabis use.

LIMITATIONS

Albeit the important contributions brought forth by the current literature, several limitations must be acknowledged. Upon reviewing the limited available evidence, one important discrepancy involves the heterogeneity among studies. For instance, studies used heterogeneous methods to measure and define violence. Accordingly, it becomes difficult to ascertain whether different constructs of violence were investigated. Further examinations into the essence of the construct should be considered for future research. Of importance, it is necessary to better understand the direction of the cannabis-violence association. In this regard, longitudinal studies should further investigate the direction of the association. Regarding the literature pertaining to policy changes, particularly for recreational cannabis, the vast heterogeneity surrounding study methodologies restrict our ability to precisely evaluate the mechanism associating cannabis and violence. A further predominant limitation in the literature regard the assessment of cannabis exposure/use patterns, such as the type of product consumed (edible, joint, beverages), number of products consumed, dosage, frequency, and THC to CBD ratio, which limits our ability to accurately determine how THC may be associated with violent tendencies. This information in relation to violence will be particularly important to define in the context of public health strategies since legalization aims at the regulation of dosage and potency of the products. This is more so important as health promotion strategies enhance health literacy by providing reliable evidence-based research.

CONCLUSION

In all, evidence-based research from meta-analyses have indeed shown that cannabis is associated to violence and therefore measures should be taken to mitigate the risk. Nevertheless, there remains questions as to the direction of the association and the potential mechanisms involved, which may be answered with the changes observed following the liberalization of cannabis. Hence, biopsychosocial research should continue to monitor the association following policy changes more thoroughly by examining different types of violent outcomes. Research should account for trends before legalization and consider the profiles of individuals using cannabis before and after legalization. This methodological consideration has been lacking in most studies in the literature. Moreover, since meta-analytical evidence has found an association between cannabis use and violence in intimate partners, further data on post-liberalization prevalence for dating and intimate partner violence is warranted. Similarly, studies on the effects of cannabis policies in at-risk populations such as individuals with SMD and prisoners leaving carceral settings is necessary. Additional biological studies using neuroimaging, for instance, are currently needed to further shed light into the mechanisms associating cannabis and violence. If causation is established, it will be more so crucial to determine a specific type of exposure pattern (e.g. quantity of cannabis consumed or its potency level) that may be more associated to violent tendencies. For all these reasons and considering the recency of policy changes on cannabis, further methodologically-sound research using longitudinal designs should examine the effects that cannabis may have on different forms of violence and seek to evaluate the trends that emerge in different populations. This should be done while evaluating the effects of possible confounding factors (e.g. other substance use, psychopathic traits).

AUTHOR CONTRIBUTIONS

AD, LD, and SP contributed to study planning and design. LD and MA conducted the literature search. LD wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Cannabis Legalization and Acute Harm From High Potency Cannabis Products: A Narrative Review and Recommendations for Public Health

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Legalization and commercial sale of non-medical cannabis has led to increasing diversity and potency of cannabis products. Some of the American states that were the first to legalize have seen rises in acute harms associated with cannabis use, e.g. Colorado has seen increases in emergency department visits for cannabis-related acute psychological distress and severe vomiting (hyperemesis), as well as a number of high-profile deaths related to ingestion of high doses of cannabis edibles. Over-ingestion of cannabis is related to multiple factors, including the sale of cannabis products with high levels of THC and consumers' confusion regarding labelling of cannabis products, which disproportionately impact new or inexperienced users. Based on our review of the literature, we propose three approaches to minimizing acute harms: early restriction of cannabis edibles and high-potency products; clear and consistent labelling that communicates dose/serving size and health risks; and implementation of robust data collection frameworks to monitor harms, broken down by cannabis product type (e.g. dose, potency, route of administration) and consumer characteristics (e.g. age, sex, gender, ethnicity). Ongoing data collection and monitoring of harms in jurisdictions that have existing legal cannabis laws will be vital to understanding the impact of cannabis legalization and maximizing public health benefits.

Keywords: cannabis, legalization, acute harms, edibles, cannabis concentrates

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INTRODUCTION

Cannabis continues to be one of the most commonly used psychoactive drugs worldwide, with recent estimates from the United Nations Office on Drugs and Crime (UNODC) suggesting over 188 million past-year users in 2017 (1). Cannabis has remained an illicit drug under international drug control treaties (in particular, the 1961 UN Single Convention on Narcotic Drugs), yet critics have opposed the criminalization of cannabis for a multitude of reasons since at least the 1960s (2, 3). For example,

cannabis use is prevalent among young adults, yet is associated with less harm than licit drugs such as alcohol and tobacco (4, 5). Criminalization of cannabis use and possession has likely done more harm than good by exposing users to the criminal justice system (6), which has disproportionately affected disadvantaged minorities populations, especially Black and Hispanic communities (7). Legalizing cannabis has the potential to restore justice to by expunging arrests and by using taxes generated by the cannabis retail market to help rebuild these communities (7). Eliminating the illicit cannabis market would greatly reduce costs associated with policing of cannabis prohibition (6). Finally, having a legal retail market would allow for better control and regulation of cannabis products, e.g. by restricting access to youth and by protecting adult users from contaminants (e.g. fungi and heavy metals) and unsafe levels of Δ^9-tetrahydrocannabinol (THC) (6).

In 2012, Colorado and Washington became the first two US states to pass referenda to legalize possession and retail sales of non-medical cannabis, with retail sales available in 2014 (6). At the time of this writing, 11 US states and the District of Columbia have legalized non-medical use and sale of cannabis, though cannabis remains illegal federally. In 2013, Uruguay became the first country to legalize at the federal level, using a middle-ground approach that involved more restrictions than the US legal retail markets (8). This was followed by the October 2018 federal legalization in Canada, where a regulated retail market was implemented (9), with similar legislation planned in countries such as Luxembourg and Mexico.

While there is potential for a net beneficial effect of legalization of non-medical cannabis use, concerns have arisen regarding increasing public health harms. Due to challenges in conducting epidemiological research (e.g. because of the legal status of cannabis and that most cannabis users worldwide also smoke tobacco), the adverse physical health effects of cannabis remain largely uncertain (2). One consistent finding has been an association between heavy, long-term use of cannabis and respiratory problems such as chronic bronchitis (10, 11). Limited evidence suggests cannabis use may elevate risk of cardiovascular disease (12, 13) and possibly testicular cancer (14). Cannabis hyperemesis syndrome (CHS) has emerged recently as a significant risk of chronic cannabis use. CHS is described as a paradoxical side effect of cannabis use (since cannabis has anti-emetic effects), and is characterized by cyclical nausea, vomiting, and abdominal pain with no clear etiology (15), though is thought to be related to changes in the endocannabinoid system and subsequent dysregulation of stress and anxiety responses (16, 17).

The long-term psychological adverse effects of regular cannabis use have been much more clearly demonstrated, though establishing causality remains an issue (2, 6, 18). Decline in cognitive function resulting from regular, heavy cannabis use has been robustly demonstrated in cross-sectional studies, prompting concerns about impairments in psychosocial functioning and educational/vocational attainment (19–21). Since the late 1980's, at least a dozen prospective longitudinal studies have documented an association between cannabis use and increased risk of subsequent psychotic symptoms or illness (22). The association between cannabis and psychosis risk has been supported by compelling evidence from animal, human laboratory, and clinical studies (22–24). A subset of cannabis users will go on to develop a cannabis use disorder (CUD), which is an amalgamation of the diagnostic terms cannabis dependence and cannabis abuse that were used prior to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Early evidence in the US suggested that about 1 in 10 people who use cannabis will develop cannabis dependence, which is lower than the conversion rates for tobacco, alcohol, cocaine, or heroin (25). A recent meta-analysis of 21 epidemiological studies conducted between 2009 and 2019 found that the risk of CUD among people who used cannabis was 22% (26). In 2012, CUDs were determined to be the leading cause of cannabis-attributable burden of disease in Canada (27). Cannabis use has also been associated with increased risk or exacerbation of other mental health problems such as anxiety and depression, though the relationship between cannabis use and mental health is complex (18, 28).

Compared to the chronic or long-term harms associated with cannabis use, acute harms have received less attention. Due to acute effects on cognitive performance, cannabis use has been associated with increased risk of motor vehicle collisions (29). Road traffic injuries were the leading cause of cannabis-attributable mortality among Canadians aged 45 years or younger in 2012 (27). Cannabis is not associated with overdose mortality, which is likely due to low risk of respiratory depression as a result of low or absent expression of cannabinoid receptors in the brainstem (30). However, a small number of deaths from cardiovascular events (13) or from hyperemesis syndrome (31) have been attributed to cannabis. In addition, the psychological consequences of acute cannabis intoxication (e.g. psychosis, suicidality, impairment-related injuries) can lead to emergency department (ED) visits and hospitalizations (32). ED visits have been linked to so-called "unexpected highs" that can occur when individuals consume more cannabis than intended (33).

While these acute harms remain low compared to harms associated with alcohol and illicit drugs such as heroin and methamphetamine, the emergence of the legal cannabis retail market has the potential to increase harms by increasing the potency and diversity of cannabis products, encouraging existing users to increase their quantity and frequency of use, and attracting new users who are unfamiliar with cannabis and may unintentionally ingest large doses. Thus, in this review, we discuss the risk of an increase in acute cannabis-related harms as legal retail cannabis markets emerge and proliferate, and then provide recommendations to public health based on evidence from states and countries that have already legalized non-medical cannabis.

DIVERSIFICATION OF CANNABIS PRODUCTS AND THE POTENTIAL RISE IN ACUTE HARMS: A BRIEF REVIEW

As legal cannabis retail markets have emerged in the US, Canada, and Europe, the products available to consumers have changed dramatically over the past decade. Two particular changes have had the biggest impact: the increasing THC potency of cannabis and the diversity of cannabis products available.

One of the most important metrics of cannabis consumption is potency, which is typically quantified as the proportion of THC in a cannabis product. Cannabis potency estimates can also include levels of cannabidiol (CBD), a non-intoxicating cannabinoid that has been demonstrated to offset or reduce the negative impact of THC on anxiety, cognition, and psychotic symptoms (34, 35). While cannabis with higher proportions of THC is generally regarded as more harmful, increasing levels of CBD in cannabis may reduce harms (35). In 2012, a meta-analysis of 75 individual estimates of THC potency worldwide found a striking 10-fold increase in THC potency of dried plant material between 1970 and 2009 (36). In England, the potency of sinsemilla (unpollinated female flower) doubled between 1995 and 2005 (37), though did not change considerably between 2005 and 2016 (38). More recently, in the United States, mean THC potency increased from 8.9% in 2008 to 17.1% in 2017, while the THC:CBD ratio increased dramatically from 23 in 2008 to 104 in 2017 (39). In Europe, mean herbal cannabis potency increased from 5% in 2006 to 10% in 2016 (40). Recent estimates in the Canadian market suggest similar (or greater) increases in the potency of cannabis. For example, one study that tracked the potency of legal and illegal cannabis products for two months following the federal legalization of non-medical cannabis use found a mean THC concentration of 16.1% in the legal market and 20.5% in the illegal market (41). Given that the global mean THC potency of cannabis was approximately 1–2% just a few decades ago (36), the emergence of dried cannabis plant material with 20% THC or more presents a serious public health concern, especially in the absence of a proportional increase in CBD levels.

While smoking dried cannabis flower has historically been the dominant method of cannabis use, the emergence of a legal retail market has led to unprecedented diversification of cannabis products and formulations, driven by both increasing popularity of less common methods of use and the creation of entirely new products (42). An existing method of cannabis use that has been gaining popularity is the ingestion of cannabis edibles, which are typically desserts that use cannabis-infused oil in the baking process (43). In addition to traditional cannabis edibles (i.e., baked goods), other oral THC products such as THC-infused candies and other foodstuffs, oils, and tinctures have become common in legal retail markets (42). The use of edible cannabis products may be preferred by medical or non-medical users who do not want to be exposed to cannabis smoke (44), and edibles have been suggested to reduce the respiratory risks associated with combustible cannabis use (10). However, one major concern with the use of edibles is the delayed and often unpredictable onset and duration of psychotropic effects as a result of the slower absorption of THC into the systemic circulation (45, 46). A recent survey of adult past-year users of cannabis in Colorado found that use of edibles was associated with greater odds of experiencing an unexpected high (33). A second existing method of cannabis use rising in popularity is vaporized cannabis (42). Vaping devices typically operate at temperatures that do not combust the cannabis product, but rather aerosolize cannabinoids for inhalation, which likely exposes the user to fewer toxicants (42). However, concerns about vaping have arisen as a result of recent injuries and deaths associated with use of vaporizers, such as the series of 98 cases of lung injury in Wisconsin and Illinois documented in 2019 (47).

Several newer trends of cannabis use have emerged, such as the combustion and inhalation of cannabis concentrates (e.g. waxes, "dabs", and "shatter") (42, 48). These products often have very high concentrations of THC, are commonly used for their greater drug-induced "high", and have been associated with a number of acute harms (42). For example, "dabs" are concentrated extracts of hashish oil created using a butane solvent, while "dabbing" refers to the behavior of heating the extract on a device and inhaling the resulting vapor, often resulting in a very large and immediate dose of THC (49). The use of "dabs" has been associated with cases of acute psychosis, cardiotoxicity, and respiratory failure, though the exact causality remains unknown (49). The use of cannabis concentrates in vaporizers has been associated with increased risk of pulmonary injury and other acute harms (50). In addition to cannabis concentrates, a recent plethora of diverse products have emerged, such as topicals (lotions, balms, creams, etc.), sublingual sprays, and even rectal and vaginal suppositories (42). Very little is known about these new cannabis products. In addition to cannabis-derived products, synthetic cannabinoids have risen in popularity recently, which is concerning given their significant association with severe adverse health effects and deaths (51, 52). While these compounds are unlikely to be marketed along with cannabis products in a legal retail market, it will be important to monitor their use as attitudes toward cannabinoid products change.

Evidence in the US has demonstrated a relationship between specific provisions in legal cannabis laws (both medical and non-medical laws) and an increase in likelihood of using alternative methods of cannabis among youths, especially edibles and vaping (53, 54). Similarly, cannabis laws that permit home cultivation were found to increase the odds of individuals making cannabis edibles at home, while laws permitting cannabis dispensaries increased the odds of purchasing edibles (55).

The increase in potency and diversity of cannabis products is concerning as it challenges the generalizability of previous studies of acute cannabis-related harms. For example, the acute effects of THC in human laboratory studies are often dose-dependent (18, 19), yet research conducted in the United States is limited to using cannabis produced by the National Institute on Drug Abuse (NIDA), which was found to be nearly one quarter of the potency of cannabis available in retail markets (56). Similarly, the majority of placebo-controlled studies of acute effects have administered dried flower by the smoked route, while very few studies have assessed the effects of edibles, and virtually no controlled studies have assessed the acute effects of newer products like concentrates, tinctures, or oils (42). Epidemiological studies have also documented associations between higher-potency cannabis and increased risk of CUD (57) and psychosis (58), though specific associations with acute harms are less clear.

Data that allow for monitoring of changes in acute cannabis-related harms after the emergence of legal retail markets are scarce, as most jurisdictions have only a few years of data since legalization, and the scope and quality of data collection varies. Most evidence for rises in acute harms have relied on

hospitalization data. Colorado state in particular has a long history of liberalization of cannabis attitudes and legislation, which, along with wider availability of cannabis, has led to greater longitudinal availability of data to describe patterns in cannabis use and related harms (59). After legalization of non-medical cannabis use in 2012 and opening of retail sales in early 2014, Colorado saw significant evidence of increasing acute harms, including increases in cannabis-related ED visits and accidental poisonings in young children, as well as a handful of deaths related to consumption of cannabis edibles (32, 59, 60).

A recent chart review of adult visits to a large academic hospital in Colorado between January 2012 and December 2016 found that gastrointestinal symptoms, acute intoxication, and psychiatric symptoms were the three most common reasons for cannabis-attributable visits to the ED (61). While visits attributable to inhaled cannabis were more common overall, visits attributable to edible cannabis were more likely to be a result of acute psychiatric symptoms and intoxication (61). Importantly, the number of ED visits at least partially attributable to cannabis significantly increased from 2012 to 2016 (62). Other ED data have similarly found increases in cannabis-attributable visits from pre- to post-legalization, especially relating to mental health (63, 64), and have specifically seen an increase in adolescent cannabis-related ED visits (65). There was a significant increase in the proportion of suicide victims who tested positive for cannabis, from 7.1% in 2004–2009 to 12.6% in 2010–2015 (32). An analysis of hospital admissions in Colorado between 2010 and 2014 found a significant increase in hospitalizations related to cyclical vomiting (66), suggesting an increase in CHS. Other data suggest an increase in the age of patients presenting with skull fractures following legalization (which was suggested to be a result of increased use of cannabis among older patients) (67), and an increase in detection of cannabis in patients presenting to Colorado hospitals with traumatic injuries (68). In addition, legalization of non-medical cannabis use in Colorado (but not Washington state) was associated with an increase in traffic fatalities (69).

Limited data on hospitalizations associated with cannabis are available in Canada as well. For example, data collected in the Canadian province of Alberta found an increase in cannabis-related ED presentations and calls to poison control between 2013 and 2019, shortly after the federal legalization of non-medical cannabis use (70). Furthermore, increases in CHS and unintentional ingestion of cannabis were documented over this period (70). Federal data collected as part of the electronic Canadian Hospitals Injury Reporting and Prevention Program (eCHIRPP) database found an overall 30.1% increase of cannabis-related cases between 2015 and 2018, though the overall rate of cannabis-related cases was relatively rare (71).

APPROACHES TO MINIMIZING ACUTE HARMS: RECOMMENDATIONS FOR PUBLIC HEALTH

One goal of cannabis legalization has been to prioritize public health by taking a harm reduction approach to regulating cannabis use (72), which conflicts with the prohibitionist model that has dominated cannabis legislation for decades (73). However, legalization without any restriction can be just as harmful to public health as prohibition (72, 73); thus, careful attention has to be paid to maximizing safety of the legal cannabis retail market. To this end, we highlight three specific areas relevant to minimizing acute harms that need to be considered when implementing cannabis legalization models: 1) early restriction of cannabis edibles and newer products for which less safety data are currently available; 2) proper labelling of cannabis products that clearly and consistently communicates dose/serving size information and health risks; and 3) a robust framework of data collection to monitor harms associated with cannabis use, which ideally should be broken down by consumer characteristics and product type to stratify risk.

Early Restriction of Edibles and High-Potency Cannabis Products

The acute harms associated with use of alternative cannabis products (i.e., other than dried flower) are less known, but increasing evidence has suggested these harms might be a significant public health issue. Survey data from Colorado found that both trying new cannabis products and using cannabis edibles were associated with greater odds of experiencing an unexpected high, and that unexpected highs often led to acute psychological harms such as paranoia, panic attacks, hallucinations, and ED visits (33). In the year or so after legalization, Colorado saw a 63% increase in cannabis-related poison center calls for children, which was largely due to accidental cannabis edible ingestion (59). Colorado also saw four high-profile deaths related to consumption of edibles that occurred shortly after the legal retail market opened (60), and accumulating evidence suggested that edibles contributed to increased rates of cannabis-related ED visits (59, 60, 74). As a result of these harms, Colorado created a task force to address safety issues related to use of cannabis edibles, which resulted in tighter regulations and stricter packaging requirements (74).

These data strongly argue in favor of restriction of sales of edible products. However, complete prohibition of edible cannabis would undermine the success of legalization, as edibles are popular products that are prevalent even in jurisdictions without legal cannabis laws (74). As a result, the data from both Colorado and Washington state favor early restriction of edibles and high-potency cannabis products; this gives time for the retail market to stabilize and for data collection systems to be implemented, allowing for increased safety when newer cannabis products are eventually legalized (74). In addition, as there currently exists very little data to judge risks associated with the use of many of these newer cannabis products, delaying their sales in legal markets can allow for more time to conduct proper placebo-controlled safety trials.

Proper Labelling of Products With Clear Information on Dose and Potential Harms

Evidence from multiple jurisdictions with a legal cannabis retail market has demonstrated that consumers often have very little

understanding of product labelling information (75). For example, data collected as part of an online cross-sectional survey conducted among youth and young adults in Canada in October 2017 found that participants had limited understanding of quantitative THC labelling (76). In Canada, THC dose information is currently presented in a way that is likely confusing to consumers, i.e. displaying a "total THC amount" that includes both THC and its inactive acid precursor THCA, as well as a "THC amount" that excludes THCA (75). Another study that conducted focus groups in Colorado and Washington states in February 2016 found that consumers had limited familiarity with labels on edible products, and had difficulty interpreting doses expressed in mg (77). Confusion in Colorado state could come from the requirement to display a range of THC potencies to reflect variation in product testing (75). Consumers' understanding of dose information can be even poorer for other types of cannabis products, such as oils that are expressed as mg THC per mL volume, which require greater numeracy skills (75).

The difficulty that consumers have in interpreting labels is compounded by factors such as the diversification of products; the same "dose" of THC is not necessarily comparable across different routes of administration (42, 75). This suggests that "dose expression" information may be needed so that consumers can compare serving sizes across different cannabis products (75), though it should be noted that this may not be entirely perfect given substantive differences in the pharmacokinetics of THC across routes of administration such as inhaled and oral (45). In addition, there are often few visual cues that signal the strength or potency of cannabis products, especially in the case of edibles, where one edible product can contain one or 20 "doses" of THC (75). Focus groups in Colorado and Washington state have demonstrated that even experienced users of cannabis edibles often cannot predict the degree of intoxication associated with edible use (44), which is likely exacerbated by unclear labelling and ineffective communication of dose.

To address the concern of effective labelling and communication of THC doses, a recent commentary by Hammond (75) outlined five specific issues to be addressed: clear labelling of cannabis products that requires minimal numeracy to understand; standardization of doses (or servings) of cannabis that does not exceed the typical amount required to become intoxicated; clarity of dose expression on labels; packaging that reinforces label information (e.g. unit-dose packaging); and labelling that can provide comparison between different products, to the extent possible. Other reviews have similarly emphasized the need for clearer labelling of serving size and dose information (59, 74). Other packaging-related issues have been raised, such as the need for packaging that deters children and has clear universal symbols to indicate that a product contains cannabis (59), and the need for consistent product testing to ensure that dose and potency information on labels is accurate (59, 78) For example, one analysis of cannabinoid content reported by state-certified laboratories in Washington state found significant variability between testing facilities, with some facilities consistently reporting higher or lower cannabinoid concentrations, likely due to systematic differences in testing methodology (78). Universal testing standards are needed to standardize dose and potency information on cannabis product labels.

In addition to providing clear information about dose and serving sizes, labels should convey health messages to inform consumers of the risks associated with cannabis use. Results of focus groups and surveys have been promising in suggesting that current cannabis users react positively towards the inclusion of health labels on cannabis products, and that health labelling may be effective in changing health-related behaviors (77, 79–81). For example, data collected as part of a survey of Canadians aged 16 to 30 years found that about 88% of respondents supported having health warnings on cannabis products, and that pictorial health warnings were perceived as more believable and effective than text-based warnings (79). Another online experimental study of university students in Alberta, Canada found that viewing cannabis packages with health warnings increased health knowledge (80). An analysis of data from the 2019 Global Drug Survey (a large international cross-sectional web-based survey) found that health labels may have the most impact among less frequent users of cannabis (81). However, an important caveat is that many consumers may not read product labels if there is too much information, as demonstrated in focus groups in Colorado and Washington (77), which supports the need for warnings that are either entirely pictorial or at least have minimal text.

Taken together, the existing data from Canada and the US strongly argue in favor of early efforts to standardize cannabis product labels with clear information that can be interpreted with minimal numeracy skills. To increase comprehension of dose and serving size information, there is increasing need to define a standard unit dose of THC, to indicate unit doses in a clear (i.e., non-numerical or minimally numerical) and consistent manner, and to apply this unit dose across products, to the extent possible. In addition, the use of pictorial health warnings on cannabis product labels has the potential to increase health knowledge and thus reduce acute harms associated with use. However, more research is needed to identify the most important messages in order to minimize the amount of information contained on a label. For example, participants in focus groups in Colorado and Washington state suggested that a link to a website for further information would be useful on cannabis labels (77). Having resources that consumers can use to find more safety information can help to minimize the scope of information required on product labels.

Robust Data Collection to Monitor Harms Associated With Cannabis Products, by Consumer Characteristics and Product Type

A recurring theme in this review has been the scarcity of data on harms associated with newer and more potent cannabis products that are emerging in legal retail markets. Thus, proper infrastructure for robust collection of data on harms associated with cannabis is crucially important in any cannabis legalization model. In particular, data should be broken down by cannabis product type, potency, and route of administration and

consumer characteristics such as age, sex, gender, and ethnicity, which will allow for stratification of risk. Multiple different types of data are required; for example, in addition to public health and safety data, market data (including information on sales, consumption, and possession) are vital to understanding how changes in regulatory approaches influence consumption patterns (74, 82). These data will likely come from multiple sources (e.g. reporting from licenced producers of cannabis, ED admissions, calls to poison control centers, federal/state/provincial surveys), but will need to be integrated by a single regulatory system to allow for monitoring of impact and performance of regulatory changes (74).

There are a number of challenges to integrating information from these data sources to monitor performance (83). One issue is the lag time between the implementation of policy changes and the availability of data, which results in delays in understanding changes in acute harms. Relatedly, existing sources of data (e.g. federal or state surveys) often do not collect detailed information on cannabis product information (quantity, potency, route of administration, etc.), and so adding in questions to address these issues takes time to implement. There can also be issues with hospital admissions or poison control data if there are not clear and consistent definitions of the relation of cases to cannabis use, though the quality of these data will improve over time with increasing data collection (83). One potential strategy to address some of these issues, as discussed by Young and colleagues (83), is the use of "social big data", i.e. data from sources such as social media, portable/wearable devices (e.g. FitBit), and online search engines. While much of this vast quantity of available data exists as free-text entries (e.g. posts on social media) that would take a human researcher an impractically long time to analyze, the emerging use of machine learning has made this approach feasible in recent years (83).

CONCLUSION

While legalization of non-medical cannabis use has the potential to improve public health and restore justice to the disadvantaged communities most impacted by cannabis prohibition, it also has the potential to increase harms in the absence of clear restrictions. Data emerging from Colorado, other US states, and Canada show that cannabis legalization has led to an increased potency and diversification of cannabis products, which in turn has been associated with increased risk of harms such as acute psychological distress, gastrointestinal and/or cardiovascular symptoms, cannabis-related injuries, and increased risk of ED visits. In order to mitigate these harms, future cannabis legalization models should incorporate three approaches: early restriction of cannabis edibles and high potency products; implementation of clear and effective labelling of cannabis products with both dose/serving size information and health risks; and integration of a robust data collection framework to monitor acute harms, including data broken down by consumer characteristics and product type to identify higher-risk populations and consumption patterns. The early restriction of cannabis edibles and other products will allow for the market to stabilize before introducing these higher-risk products, and will allow for more data collection to assess the extent of existing harms. While more data on product labelling are needed to find the right balance between clarity and scope of information, existing data suggest that the use of quantitative THC data alone can limit understanding, while the use of pictures and graphics improves label effectiveness and believability. Data collection and monitoring frameworks will need to take advantage of existing data sources such as hospitalizations, poison center calls, and federal or state surveys. In addition, there may be a role of "social big data", e.g. using social media data to monitor trends and patterns in cannabis consumption and related harms in real time. The true impact of cannabis legalization on public health will not be known for quite some time. For now, the goal should be to continue collecting data and to learn from the jurisdictions that have already legalized non-medical cannabis use.

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JM and BF: conception of the manuscript. JM: writing the first draft. All authors contributed to the article and approved the submitted version.

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Young Adults With Higher Motives and Expectancies of Regular Cannabis Use Show Poorer Psychosocial Functioning

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Background: Young adults regularly using cannabis represent a uniquely vulnerable yet heterogeneous cohort. Few studies have examined user profiles using cannabis use motives and expectations. The association between user profiles and psychosocial functioning among only regular users remains unexplored. This exploration is important to improve public education efforts and design tailor treatment approaches.

Methods: Regular cannabis users (at least weekly; $n = 329$) completed an online survey via Amazon Mechanical Turk. The survey measured levels of cannabis use, other substance use, motives and expectations of cannabis use, symptoms of psychosis, depression, anxiety and stress, and reckless behavior such as getting high before work or driving under the influence of cannabis. Latent class analysis was performed using motives and expectations to identify data driven patterns of regular cannabis use. Classes were then used to investigate mental health and behavioral correlates of differences in motives and expectations.

Results: A 2-class solution provided the best fit to the data; Class 1: Low Motives and Expectancies ($n = 158$) characterized by lower endorsement across all motivation and expectation variables, and Class 2: High Motives and Expectancies ($n = 171$) characterized by endorsing multiple motivations, and higher positive and negative expectations of cannabis use. Classes differed in a range of cannabis use variables; e.g., greater proportion of peer use in Class 2. The High Motives and Expectancies users reported higher symptoms of psychosis (positive and negative symptoms), depression, anxiety, and stress. A higher proportion met the criteria for a cannabis use disorder compared with Low Motives and Expectancies users. High Motives and Expectancies users reported higher mean problems with nicotine dependence and illicit drug use other

than cannabis and were more likely to get high before work and drive under the influence of cannabis.

Conclusions: There is heterogeneity among young regular cannabis users in their motivations and expectancies of use and associated psychosocial functioning. Understanding motives and expectancies can help segregate which users are at higher risk of worse functioning. These findings are timely when designing targeted assessment and treatment strategies, particularly as cannabis is further decriminalized and accessibility increases.

Keywords: cannabis (marijuana), latent class, regular users, psychosocial functioning, young adult, motives, expectancies

INTRODUCTION

Cannabis, also known as marijuana, is the most widely consumed illicit substance worldwide, particularly among young adults (1). Young adults with cannabis abuse or dependence represent 7.5% of the total population and 62.5% of all those with cannabis use disorders (2). Increasingly, cannabis is being decriminalized for medicinal and recreational purposes across the globe, including some states in the United States (US). In the US states which have legalized cannabis, the price has decreased making cannabis more accessible. Likewise, the potency of cannabis products has increased, which has been linked to poorer psychosocial functioning (3, 4). One report suggests that potency, determined by the percentage of Δ^9-tetrahydrocannabinol (THC) responsible for the "high" that users experience, has increased from 9 to 30% in the past three decades (5). Whilst laws that support the legalization of cannabis try to achieve social justice aims (e.g., reducing the prison population) and generate tax revenue, cannabis-related psychosocial harms are also at risk to increase contributing to a greater burden of disease, such as increased hospital admissions, and higher social and economic damage (6, 7).

Cannabis use typically begins in adolescence and peaks in young adulthood (8). The prevalence of usage has increased in both age groups (9, 10), however is highest amongst young adults. This is concerning given that the perception of harm associated with regular use in this cohort has been decreasing over time (11). Young adults report the highest reluctance to seek treatment for cannabis-related problems compared to any other age group, therefore hindering their opportunity for recovery from psychosocial harm (12). As such, young adults represent a uniquely vulnerable group, as exposure to cannabis can result in harmful consequences for their mental health, employment and education, and increased risk of driving related accidents and fatalities (13–16). As such, research that focuses solely on young adults will help improve public education efforts and the design of more tailored treatment strategies.

Regular cannabis use is typically the strongest predictor of later psychosocial impairment (13), next to potency (17, 18) and age of onset (10). Despite this, not all regular users, hereby defined as at least weekly consumption, report poor psychosocial functioning (19–21), with evidence suggesting the proportion is only one third of regular users (22). Psychosocial dysfunction experienced by regular users includes increased symptoms of psychosis (23), apathy (24), depression and anxiety (25), poor employment and educational outcomes (26), and increased risk of motor vehicle crashes (27). Despite clear, documented harms associated with the regular consumption of cannabis, it is unclear how to disentangle which regular users are at higher risk. Understanding the features which segregate regular users is necessary to inform prevention and treatment strategies targeting young adult users.

Previous research investigating cannabis-related harms has almost always focused on comparing groups by their frequency of use, for example comparing daily users, occasional users (e.g., monthly), and abstainers (28–30). Yet no study, to the authors' knowledge, has examined how psychosocial functioning varies in exclusively regular cannabis users. A focused approach to understanding subgroups of regular cannabis users is required in order to identify the nuanced differences in regular user profiles and how this relates to subsequent functioning. Research which groups together regular users and compares them against occasional users and abstainers does not create clinically meaningful and tailored intervention strategies for the diverse regular users that seek treatment (31). In addition, not all regular users meet criteria for a cannabis use disorder (CUD), which suggests that further investigation is required to understand exactly how regular users differ from one another (32). One means of classifying subtypes of regular users, that does not rely on comparison according to frequency of use, is through exploring subjective experiences, specifically a person's motivations for use and any positive or negative consequences they expect from using cannabis.

The association between motivations and expected outcomes for cannabis use, and adverse psychosocial functioning, has received growing attention. Emerging evidence shows that the motivation for using cannabis can separate problem and non-problem users (33). There are several motives commonly referred to within the literature, which include coping (e.g., to forget problems), enhancement (e.g., pleasant feelings), social (e.g., improves parties), conformity (e.g., fitting in), expansion (e.g., increasing creativity), and routine (e.g., boredom). One study found social, enhancement and coping motives were associated with higher consumption (34), whilst another study found that

cannabis dependent users highly endorsed every motivation for their use, and cannabis abusers only endorsed enhancement and expansion motives (35–39). Various studies have pointed to coping-related motivations as the most robust predictor of worse psychosocial functioning (40).

Another mechanism to disentangle the vast differences in psychosocial functioning between regular users is by examining positive and negative expectations of cannabis use. One study found that negative expectancies (e.g., being confused) were associated with greater cannabis dependency, while positive expectancies (e.g., feeling more outgoing) were associated with greater weekly consumption. Coupled together, both high positive and negative expectancies were linked to impaired psychological functioning, such as depression and anxiety (41). Another study found that positive expectancies, but not negative expectancies, were associated with worse mental health outcomes and problems such as missing school or work (42). Despite evidence supporting the role of subjective experiences in explaining varying patterns of psychosocial functioning, motivations, and expectations are yet to be collectively investigated in a cohort of only young adult regular users.

One of the difficulties associated with examining motives or expectancies around cannabis use is that any one user may endorse multiple motivations or outcomes from cannabis use. Consequently, an individual's personal pattern of endorsement across these broad motives and expectancies may be more relevant to explaining the heterogenous outcomes of regular users than focusing on any one variable in isolation. Latent class analysis (LCA) is an analytical tool that permits such an examination by identifying subgroups within a heterogeneous sample who share a similar pattern of endorsement across multiple items (43, 44). Many studies in recent years have used LCA to identify subtypes of cannabis users (45–49), including some who have looked at motivations and expectations (8). Studies examining motives and expectancies have found endorsing multiple motivations and negative expectations is associated with poorer functioning. However, none of these studies have estimated such models within exclusively regular cannabis users. As such, class formation in these samples will have been heavily influenced by the frequency of use and thus a refined understanding of the motives and expectancies within an exclusively regular using sample will have been diluted.

A comprehensive approach is needed to disentangle the characteristics associated with varied psychosocial functioning in regular cannabis users, particularly during young adulthood where life-long behavioral patterns are established, including continuation of regular cannabis use (6). This research is timely given the recent trends toward decriminalizing cannabis products in several international jurisdictions which has seen an increase in cannabis-related hospital admissions (3, 4). An increase in dependent users, including young adults, is also likely as more states move toward legalization for both medicinal and recreational purposes, and the availability of cheaper, and more potent products enter the market (50). As such, there is a need to develop an improved understanding of factors that predict individuals who go on to problematic patterns of use. This study aimed to characterize common motivation and outcome expectancy patterns in a sample of exclusively regular cannabis users. Whilst we had no a *priori* hypotheses regarding the number of LCA subgroups that would be identified, we expected to find at least one latent class of cannabis users with a higher endorsement of coping motives, and one latent class of users with higher positive expectations. Once identified, we then aimed to characterize the psychosocial functioning of each class across a range of outcomes such as psychopathology, education and employment, and engagement in reckless behaviors.

MATERIALS AND METHODS

Participants and Procedure

Regular cannabis users ($n = 329$) from the United States were recruited in August 2015 via Amazon Mechanical Turk (MTurk). Inclusion criteria included: (1) 18–30 years old; (2) cannabis use at least weekly for the past 12 months; (3) fluent English; (4) no other drug use more than once a month in the past 12 months; and (5) no diagnosis or treatment of problematic alcohol and drug use besides cannabis. Only eligible participants were reimbursed US$4.50 for their time, which was consistent with the recommended hourly rate at the time of data collection. Written informed consent was provided prior to participation. Ethical approval was granted from the Monash University Human Research Ethics Committee (CF15/1235–2015000576).

Of participants deemed eligible to continue, 357 completed the questionnaire. Despite past research indicating attention levels are similar across MTurk, convenience sampling and high-quality sampling methods (51), we embedded validity item checks designed to test if the participant was paying attention to further increase the quality of data collected. Only 28 participants were further excluded and not reimbursed for failing to correctly answer at least 70% of the embedded validity item checks (i.e., >14/20), leaving 329 participants for analysis (52, 53).

Measures

Indicators Used in LCA

The 24-item Extended Marijuana Motives Measure (Extended-MMM) examines different motivations for using cannabis via six subscales: Coping (e.g., "To forget my worries"), Enhancement (e.g., "Because I like the feeling"), Social (e.g., "To be sociable"), Conformity (e.g., "To be liked"), Expansion (e.g., "To know myself better"), and Routine (e.g., "Out of boredom"). The scale demonstrates adequate internal reliability (Cronbach's α 0.68–0.85), factorial validity, and criterion-related validity (54). Items were measured using a 5-point Likert scale (1 = *Almost Never*, 5 = *Almost Always*), with higher scores indicating a greater endorsement of each motivation (40).

The 45-item Cannabis Expectancy Questionnaire (CEQ) measures anticipated consequences from using cannabis via two subscales: Positive Cannabis Expectancy (e.g., "Smoking cannabis makes me happy") and Negative Cannabis Expectancy (e.g., "Smoking cannabis makes me confused"). Both subscales demonstrate high internal consistency ($\alpha = 0.89$–0.93) and established criterion validity across two samples. Items were measured using a 5-point Likert scale (1 = *Strongly Disagree*, 5 = *Strongly Agree*). Higher scores indicate an increased positive or

TABLE 1 | Items asked to measure levels of cannabis use.

Questions	Available options
What age were you when you tried cannabis/marijuana for the first time?	10–30 years old
What age were you when you started to use cannabis/marijuana regularly?	10–30 years old
When do you usually use cannabis?	All day (yes or no)
With whom do you usually use cannabis?	Alone OR Friends/partner OR Family OR Others
Where do you usually use cannabis?	In public OR At home OR At friend's house
Which of the following do you usually use at the same time as using Marijuana/Cannabis?	Alcohol OR Other drugs
About what proportion of your friends and acquaintances currently use Marijuana/Cannabis?	Few/None OR Half or more
When using marijuana, what type do most commonly use?	Mostly dried heads OR Mostly dried leaves OR Sinsemilla OR I don't know
Which route of administration do you usually use?	Joint OR Pipe OR Water Pipe/Bong OR Blunt OR Vaporizer OR Other
On a scale from 1 to 10 (where 1 = sober, 5 = stoned, 10 = very blazed), how high do you usually get?	1–10

negative expected outcome from cannabis use (55–57). The total scores from the Extended-MMM and CEQ subscales served as the continuous indicators in the LCA analysis.

Measures of Cannabis Use

Levels of cannabis use were measured across various domains. See **Table 1** for the items written to measure levels of cannabis use.

Measures of Psychosocial Functioning

The 42-item Community Assessment of Psychic Experience (CAPE) measures positive psychotic experiences (20-items), negative psychotic experiences (14-items), and depressive symptoms (8-items). The scales demonstrate good stability, reliability ($\alpha = 0.81–0.83$) and discriminant validity. Participants rated both frequency and distress of symptoms on a 4-point Likert scale. Higher scores indicate greater levels of psychotic-like symptoms, with a cut-off score of 50 on the frequency dimension of the positive subscale indicating a possible psychotic disorder (58, 59). In the analyses, only the frequency measure of the positive and negative psychotic experience subscales was used.

The 21-item Depression Anxiety Stress Scale (DASS-21) measures symptoms of depression, anxiety and stress. The scale demonstrates good reliability ($\alpha = 0.87–0.94$) and concurrent validity. Items were measured on a 4-point Likert scale (0 = *Never*, 3 = *Almost always*), with higher scores indicating greater symptom levels. Cut-off scores above 4 for depression, 3 for anxiety and 7 for stress indicate above normal symptoms (60, 61).

The 18-item Apathy Evaluation Scale was used to measure levels of apathy. Good reliability ($\alpha = 0.94$) and validity of this scale have been previously established (62). Items were measured on a 3-point Likert scale (1 = *Not at all*, 3 = *Somewhat a lot*). Scores ranged from 18 to 72, with scores above 38 indicating apathy (63).

The 16-item Cannabis Use Problems Identification Test (CUPIT) is a self-report measure used to detect problematic cannabis use. It has two subscales, "Impaired Control" and "Problems." The scale demonstrates high internal reliability ($\alpha = 0.83–0.92$) and good construct, discriminative, diagnostic and predictive validity. Items were measured on different Likert scales (e.g., 1 = *Never*, 5 = *Always/All the time*). Higher scores indicate a higher likelihood of cannabis-induced problems and dependence. A total cut-off score of 12 indicates risk of developing a CUD, whilst 20 indicates meeting criteria for a CUD. The criteria for diagnosis are in-line with the Diagnostic Statistical Manual, 4th edition (DSM-IV) and the International Classification of Diseases, 10th Edition [ICD-10 (64)].

An additional *ad hoc* item was written to further measure psychological dysfunction. It stated: "Have you ever sought treatment for issues surrounding mental illness (e.g., depression, anxiety, psychosis, etc.)?" which was scored as either "Yes," or "Never."

To measure reckless behavior, we asked two questions: (1) "Do you ever drive whilst stoned/high?" which was scored as either "Rarely/Never" or "Sometimes/Always," and (2) "Do you ever use cannabis/get high just before or during work?" which was scored as either "Never/Rarely" or "Sometimes/Often."

Covariate Adjustment Variables

Analyses were adjusted for the following demographic variables: age, gender, education, employment, Caucasian ethnicity, problematic illicit drug use (other than cannabis), nicotine dependence, and alcohol-related problems. The alcohol and other drug use measures are listed below.

The 10-item Drug Abuse Screening Test (DAST) measures illicit substance abuse using a dichotomous "Yes" or "No" response format (65). Questions were adapted to measure lifetime use rather than for the previous 12 months. Higher scores indicate increased risk of harm from illicit drug use. The scale was categorized using three cut-off points: scores of 0 indicated "low" risk of previous illicit drug problems; scores of 1–2 indicated "moderate" risk; and scores of 3 and above indicated "high" risk. The scale demonstrates high internal consistency ($\alpha = 0.86–0.94$) and good criterion validity (66, 67).

The 6-item Fagerström Test for Nicotine Dependence (FTND) measures level of dependence on nicotine. Higher scores indicate a higher level of nicotine dependence. The FTND was categorized using three cut-off points: scores of 0–2 indicated "low" risk of nicotine dependence; scores of 3–4 indicated "low/moderate" risk; and scores of 5 and above indicated "moderate/high" risk. The scale demonstrates moderate internal consistency ($\alpha = 0.72–0.74$) and good convergent and discriminant validity (68).

The 10-item Alcohol Use Disorders Identification Test (AUDIT) measures alcohol dependence and specific consequences of harmful drinking. Higher scores indicate more

hazardous alcohol consumption. The scale was categorized using three cut-off points: scores of 0–7 indicated "low" risk of hazardous drinking and related problems; scores of 8–15 indicated "moderate" risk; and scores of 16 and above indicated high risk.

Statistical Analysis

Latent class analysis (LCA) was used to classify regular cannabis-users into subtypes based on their responses across the coping, enhancement, social, conformity, expansion, and routine motives subscales, and positive and negative expectancies subscales. Specifically, a series of LCA models (from 2 to 6 classes) were performed using Mplus [version 7.2 (69, 70)]. All indicator variables were *z*-score standardized prior to LCA to assist interpretability. The optimal number of latent classes was identified based on low Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values (71, 72), and the Vuong–Lo–Mendell–Rubin (VLMR) and Lo–Mendell–Rubin (LMR) adjusted likelihood ratio tests which provide a *p*-value comparing the fit of a model with k-classes to a null hypothesis model comprising k-1 classes (69). Entropy values, which indicate the degree of homogeneity within, and independence between, each class was also used to characterize the classes (73), but as recommended by others (74) was not used to determine the optimal number of classes. Entropy values >0.80 suggest a strong probability that an individual belongs to the class for which they have the highest probability of membership (i.e., "most likely class membership"), and thus this most likely class variable can be used as an observed variable in subsequent regression analysis (75).

Once the best fitting LCA model was identified, we estimated a series of regression models where we regressed the outcomes of interest on a categorical variable denoting the participants' most likely class membership. The correlates were broadly classed as demographic factors (i.e., gender, marital status, income, age), cannabis use factors (e.g., preferred route of administration), and psychological and substance use factors. All analyses were adjusted for age, gender, education, employment, Caucasian ethnicity, and alcohol-related problems, nicotine dependence and problematic illicit drug use other than cannabis. Specific covariates were removed if they were used as the dependent variable (e.g., when the AUDIT total score was measured, AUDIT was removed as a covariate). Missing data in the criterion variable ranged from 0 to 19.5% (e.g., the latter for "Route of administration") and were handled using Full Information Maximum Likelihood (FIML) estimation (51). There were no missing data in any of the predictor or covariate variables.

RESULTS

Demographic Information

The mean reported age was 25.95 (SD = 3.29) years. The sample comprised 133 females and 196 males representing an approximate 3:2 ratio in favor of males, consistent with prevalence rates of regular cannabis users in other Western nations (34). Overall, most participants identified as Caucasian (77%) and in a relationship (44%), with roughly a quarter living alone (26%). Three-quarters (75%) had completed, or were completing, either university or trade school. Most participants were employed (78%). There were no significant differences between genders on demographic factors, except that more females (60%) endorsed being in a relationship than males (32%).

TABLE 2 | Fit indices for the estimated latent class models ($n = 329$).

	2-class model	3-class model	4-class model	5-class model	6-class model
AIC	7022.7	6827.764	6684.699	6618.802	6507.826
BIC	7117.601	6956.83	6847.93	6816.197	6739.385
Entropy	0.78	0.853	0.879	0.83	0.879
VLMR (*p*-value)	0.0003	0.0601	0.0651	0.3988	0.5657
LMR (*p*-value)	0.0004	0.0625	0.068	0.4038	0.5716

AIC, Akaike Information Criteria; BIC, Bayesian Information Criterion; VLMR, Vuong-Lo-Mendell-Rubin Likelihood Ratio Test; LMR, Lo-Mendell-Rubin Adjusted LRT Test; p-value testing the null hypothesis that a model with one less class has better fit.

Class Solution

Table 2 presents the fit statistics for 2- through to 6-class latent class models. The VLMR and LMR suggested that a 2-class model was significantly better fitting than a 1-class model, while there was only weak evidence to suggest a 3-class model was better than a 2-class model. The AIC and BIC values were found to continue to increase across the models, with models with more than 6 classes not estimable or had class sizes that were impractically small. Given the AIC and BIC did not reach a low point, we used the LMR and VLMR results and retained a 2-class model (entropy = 0.78) for further analysis. Given that there was some weak evidence for a 3-class model, we also conducted all subsequent analyses using the 3-class model but provide this as **Supplementary Material** for the interested reader. Where relevant, we compare the results of the 2- and 3-class models in text.

2-Class Model

The 2-class model features (seen in **Figure 1**) were largely differentiated by magnitude differences across the LCA indicators. Class 1 was named Low Motives and Expectancies (48% of the sample) and Class 2 named High Motives and Expectancies (52% of the sample). The High Motives and Expectancies class was higher on all Extended-MMM factors and reported higher negative and positive expectations from cannabis use, compared with Low Motives and Expectancies class. The magnitude of differences across variables was large and ranged from Cohen's d = 0.50 (Negative Expectancies) to d = 1.40 (Social Motives). For comparison, the classes found in the 3-class model (see **Supplementary Material**) were largely consistent with the 2-class model. Specifically, Class 1 in the 3-class model was similar to Class 1 of the 2-class model, comprised similar low motives and expectancies, with Class 2 of the 2-class model appearing to be split into two separate groups. The latter two groups differed marginally on variables such as negative expectations and social motives, however the most discriminating factor was the Conformity motivation variable.

Given the consistency in classes, we continue to present the more parsimonious 2-class solution in subsequent analyses.

Correlates of Class Membership

The 2-class model was the most effective in segregating regular users, based on their motives and expectancies of cannabis use. We examined whether the classes were associated with a range of psychosocial correlates, inspecting the marginal mean differences between Class 1 (Low Motives and Expectancies) and Class 2 (High Motives and Expectancies) across demographic, cannabis use, mental health ,and substance use factors. **Table 3** highlights demographic variables. Class 2 were more likely to be employed and have a higher mean age, although the difference in age was negligible (∼1 year).

Table 4 highlights the differences between classes on levels of cannabis use. Class 2 had an earlier age of first use and regular use and reported higher scores when asked "how high" they like to get on a scale of 1–10. Class 2 also had higher percentages of users who use cannabis all day and who have half or more of their peers using cannabis and were more likely to get high just before or during work and drive while under the influence of cannabis. Class 2 were more likely to use cannabis near daily, while Class 1 were more likely to use only 1–2 times per week. In addition, Class 2 had a higher percentage who preferred using with friends/partners (89%, $p < 0.01$) and family members (19%, $p < 0.01$) compared to Class 1 (76 and 8%, respectively). Class 2 were more likely to engage in cannabis use in public places (45%, $p < 0.05$), at a friend's house (81%, $p < 0.01$), or within their own home (96%, $p < 0.05$) compared to Class 1 (32, 66, 86%, respectively). There were no differences between classes on their preference to use alone, preferred route of administration, or preferred type of marijuana except for sinsemilla which was more highly endorsed by Class 2.

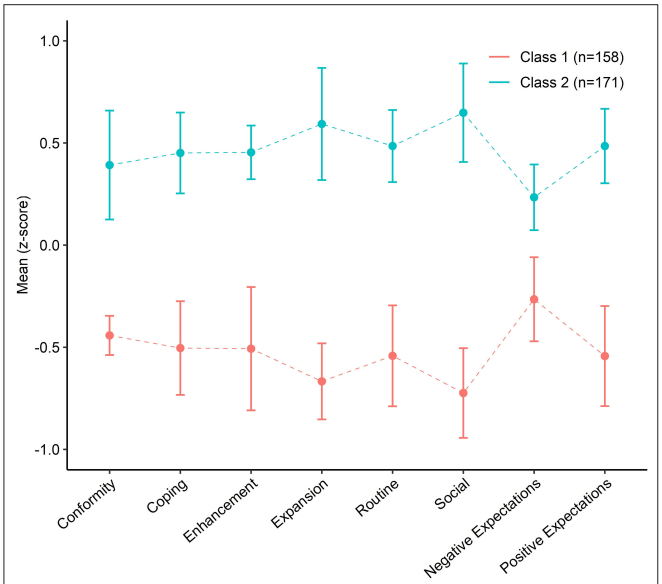

FIGURE 1 | Latent profile of participants based on marijuana use motives and cannabis use expectancies. Error bars represent 95% confidence intervals.

Table 5 highlights the differences between classes across a range of mental health and substance use variables. Class 2 had higher symptoms of psychosis (positive and negative symptoms), depression, anxiety, and stress compared with Class 1. Class 2 also reported higher problematic cannabis use and were flagged as more likely to meet the criteria of a CUD than Class 1. Class 1 reported lower mean problems with nicotine dependence and drug use other than cannabis compared to Class 2.

Notably, when conducting these analyses with the 3-class model, there were little differences in interpretation since the pattern of results comprised Class 1 being different from both Class 2 and 3, but few meaningful effects differentiating Class 2 and 3. The only variables found to differentiate Class 2 and 3 were positive psychosis symptoms, anxiety symptoms, and the CUPIT Problems subscale score, which were all higher in Class 3 than Class 2.

DISCUSSION

This is the first study to examine the profiles of exclusively regular cannabis users during young adulthood, using latent class analysis. In particular, this study focused on users' motivation and their expected outcomes of cannabis use as the basis of each

TABLE 3 | Means and confidence intervals of demographic outcome variables (2-class model)[a].

Variable	Low motives and expectancies ($n = 158$) *M* (95% CI)	High motives and expectancies ($n = 171$) *M* (95% CI)	Significant contrasts
Age	26.48 (26, 26.97)	25.45 (24.98, 25.92)	C1>C2**
Percentage of males	56% (49%, 63%)	63% (56%, 70%)	
Percentage in a relationship	47% (41%, 54%)	41% (34%, 47%)	
Percentage who have completed secondary/high school	78% (72%, 85%)	74% (67%, 80%)	
Percentage who are currently employed	72% (65%, 78%)	84% (78%, 89%)	C1<C2*
Percentage who have Caucasian ethnicity	78% (71%, 84%)	75% (69%, 82%)	
Percentage who live alone	28% (22%, 35%)	25% (19%, 30%)	

*$p < 0.05$, **$p < 0.01$.

[a]*Analyses were adjusted for age, gender, education, employment, Caucasian ethnicity, and total scores of the AUDIT, DAST and FTND.*

TABLE 4 | Means and confidence intervals of cannabis use variables (2-class model)[a].

Variable	Low motives and expectancies ($n = 158$) *M* (95% CI)	High motives and expectancies ($n = 171$) *M* (95% CI)	Significant contrasts
Age of first use	16.94 (16.51, 17.36)	16.30 (15.9, 16.71)	C1>C2*
Age of regular use	20.40 (19.93, 20.88)	19.14 (18.68, 19.59)	C1>C2***
Self-reported "high" during use (10 = very blazed)	5.50 (5.22, 5.78)	6.40 (6.13, 6.68)	C1<C2***
Percentage who use cannabis all day	7% (3%, 11%)	27% (20%, 34%)	C1<C2***
Percentage with half or more peers using cannabis	44% (37%, 52%)	74% (67%, 81%)	C1<C2***
Percentage who sometimes/always drive high	18% (12%, 24%)	34% (27%, 41%)	C1<C2**
Percentage who sometimes/often go to work high	13% (7%, 18%)	32% (25%,39%)	C1<C2***
Percentage usually using cannabis and alcohol	20% (14%, 26%)	17% (12%, 23%)	
Number of days using cannabis per week			
1–2 times	0.46 (0.39, 0.54)	0.25 (0.19, 0.32)	C1>C2***
3–5 times	0.30 (0.23, 0.38)	0.28 (0.22, 0.35)	
6–7 times	0.23 (0.17, 0.3)	0.47 (0.39, 0.54)	C1<C2***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a]*Analyses were adjusted for age, gender, education, employment, Caucasian ethnicity, and total scores of the AUDIT, DAST, and FTND.*

TABLE 5 | Means and confidence intervals of mental health and substance use outcome variables (2-class model)[a].

Variable	Low motives and expectancies ($n = 158$) *M* (95% CI)	High motives and expectancies ($n = 171$) *M* (95% CI)	Significant contrasts
Mental health outcomes:			
Total Apathy Evaluation Scale score	42.61 (41.55, 43.67)	42.4 (41.39, 43.42)	
CAPE Positive Psychotic Experiences subscale	24.82 (23.8, 25.83)	27.83 (26.85, 28.81)	C1<C2***
CAPE Negative Psychotic Experiences subscale	21.23 (20.11, 22.34)	23.27 (22.2, 24.34)	C1<C2*
DASS-21 Depression subscale	2.71 (2.09, 3.33)	3.99 (3.4, 4.58)	C1<C2**
DASS-21 Anxiety subscale	1.9 (1.43, 2.36)	3.34 (2.89, 3.78)	C1<C2***
DASS-21 Stress subscale	2.83 (2.3, 3.37)	4.62 (4.11, 5.13)	C1<C2***
Percentage who have ever sought mental health treatment	15% (10%, 21%)	17% (12%, 22%)	
Problematic cannabis use:			
Total CUPIT score	25.29 (23.73, 26.84)	33.33 (31.83, 34.82)	C1<C2***
CUPIT Impaired Control subscale	22.86 (21.53, 24.19)	29.74 (28.46, 31.01)	C1<C2***
CUPIT Problems subscale	2.42 (1.96, 2.89)	3.59 (3.14, 4.04)	C1<C2**
CUPIT Cut-off score ≥12	95% (92%, 99%)	99% (98%, 100%)	
CUPIT Cut-off score ≥20	74% (66%, 81%)	96% (94%, 99%)	C1<C2***
Substance use outcomes:			
Total AUDIT score	11.4 (10.41, 12.39)	12.62 (11.67, 13.57)	
Total DAST score	1.05 (0.85, 1.26)	1.45 (1.26, 1.65)	C1<C2**
Total FTND score	0.78 (0.46, 1.1)	1.29 (0.98, 1.6)	C1<C2*

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a]*Analyses were adjusted for age, gender, education, employment, Caucasian ethnicity, and total scores of the AUDIT, DAST, and FTND.*

profile. The LCA model in this study identified two different classes of regular cannabis users: Class 1 *Low Motives and Expectancies*, and Class 2 *High Motives and Expectancies*. As expected, one latent class (i.e., Class 2) had higher positive expectancies for using cannabis. Interestingly, coping did not emerge as a sole discriminating factor in either the 2- or 3-class model, despite past research suggesting that coping was one of the most robust motivational predictors of poorer outcomes. Instead, our study found that the class who experienced the worst psychosocial impairment (i.e., Class 2) reported higher scores across all motivational indicators, which was found in only one other study by Bonn-Miller et al. (34). It is worth noting that whilst Bonn-Miller et al. examined current users of varying frequencies, the majority used at least weekly, suggesting that

perhaps among regular users, coping is less of a discriminating motivator. Overall, Class 2 represented 52% of the sample, which is in line with past research demonstrating heterogeneity in the psychosocial functioning, mental health and behavioral outcomes of regular users. We note all regression analyses controlled for demographic variables, problematic alcohol use, nicotine dependence, and other drug use.

Our findings suggest that the motivations and expected outcomes of cannabis use are associated with patterns of use. In line with past research on risk factors for poorer functioning, Class 2 were more likely to be near daily users, whilst Class 1 were more likely to use cannabis 1–2 times per week. Likewise, Class 2 were more likely to prefer sinsemilla, a more potent cannabis variety, and had a lower mean age of first use and regular use, compared with Class 1. A novel contribution to the literature was assessing patterns of use among regular users beyond simple frequency or mode of cannabis use. Specifically, the High Motives and Expectancies users (Class 2) had a higher mean self-reported "high" when using cannabis, were more likely to have half or more of their peers use cannabis, and were more likely to use cannabis all day compared to the Low Motives and Expectancies users (Class 1). Likewise, Class 2 had a higher percentage who preferred using with friends, partners, and family, and use cannabis in public, at a friend's house, or at home compared to Class 1. These findings support the notion of heterogeneous use patterns even among regular users.

Across mental health indicators, the High Motives and Expectancies users had significantly higher symptoms of positive and negative psychotic experiences, depression, anxiety, and stress compared with the Low Motives and Expectancies users. This supports past research which has shown that endorsing multiple motivations for using cannabis (40, 41) and having higher positive expectations of cannabis use (27) is associated with worse mental health outcomes. However, with a low prevalence of mental health symptoms across groups, and only Class 2 exceeding the cut-off score of above normal anxiety symptoms, this finding should be interpreted with caution. The only mental health outcomes that Class 1 and Class 2 did not differ on was apathy levels and whether they had ever sought treatment for mental health issues. That said, it is worth noting both groups scored a mean above 38 indicating they were both clinically apathetic.

When compared on patterns of substance use, the High Motives and Expectancies (i.e., Class 2) users showed worse functioning. On the CUPIT, Class 2 scored significantly higher than Class 1 on the total score and both subscales, indicating worse problematic cannabis use and impaired control. Interestingly, whilst not significantly different, the percentage of users who scored above the cut-off score to indicate risky cannabis use was very high at 95 and 99% for Class 1 and 2, respectively. Whilst there was a significant difference between Class 1 and 2 regarding an indication of a CUD, the vast majority of both classes still exceeded the cut-off score with 74 and 96%, respectively. Given the relatively low prevalence of mental health symptoms highlighted earlier, and the high percentage of users exceeding cut-off scores above what past research indicates is prevalent within regular users, our findings suggest the CUPIT may not be sensitive enough to distinguish between problematic and non-problematic cohorts who already endorse using cannabis regularly. In addition, Class 2 had a higher nicotine dependence and higher abuse of illicit drugs other than cannabis compared with Class 1, but there were no differences on problematic alcohol use.

Across other psychosocial indicators, interestingly, Class 2 had a higher percentage of users who were currently employed compared with Class 1. However, this study did not distinguish between secure vs. insecure forms of current employment, so it is difficult to ascertain whether this indicates better or worse functioning. In contrast, Class 2 were more likely to engage in reckless behavior such as attending work whilst high on cannabis or driving under the influence of cannabis. This is concerning given that acute cannabis consumption increases the risk of motor vehicle crashes and fatalities (16), decreases workplace performance and increases absenteeism (11). The public health and economic implications for understanding which patterns of regular use are associated with increased reckless behavior is important for improving public awareness campaigns and tailoring treatment regimes.

The implications of this study are 2-fold. From a clinical perspective, our results highlight the importance of better understanding users' motivations and expectations of cannabis use in addition to the standard objective measures of frequency, potency, and age of onset. Young adults consume the highest quantity of cannabis compared to other age groups and are the least likely to seek treatment for cannabis-related problems (7, 33), which is why targeted intervention and prevention strategies are required to minimize impaired functioning later in life (32). As demonstrated by this study, and as supported by past research, there is large heterogeneity between subtypes of regular users (13, 37). Our results not only found that one class of regular users had higher motives and expectancies, each class significantly differed across a range of cannabis use variables such as their preference to use cannabis all day or the percentage of peers they associate with who also use cannabis. These additional comparisons were made to further disentangle the different subtypes of regular cannabis users and aid the creation of tailored treatment strategies. Implementing a "one-size-fits-all" approach to the assessment and treatment of psychosocial impairment will likely have limited success, particularly if the focus is largely on asking about regular use or administering questionnaires such as the CUPIT in isolation (31, 40). Comprehensive and tailored approaches toward assessing and treating cannabis use problems for young adults, particularly those which recognize the nuanced differences in regular users, are needed to reduce associated impairment.

Second, there are public health and policy implications, particularly given the large proportion of young adults who are open about using cannabis regularly yet have a low perception of harm associated with this drug (11). The results of our study show that regular users who are highly motivated and experience higher positive and negative expectations associated with cannabis use have poorer psychosocial functioning. However, as this study did not investigate causality, it is possible that the reverse is also true, and that the onset of psychosocial dysfunction

preceded the onset of regular cannabis use. Nevertheless, these findings aim to improve public education efforts targeting regular cannabis users during and even before young adulthood about the association between motivations and expectations for cannabis use and mental health, substance use, and behavioral outcomes. Improving education about the associated risks will allow young adults to make more informed decisions about cannabis. For jurisdictions looking to decriminalize use, and for those where cannabis is already legal, early intervention, and education about the risks of being highly motivated and expecting positive outcomes from cannabis use is key to decreasing associated mental health issues, cannabis dependency, reduced safety and productivity in the workplace, and increased motor vehicle crashes and fatalities. Whilst it is not inevitable that the legalization of recreational cannabis use will result in increased psychosocial impairment, the largely unregulated potency of cannabis, increased availability and decrease in costs are not encouraging. Our recommendations support the growing literature encouraging governments to use part of their tax revenue to monitor the long-term negative consequences of cannabis use in order to minimize the associated social and economic costs and burden of disease (3–10).

This research is not without limitations. First, the cross-sectional design prevents the inference of causality. However, longitudinal research shows cannabis use usually precedes the onset of psychosocial dysfunction in young adults, and not the reverse, and that baseline characteristics such as motives can predict later psychosocial dysfunction (13, 37). Second, the reliance on self-report measures potentially biases the results. This can result from memory recall issues, common in regular users (76), or reporting socially desirable answers (77). That said, past research supports the accuracy of self-reported cannabis use as equivalent to biological measures such as urine tests (78). Third, the modest sample size and exclusive recruitment from MTurk users in the United States may result in lower generalization of results. MTurk is nevertheless the largest method of online crowdsourcing (79), and provides researchers access to hard-to-reach populations such as non-treatment seeking cannabis users (80). To further support the findings of this paper, future studies would benefit from recruiting regular users across different recruitment platforms, and over multiple time points to detect changes in mental health functioning, levels of cannabis use, and reckless behavioral patterns.

In conclusion, the present study has demonstrated that young adults who use cannabis on a regular basis are not a homogenous sample. The High Motives and Expectancies class experienced higher symptoms of psychosis, depression, anxiety, and problematic cannabis use, and were more likely to engage in reckless behavior such as attending work high or driving under the influence of cannabis. Understanding how these patterns of use are associated with poorer psychological functioning can help inform treatment design, utilizing a more person-centered approach. Future work should also build on these findings to examine whether patterns of regular use vary over time, and whether recovery is more effective with targeted interventions. Our findings also support the call to action for future studies to move away from focusing on only comparing regular users to occasional and non-users. As more jurisdictions continue to decriminalize cannabis for medicinal and recreational purposes, it is imperative that we understand the factors which place young adults at increased risk of harm.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://osf.io/742hp/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Monash University Human Research Ethics Committee (ethical approval number: CF15/1235–2015000576). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DA, GY, and MY planned and developed the study protocol. DA collected the data. DA, GY, and LH analyzed data. DA, GY, LH, VL, LP, NS, and MY interpreted the results and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.599365/full#supplementary-material

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Investigating Relationships Between Alcohol and Cannabis Use in an Online Survey of Cannabis Users: A Focus on Cannabinoid Content and Cannabis for Medical Purposes

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Cannabis is commonly used among people who drink alcohol, but findings are mixed regarding the direction of this relationship. The type of cannabis used [high-cannabidiol (CBD) vs. high-delta-9tetrahydrocannabinol (THC)] and motives for use (i.e., whether cannabis is used to treat a medical condition) may influence the relationship between cannabis and drinking. Specifically, CBD has shown preclinical promise in reducing alcohol consumption, and medical cannabis users report using cannabis to reduce drinking. This study leverages survey data from cannabis users who drink alcohol (N = 533). Respondents were categorized as using cannabis to treat (CTT) a medical condition or as individuals whose cannabis use is not intended to treat (NCTT) a medical condition and grouped based on the THC/CBD ratio of the flower or edible cannabis they typically use (e.g., "High-THC/CBD," "Medium-THC/CBD" and "Low-THC/CBD"). The CTT group (n = 412) reported drinking significantly less frequently than the NCTT group (n = 121). Cannabinoid content of flower cannabis was associated with alcohol consumed on cannabis-use days, such that individuals in the High-THC/CBD group drink more on cannabis-use days compared to the Medium-THC/CBD group. Cannabinoid content of edible cannabis was associated with drinks per drinking occasion, such that the High-THC/CBD group consumed the most drinks and the Low-THC/CBD group consumed the fewest. For both edible and flower groupings, higher-THC/CBD cannabis was associated with more frequent co-use than lower-THC/CBD cannabis. Results suggest that whether someone uses cannabis to treat a medical condition may impact their drinking frequency, and the cannabinoid content in flower and edible cannabis impacts alcohol consumption.

Keywords: alcohol, cannabis, tetrahydrocannabinol (THC), cannabidiol (CBD), polysubstance use

INTRODUCTION

Amidst the changing legal landscape surrounding cannabis in the United States, cannabis and alcohol co-use is becoming increasingly common (1). However, insufficient research exists to clarify the effects of cannabis use on alcohol consumption patterns. Studies in this area have been conflicting, with some suggesting that cannabis use is associated with increased drinking (i.e., "complementarity") and others suggesting that cannabis decreases alcohol consumption (i.e., "substitution") (2, 3). Motives for use (e.g., using to treat a medical condition) and cannabinoid content [e.g., high-cannabidiol (CBD) vs. high-delta-9tetrahydrocannabinol (THC)] may impact the association between cannabis and alcohol use.

A recent systematic review on alcohol and cannabis substitution and complementarity, which included 64 articles spanning human and animal studies, found that 30 studies supported substitution, 17 suggested complementarity, 14 supported neither and 4 supported both (4). One notable finding from this review was that all studies conducted on medical cannabis patients supported substitution. Specifically, one U.S.-based study found that 40% of medical users report using cannabis to decrease alcohol intake (5). Another study conducted across three U.S. dispensaries found that participants reported a 42% reduction in alcohol consumption after they started using medical cannabis (6). Three Canadian studies reported that participants substitute medical cannabis for alcohol at a rate of 25–52% (7–9). Further, alcohol consumption has decreased significantly in states with legalized medical cannabis (10), and medical users have been shown to drink less and have fewer alcohol-related problems than recreational users (11). Conversely, one study using data from the National Survey on Drug Use and Health found that individuals in states that had implemented medical cannabis legalization were more likely to engage in binge drinking (12).

No prior studies have explored how cannabinoid content influences the relationship between cannabis and alcohol. A recent review of the existing evidence suggested that CBD may mitigate symptoms of alcohol use disorders (AUD) (13). Although little work has been done in this area among humans, preclinical literature shows that CBD decreases drinking motivation and consumption and reduces the reinforcing properties of alcohol in mice (14–16), and decreases cue- and stress-induced alcohol-seeking, reinstatement, anxiety, and high impulsivity in rats (17). The preclinical literature on the impact of THC on alcohol consumption is inconsistent. THC *decreases* alcohol intake in rats (18) and inhibits locomotor sensitization (a rodent marker of dependence) induced by ethanol (19), suggesting that THC is associated with decreased alcohol consumption. Conversely, CB_1 knockout mice (i.e., mice lacking in the cannabinoid receptor to which THC binds) show reduced alcohol intake (20), and alcohol intake is also reduced by CB_1 antagonists (21), suggesting that activation of CB_1 by THC may be associated with greater alcohol intake.

No published human laboratory studies to our knowledge have used alcohol and cannabis co-administration procedures to explore the impact of acute cannabis use on alcohol consumption within a given co-using session. However, as reviewed in Yurasek et al. (22), national survey data suggest that simultaneous alcohol and cannabis co-use is associated with increased quantity and frequency of drinking (1) and that individuals who report higher levels of cannabis use generally report greater alcohol consumption compared to those who use less cannabis (23). Similarly, college students who drink heavily are more likely to have used cannabis in the past year compared to those who drink less (24) and those who use cannabis are more likely to drink alcohol, binge-drink and experience adverse alcohol-related outcomes (25).

The present study leverages a convenience sample of online survey data to compare alcohol use patterns across cannabis users who were identified as using cannabis to treat a medical condition (CTT) and individuals who report that their cannabis use is not intended to treat a medical condition (NCTT). We also compare outcomes across individuals who report different THC/CBD ratios in their typical flower and edible cannabis. Cannabinoid content is an important and novel variable that is not typically included in survey research on alcohol and cannabis use. We hypothesize that the CTT group will report (1) lower drinking frequency, (2) fewer drinks per drinking occasion (DPDO), (3) lower alcohol and cannabis co-use frequency, and (4) indicate that they drink less alcohol on days when they use cannabis compared to NCTT users. We further hypothesize that those who use cannabis with Low-THC/CBD ratio will report (1) lower drinking frequency, (2) fewer DPDO, (3) lower co-use frequency, and (4) indicate that they drink less alcohol on days when they use cannabis compared to individuals who consume cannabis containing a Medium- or High-THC/CBD ratio. We also hypothesize that those using High-THC/CBD cannabis will report higher scores on all outcome measures compared to those using Medium-THC/CBD cannabis.

METHODS

Procedures

The study was approved by our University's Institutional Review Board. Our voluntary, anonymous survey was hosted on Qualtrics.com and distributed on social media from May 2017 to January 2020. The social media advertisement targeted individuals aged 21 and older living in states with legal access to medical and recreational cannabis and who "liked" cannabis-related pages (e.g., on Facebook, Instagram, Reddit, Tumblr). The advertisement was also posted at local medical and recreational cannabis clinics and advertised on the radio, online news sources and our university website. The advertisement asked prospective respondents if they are "interested in contributing to research regarding cannabis and health."

Of the respondents included in this sample ($N = 533$), 232 reported that they saw the advertisement on social media, 158 saw it at a cannabis clinic, 3 heard about it on the radio, 9 saw it on the university webpage, 1 saw it in an online newspaper, 87 did not disclose where they saw it and 43 reported hearing about it in some other way, such as word of mouth. Anyone 21 years of age or older was allowed to take the survey. Interested individuals clicked on the Qualtrics link that directed them to the informed

consent page. This page explained the purpose of the survey and participation was clearly stated as voluntary, with the option to withdraw at any time. Respondents who provided consent were re-directed to the survey hosted through Qualtrics. The survey took ∼15 min to complete. Participants were not compensated for participation.

Measures

Participants were queried on demographics, substance use and health. They were asked how often they used various cannabis products (e.g., flower cannabis, edible cannabis) on a 13-point scale ranging from "*Never*" to "*Daily use*." Note that some individuals took the survey despite not being cannabis users (i.e., indicating "never" for all forms of cannabis use). They were excluded from all analyses. Participants were asked to indicate the potency of THC or CBD is in the product(s) they typically use. Estimates for cannabinoid concentrations were provided as percent THC/CBD (potency) for flower and THC/CBD milligrams for edibles. Cannabis products purchased from dispensaries are required to have their THC and CBD content listed on the packaging, so it is reasonable to expect that individuals taking the survey would know their product's content. All subjects provided estimates of the THC and CBD content of their typical cannabis.

Respondents were also asked whether they drank alcohol (yes/no) and if "yes," they were asked how often they drink on a 7-point scale ranging from "*Less than once a month*" to "*Daily*." They were asked to indicate how many drinks they consume on average when they drink, with standard equivalents provided for beer (12 oz), wine (5 oz), and hard liquor (1.5 oz). Individuals were asked to indicate on a 7-point scale, "*How often do you use cannabis and drink alcohol at the same time? (Using one while feeling the effect from the other)*" with responses ranging from "*Never*" to "*Every day*." Respondents were asked to indicate on a 5-point Likert scale, "*On the days when you use cannabis, do you usually drink more alcohol than usual, less alcohol than usual, or about the same amount?*" with responses ranging from "*Much less alcohol*" to "*Much more alcohol*."

Participants were asked whether they have been diagnosed with or experience medical issues commonly reported by medical cannabis patients. They were asked to use a nominal yes/no scale to indicate whether they experience any of the following conditions: chronic pain, migraines, anxiety or depression, cancer, post-traumatic stress disorder (PTSD), a sleep disorder (e.g., insomnia, sleep apnea) or any "other" condition (they were provided a text field to state the condition). Chronic pain, migraines, anxiety, depression, cancer, post-traumatic stress disorder (PTSD) and sleep disorder were included as specific questions in the survey due to substantial evidence that they are common conditions for which people seek out medical cannabis (26, 27). Participants were then asked whether they use cannabis to treat each condition(s) that they endorsed experiencing (including anything they listed in the "other" category).

Creation of Variables for Analysis

Survey participants were cannabis users who were categorized into groups based on whether they (1) use cannabis to treat a medical condition (CTT) or whether their cannabis use is not intended to treat a medical condition (NCTT), and (2) according to the average THC/CBD ratio in the edible and flower cannabis that they typically use. Participants were classified as CTT ($n = 412$) if they reported using cannabis to alleviate symptoms of any of the medical conditions queried in the survey or for any "other" medical reason; otherwise, they were classified as NCTT ($n = 121$).

To classify participants according to the average THC/CBD ratio in the cannabis flower that they reported smoking most often, we used responses to "*How much THC is in the cannabis flower that you smoke most often?*" and "*How much CBD is in the cannabis flower that you smoke most often?*" If they used a ratio of 10:1 THC/CBD or higher, they were classified in the High-THC/CBD flower group ($n = 182$); if they used a ratio of 1:1 THC/CBD or less, they were classified in the Low-THC/CBD flower group ($n = 113$) and if they used any ratio of THC/CBD above 1:1 and below 10:1, they were classified in the Medium-THC/CBD flower group ($n = 195$).

Similar groupings were created based on participants' self-reported content of the edible cannabis they typically use. Responses to "*On average, how many milligrams (mg) of THC do you consume at one time when using an edible*" and "*On average, how many milligrams (mg) of CBD do you consume at one time when using an edible*" were used to create the same categories for edible cannabis use. If participants reported using a ratio of 10:1 THC/CBD or higher, they were classified in the High-THC/CBD edible group ($n = 99$); if they used a ratio of 1:1 THC/CBD or less, they were classified in the Low-THC/CBD edible group ($n = 143$); and if they used any ratio of THC/CBD above 1:1 and below 10:1, they were classified in the Medium-THC/CBD edible group ($n = 174$). If individuals reported using "0" THC and >0 CBD, they were classified in the Low-THC/CBD group, and if they reported "0" CBD and >0 THC, they were classified in the High-THC/CBD group. Note that commercial CBD products are typically extracted from whole hemp plants and include traces of other cannabinoids, including THC (28), and even cannabis plants bred to be high in CBD contain trace amounts of THC (29). For this reason, considering individuals who used some CBD and "0" THC in the Low-THC/CBD group is appropriate, as they likely are consuming very low levels of THC in their high-CBD products.

Note that some individuals reported only flower (no edible) use; they were only included in the analyses using the flower groupings and comparing CTT to NCTT groups. Some individuals reported only edible (no flower) use; they were included only in analyses using the edible groupings and comparing CTT to NCTT. Individuals could be in different cannabinoid groups for flower and edible if they reported using different THC/CBD ratios in their flower and edible products. For example, if someone reported typically using a high THC, low CBD edible, they would be in the High-THC/CBD group for the analyses using the edible-based groupings. However, if they also used a low THC, high CBD flower product, they would be included in the Low-THC/CBD group for analyses using the flower-based groupings.

TABLE 1 | Demographic characteristics for individuals who use cannabis to treat a medical condition (CTT) and individuals whose cannabis use is not intended to treat a medical condition (NCTT).

Characteristic [Mean (SD)]	Overall ($N = 533$)	CTT ($n = 412$)	NCTT ($n = 121$)	*p*-Value
Demographics				
Age	34.9 (14.3)	35.07 (14.0)	34.1 (15.6)	0.530
Gender (% female)	**43.7%**	**47.3%**	**29.8%**	**0.001**
Race (% white)	76.5%	78.7%	74.1%	0.294
Education (% bachelors or higher)	39.8%	39.8%	38.8%	0.951
Employment (% full time employed)	58.0%	56.6%	61.7%	0.359

p-values associated with chi-square tests for categorical variables and t-tests for age. For race, tests were run across groups comparing white individuals vs. all other racial identifications, for education they were run comparing bachelors or higher vs. less than bachelors and for employment they were run comparing full time employed vs. all other employment statuses. Note that not all subjects answered every question so group ns for each demographic variable may be less than total n for that group. Significant group differences between CTT and NCTT are denoted by bold text.

Data Analytic Strategy

Data were analyzed using SPSS (Version 27). To analyze demographic differences between CTT and NCTT users, independent samples *t*-tests were conducted on continuous variables (e.g., age), and chi-squared tests were conducted on categorical variables (education, gender, and employment status) (**Table 1**). To analyze demographic differences across the cannabinoid groupings, ANOVA was performed on age and chi-square tests were conducted on categorical variables. Gender differed across the CTT and NCTT groups (Chi square = 10.97, $p = 0.001$), with a larger percentage of males in the NCTT group. Age and employment were different across the flower groupings ($p < 0.001$), with the Low-THC/CBD group being the oldest and containing a higher percentage of unemployed, disabled or retired individuals (Chi Square = 16.43, $p = 0.037$). Age was different across the edible groups ($p < 0.001$), with the Low-THC/ CBD group being the oldest. Thus, gender was included as a covariate in CTT vs. NCTT analyses, age and employment were included in analyses using the flower groupings, and age was included in analyses using the edible groupings. Six participants did not provide their gender, five did not provide their age and four did not provide employment information.

We ran Ordinary Least Squares (OLS) regression models in which hypotheses were tested using two orthogonal contrast codes to examine group differences in drinking frequency, DPDO, co-use frequency, and response to the question: "*On the days when you use cannabis, do you usually drink more alcohol than usual, less alcohol than usual, or about the same amount?*" To test the hypothesis that the low-THC/CBD group will drink less than the other two groups, the low-THC/CBD group was coded as "−2," and the Medium- and High-THC/CBD groups were both coded as "1" (Contrast 1). To test the hypothesis that the High-THC/CBD group will drink more than the Medium-THC/CBD group, the Low-THC/CBD group was coded as "0," the High-THC/CBD group was coded as "1" and the Medium-THC/CBD group was coded as "−1" (Contrast 2). In each model, the outcome of interest (e.g., "DPDO") was regressed on both contrast codes and relevant covariates[1].

RESULTS

Participant Characteristics

A total of 1,188 participants completed the survey, and 45% ($n = 533$) reported drinking alcohol. Thus, the present analysis included $N = 533$ individuals who reported drinking alcohol, 77% ($n = 412$) of whom reported using cannabis to treat a medical condition (CTT). Differences in sample characteristics between CTT and NCTT groups are described in **Table 1**.

Alcohol Use Differences Between CTT and NCTT Groups

In all regression models below, slope values are reported as standardized regression coefficients (unstandardized betas are included in **Table 3**). Significance was set at $p < 0.05$. Controlling for gender, there was a significant association between the CTT vs. NCTT contrast $b = 0.100$, $t_{(521)} = 2.266$, $p = 0.024$ and drinking frequency. Examination of group means shows that the CTT group drank least often (**Table 2**). The CTT vs. NCTT contrast was not associated with any other outcome variables.

Alcohol Use Differences Based on THC and CBD Content of Cannabis

Controlling for age and employment, Contrast 2 was associated with responses to the question "On the days when you use cannabis, do you usually drink more alcohol than usual, less alcohol than usual, or about the same amount?" $b = 0.105$, $t_{(475)} = 2.329$, $p = 0.02$. The High-THC/CBD group reported the highest scores (higher scores correspond to drinking more alcohol while lower scores indicate drinking less alcohol) and the medium-THC/CBD group reported the lowest scores[2]. In the model in which co-use frequency was the criterion, Contrast 1

[1]Note that for all outcome variables, response options were ordinal, Likert-style scales. However, because all questions included 5 or more ordered response options, these variables were treated as continuous data (30–33) and thus were appropriate dependent variables for the OLS regression approach. For alcohol frequency, 11 response options ranged from less than once a month to daily, which corresponded to values of 1–7. For DPDO, 10 response options ranged from 1 drink to "10 or more drinks" coded as 1–10. For "*On the days when you use cannabis, do you usually drink more alcohol than usual, less alcohol than usual or about the same amount*," there were 5 response options ranging from "much less alcohol" to "much more alcohol" and coded from 1 to 5. For alcohol and cannabis co-use frequency, there were 7 response options ranging from "Never" to "Everyday" and coded from 0 to 6.

[2]Specifically, in the Low-THC/CBD group, 54.9% reported drinking much less, 20.4% reported drinking a little less, 22.1% reported drinking about the same amount, 2.7% reported drinking a little more, and 0% percent reported drinking much more. In the Medium-THC/CBD group, 58.5% reported drinking much less, 17.4% reported drinking a little less, 21.0% reported drinking about the same amount, 1.5% reported drinking a little more, 0% percent reported drinking much more and 1.5% did not answer. In the High-THC/CBD group, 47.8% reported drinking much less, 15.4% reported drinking a little less, 34.6% reported drinking about the same amount, 1.1% reported drinking a little more, 0% percent reported drinking much more, and 1.1% did not to answer.

TABLE 2 | Group Means for All Outcomes.

Outcome of interest	CTT ($n = 412$), Mean (*SD*)	NCTT ($n = 121$), Mean (*SD*)	
Drinking frequency	2.04 (1.9)	2.57 (2.1)	
Drinks per drinking occasion	2.89 (1.9)	3.31 (1.9)	
Co-use frequency	2.61 (1.5)	2.81 (1.5)	
Drink more or less on cannabis use days	1.73 (0.9)	1.90 (0.9)	
Outcome of interest	**Flower high-THC/CBD ($n = 182$), Mean (*SD*)**	**Flower medium-THC/CBD ($n = 195$), Mean (*SD*)**	**Flower low-THC/CBD ($n = 113$), Mean (*SD*)**
Drinking frequency	2.21 (2.1)	2.12 (1.8)	2.20 (2.1)
Drinks per drinking occasion	3.23 (2.1)	3.01 (1.8)	2.68 (1.7)
Co-use frequency	2.88 (1.6)	2.76 (1.3)	2.42 (1.6)
Drink more or less on cannabis use days	1.89 (0.9)	1.65 (0.9)	1.73 (0.9)
Outcome of interest	**Edible high-THC/CBD ($n = 99$), Mean (*SD*)**	**Edible medium-THC/CBD ($n = 174$), Mean (*SD*)**	**Edible low-THC/CBD ($n = 143$), Mean (*SD*)**
Drinking frequency	2.27 (2.0)	2.16 (2.0)	2.11 (2.0)
Drinks per drinking occasion	3.43 (1.8)	3.15 (2.0)	2.63 (1.8)
Co-use frequency	2.88 (1.4)	2.78 (1.5)	2.46 (1.6)
Drink more or less on cannabis use days	1.84 (0.9)	1.73 (0.9)	1.75 (0.9)

Note that not every participant answered every question, so ns for each outcome may be less than total group ns listed.

was significant $b = 0.121$, $t_{(412)} = 2.387$, $p = 0.017$. Using flower-based groupings, neither contrast was associated with any other outcome variable.

Using the edible groupings, controlling for age, Contrast 1 was associated with DPDO $b = 0.116$, $t_{(406)} = 2.360$, $p = 0.019$ and co-use frequency $b = 0.121$, $t_{(357)} = 2.220$, $p = 0.027$. Using the edible-based grouping, neither contrast was significantly associated with any other outcome variable. All significant regression results are listed in **Table 3**.

DISCUSSION

Analyses demonstrated that CTT users drink less frequently than NCTT users, consistent with prior research demonstrating that medical cannabis use is associated with decreased drinking (5, 10, 11). No other differences emerged between these groups. It should be noted that categorization within the CTT group does not indicate strictly medical use. Being included in the NCTT group suggests recreational use, however, we did not explicitly ask about cannabis use motives. The lack of expected group differences may be due to the fact that these groups do not necessarily correspond to the medical and recreational groups tested in prior studies. Further, other factors not measured in this study (e.g., personality traits, social behaviors, lifestyle factors) may differ between these groups and contribute to this pattern of results.

We demonstrated that the THC/CBD ratio that participants consume in their typical flower and edible products impacts alcohol-related outcomes. Individuals who consume edibles containing lower THC/CBD ratios drink fewer DPDO and co-use less frequently compared to those using cannabis containing higher THC/CBD. Because individuals in the Low-THC/CBD group likely consumed a higher overall amount of CBD, this finding is consistent with preclinical literature suggesting that CBD reduces drinking and alcohol-seeking behavior (14–17). However, due to our retrospective design (and possible self-report bias and other limitations discussed in the limitations section), these data do not allow us to draw causal conclusions regarding the influence of THC or CBD on alcohol consumption.

Using the flower-based groupings, individuals in the High-THC/CBD group had higher scores on the question "*On the days when you use cannabis, do you usually drink more alcohol than usual, less alcohol than usual, or about the same amount?*" compared to the medium-THC/CBD group. Higher scores correspond to drinking more alcohol, and lower scores indicate drinking less alcohol on cannabis-using days. One explanation may be that it is not the THC/CBD ratio *per se* that impacts drinking more in a given sitting while using cannabis, but total THC or total CBD content. Future studies that could tightly control THC and CBD dose prior to an alcohol self-administration session could shed light on this relationship. Also note that in response to this question, all three cannabinoid groups reported drinking less alcohol on cannabis use days on average (see **Table 2**; note that a "1" response to this question corresponds to "much less alcohol" and a "2" corresponds to "a little less alcohol"), and no participant across the entire sample endorsed drinking "much more alcohol." This suggests that cannabis users in this study are not at risk for drinking much more alcohol on the days that they use cannabis, regardless of the cannabinoid content of their typical products and whether or not they are using cannabis to treat a medical condition. Although intoxication was not explicitly measured in this study, cannabis may increase overall intoxication such that fewer drinks are needed for individuals to achieve their desired levels of intoxication. Consistent with this idea, one human alcohol and THC co-administration study found that THC combined with alcohol was associated with decreased participant ratings of wanting more alcohol, which suggests that cannabis may dampen or replace the desire to drink (34). Notably, individuals in the low-THC/CBD group co-used less frequently than those in the higher groups. This may be due to the less intoxicating properties of the lower-THC/CBD being less rewarding when combined with alcohol, although it could also reflect characteristics of

TABLE 3 | Results from regression models with significant group contrast effects.

Model	Unstandardized B	Std Error	Standardized β	*t*	*p*	*F*	*df*	*p*	R^2	adj R^2
Drinking frequency: CTT vs. NCTT										
Overall model						3.722	2,521	**0.025**	0.014	0.010
Gender	0.208	0.176	0.052	1.178	0.239					
CTT vs. NCTT	0.240	0.106	0.100	2.266	**0.024**					
Drink More/Less on Cannabis Days—Flower Groupings										
Overall model						3.829	4,475	**0.004**	0.031	0.023
Age	0.006	0.003	0.095	2.002	**0.046**					
Employed	0.077	0.037	0.096	2.084	**0.038**					
Contrast 1	0.032	0.033	0.045	0.961	0.337					
Contrast 2	0.109	0.047	0.105	2.329	**0.020**					
Frequency of alcohol + cannabis co-use—flower groupings										
Overall model						1.502	4,412	0.201	0.014	0.005
Age	0.003	0.005	0.024	0.470	0.639					
Employed	0.002	0.068	0.001	0.028	0.978					
Contrast 1	0.141	0.059	0.121	2.387	**0.017**					
Contrast 2	0.057	0.085	0.033	0.665	0.506					
Drinks per drinking occasion—edible groupings										
Overall model						12.271	3,406	**<0.001**	0.083	0.076
Age	−0.033	0.007	−0.240	−4.947	**<0.001**					
Contrast 1	0.154	0.065	0.116	2.360	**0.019**					
Contrast 2	0.130	0.116	0.054	1.128	0.260					
Frequency of alcohol + cannabis co-use—edible groupings										
Overall model						1.652	3,357	**0.177**	0.014	0.005
Age	0.003	0.006	0.028	0.528	0.598					
Contrast 1	0.128	0.058	0.121	2.220	**0.027**					
Contrast 2	0.053	0.103	0.027	0.513	0.608					

Bold font in p-value column indicates significant effects. In all models, Contrast 1 is the comparison of the Low-THC/CBD group to the other two groups, such that the Low-THC/CBD group is coded "−2," and the Medium- and High-THC/CBD groups are both coded "1." Contrast 2 is the comparison of the Medium- and High-THC/CBD groups, such that the Low-THC/CBD group is coded "0," the Medium-THC/CBD group is coded "−1" and the High-THC/CBD group is coded "1".

the low-THC/CBD users, such as personality or lifestyle factors that impact the circumstances in which they use cannabis. Implications from these findings are limited, given that we did not assess the timespan during which individuals were using alcohol and cannabis each day. Future studies leveraging daily diary or Ecological Momentary Assessment methods could shed further light on the notion that cannabis intoxication may influence alcohol consumption.

LIMITATIONS AND FUTURE DIRECTIONS

This study has several methodological limitations. Data came from a convenience sample and relied on self-report. It is well-established that individuals tend to underreport substance use (35). The survey data is also subject to selection bias, as most individuals who participated were recruited through targeted social media ads as a result of "liking" cannabis-related content or through cannabis clinics. These participants were likely to be "pro-cannabis," limiting our ability to generalize these results to individuals who have less experience with cannabis, who live in a state where cannabis has not been legalized, or who have a more neutral or negative attitude toward cannabis use. However, participant bias is a common limitation of online behavioral research and does not negate the utility of such data. Our sample was also limited in that it lacked racial diversity and was composed of 77% white individuals. This limits the extent to which results can be generalized to other populations. Future studies should include a more diverse population.

The survey did not ask about cannabis use motives (e.g., increasing social enjoyment, relaxation, stress-relief) beyond whether cannabis was used to treat a medical condition. This information would better characterize the sample and should be included in future studies. Further, there was scant prior data on which to base our classification of CTT and NCTT users. Individuals were classified as CTT users if they endorsed using cannabis to treat one or more major medical conditions for which medical cannabis is typically used (26, 27). These respondents may also use cannabis in situations in which they do not intend to treat a medical condition, as existing research suggests that recreational and medical motives for cannabis use often overlap. For example, over half of individuals using medical cannabis legally in the U.S. also report some recreational use (36). Thus, classification of cannabis users into distinct groups that accurately reflect their medical and recreational motives is a challenge across the field. Further research is needed to better understand how to make such classifications.

The survey was also retrospective, and the accuracy of future studies could be improved through leveraging real-time data collection methods such as daily diaries or Ecological Momentary Assessment.

CONCLUSIONS

Results suggest that using cannabis to treat a medical condition, and the THC/CBD content of flower and edible cannabis people use, play a role in determining the relationship between cannabis use and alcohol consumption. Future studies are needed to better understand this association. In particular, future research would ideally include participants that fall into more clearly defined and distinct medical and recreational groups. Research that involves daily assessments to better understand the temporal associations between alcohol and cannabis use, and laboratory studies in which alcohol is co-administered alongside tightly-controlled THC and CBD doses will be necessary to draw meaningful conclusions about the nature of these relationships.

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 University of Colorado Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RM and KH developed and implemented the online survey. RM and CA prepared data and created relevant study variables. CA and HK conducted data analysis. HK conceived of the study idea and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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A Multiple Correspondence Analysis of Patterns of CBD Use in Hemp and Marijuana Users

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Background: With the passing of the 2018 Agriculture Improvement Act that legalized hemp-derived products, i.e., cannabidiol (CBD), the use of CBD has increased exponentially. To date, the few studies that have characterized individuals who use CBD suggest that co-use of CBD and tetrahydrocannabinol (THC)-dominant cannabis, i.e., marijuana, is highly prevalent. It is, therefore, important to investigate the relationship between CBD use and marijuana use to understand the antecedents and consequences of co-use of these two cannabis products.

Methods: We conducted an online survey using structured questionnaires to determine differences in CBD users with (CBD+MJ) and without co-morbid marijuana use. Group comparisons were carried out using chi-square tests and ANOVA. Multiple correspondence analysis (MCA) with bootstrap ratio testing was performed to examine the relationship between the categorical data.

Results: We received 182 survey responses from current CBD users. CBD+MJ had more types of CBD administration ($F = 17.07$, $p < 0.001$) and longer lifetime duration of CBD use ($\chi 2 = 12.85$, $p < 0.05$). Results from the MCA yielded two statistically significant dimensions that accounted for 77% of the total variance. Dimension 1 (representing 57% of the variance) associated CBD+MJ with indication of CBD use for medical ailments, use of CBD for more than once a day for longer than 2 years, applying CBD topically or consuming it via vaping or edibles, being female, and, having lower educational attainment. Dimension 2 (representing 20% of the variance) separated the groups primarily on smoking-related behaviors where CBD+MJ was associated with smoking CBD and nicotine.

Conclusions: Identifying the factors that influence use of CBD and marijuana can inform future studies on the risks and benefits associated with each substance as well as the impacts of policies related to cannabis-based products.

Keywords: cannabidiol, marijuana, multiple correspondance analysis, cbd, thc, HEMP

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INTRODUCTION

The *cannabis sativa* plant species contains a multitude of varieties, such as hemp and marijuana (MJ), with various active elements known as phyto-cannabinoids. Hemp and MJ are commonly differentiated according to their concentration levels of delta-9 tetrahydrocannabinol (THC), the main psychoactive phyto-cannabinoid found in *cannabis sativa*. Hemp is classified as *cannabis sativa* with a THC concentration lower than 0.03%, while those with a concentration >0.03% are classified as MJ (1, 2). Prior to 2018, both hemp and MJ were classified as schedule I substances. In December of 2018, the United States Senate passed The Agriculture Improvement Act. Under this new law, hemp was rescheduled from a DEA schedule I substance to a schedule V substance. This reclassification identifies hemp and hemp-derived products, such as cannabidiol (CBD), as a substance of medicinal value with no addictive properties and legalizes it nationally. CBD's appeal as a medicinal agent is based upon its favorable tolerance in both human and animal models (3–5). These models found a lack of habit-forming potential (6, 7) and rare incidents of adverse side-effects (8) from CBD use compared to THC (9–11).

To date, cannabis research has focused largely on THC and CBD given that they are the main phyto-cannabinoids found in *cannabis sativa* (7, 10, 12)]. In isolation, THC has been shown to induce psychoactive and appetitive effects (13) and impact cognitive abilities, including but not limited to attention, and episodic memory (14, 15). CBD, on the other hand, has been shown to have anxiolytic (16), antipsychotic (17), and neuroprotective effects (18–21).

Studies have found high co-use of THC and CBD, i.e., >50% in CBD users (22, 23) that highlight the need to understand how the two substances interact. To date, however, our knowledge of this interaction remains largely inconclusive. While it has been suggested that CBD does not impact THC's subjective and reinforcing properties (24), its modulatory role on THC's effects on cognition is mixed. For example, some studies have found that CBD has a protective effect on THC-related episodic memory deficits (25), such that cannabis users who smoked cannabis high in cannabidiol content showed no memory impairment. On the other hand, CBD was not found to modulate THC's effect on attention (26, 27). Timing of administration and THC/CBD ratio further complicates this interaction (28). For example, when CBD is administered prior to THC it has been shown to potentiate its effects, but this potentiation does not occur when they are administered concurrently (28).

Thus, there is a critical gap in the knowledge surrounding co-use of CBD and THC. This paucity in the literature combined with the increasing prevalence of both CBD and MJ use, highlight the importance of examining simultaneous use of CBD and MJ. The purpose of the present study was to investigate multivariate patterns that are associated with isolated use vs. co-use of MJ and CBD.

METHODS

The present cross-sectional survey study was conducted with Internal Review Board approval from the University of Texas at Dallas.

Respondents

We recruited adults who self-reported CBD use via online advertisements posted on Dallas-Fort Worth and CBD forums (Reddit, Craigslist, Discord, and NextDoor). Inclusion criteria for all respondents was as follows: the endorsement of current CBD use, aged 18 years or older, and, written informed consent.

The study was conducted online in its entirety via Qualtrics Research Software (29). Respondents from the advertisements were directed to the web-based survey in order to participate in the study. The first page of the survey described the informed consent procedures. In order to ensure understanding of the purpose and procedure of the study, the respondents were asked to answer three multiple choice questions about the study. Answering all of the questions correctly was a pre-requisite for informed consent. Those who answered all of the questions correctly were then asked to provide a digital signature to document informed consent to participate in the study. After the digital signature page was completed, the survey assessments began. Those who did not provide a digital signature could not progress with the survey assessments. No identifying information was collected in this survey.

Compensation for study participation was optional. Those who opted for compensation were directed to a different survey. This kept the "data collection" survey and "optional compensation" survey separate such that information could not be linked to respondents' identifying information, thus ensuring anonymity. Following compensation, information from the "optional compensation" survey was destroyed.

Assessments

The survey used in the present study was adapted from Corroon and Phillips (22) and was created using Qualtrics survey software (29). This survey included questions designed to measure respondent history of use, rate of use, method of self-administration, and the medical indication of CBD use. We also collected sociodemographic data including biological sex, age, and highest level of education. In order to measure respondents' cannabis, nicotine, and alcohol use behavior the following assessments were included in the survey: the Cannabis Use Disorders Identification Test—Revised [CUDIT-R (30)], The Fagerstrom Test for Nicotine Dependence—Revised, [FTND-R; (31)], and the Alcohol Use Disorder Identification Test [AUDIT; (32)]. Quality control of participant responses was carried out using recommendations from Teitcher et al. (33) that examined response times as a metric to detect outliers and examining response patterns to detect dubious responses.

Data Analyses

All analyses were conducted in RStudio (34) using R 3.6.3 (35). Descriptive statistics were calculated to examine CBD use

characteristics, sociodemographic variables, methods of CBD administration, medicinal CBD use, cannabis, nicotine, and alcohol use characteristics. Chi-square and ANOVA tests were used for comparisons of MJ endorsement groups across variables.

To elucidate possible relationships between multiple variables, multiple correspondence analysis (MCA) in the ExPosition package (36) was used. MCA is an extension of correspondence analysis (CA) and a generalization of principal component analysis (PCA). It is a multivariate analysis technique that allows for the investigation of potential relationships between multiple categorical variables (37–40). Similar to PCA, MCA dimensions are orthogonal to each other and independently explain as much of the variance as possible (41, 42). The Kaiser line test was performed to determine the number of dimensions to retain for further analysis. This test is based on the Kaiser criterion, which recommends retention of dimensions with eigenvalues $\geq$1. The purple points in **Figure 1**, show dimensions with eigenvalues that meet Kaiser criterion. The line is generated based on the relative location of the "elbow" of the scree plot where the variance represented by one dimension is not statistically different than that of the next (43). MCA reduces the number of dimensions seen in a given dataset and converts both variables and respondents into factor scores. This factor score calculation and data dimension reduction allow for the visual representation of both variables and respondents along a two-dimensional plane. When examining the factor plots, points (representing variables or respondents) that are plotted closer together have a greater association with each other (38, 39, 44, 45). Variable stability and statistical inferences pertaining to MJ group differences were evaluated via bootstrap resampling (46), bootstrap ratio and 95% confidence interval calculation (47), all of which were carried out with the InPosition package (36). The significance threshold for all analyses was set at $p < 0.05$.

RESULTS

Participant Characteristics

Two hundred and forty-five individuals responded to the online survey. Of these, 53 had partial data and were excluded. Of the complete surveys, nine had response times classified as outliers using the graphics package from R 3.6.3 (35) and were consequently excluded. Lastly, one respondent's response pattern exhibited signs of malingering and was also excluded. In this study, malingering was defined as having the same response (e.g., all "yes" or "10") to all of the survey questions that also then conflict with each other. In this particular case, the respondent endorsed the most extreme answer in the Likert scale questions and answered "yes" for every yes or no binary question. This pattern revealed inconsistent responses across similar questions. After these quality control steps, a total of 182 respondents were included in further analyses (112 males, 70 females). See **Table 1** for respondents' demographic and drug use information. Respondents were classified into concurrent MJ and CBD use (CBD + MJ) ($N = 105$), and, CBD only use ($N = 77$). The two groups were significantly different in age [$\chi^2(5) = 15.67$, $p = 0.008$], education [$\chi^2(7) = 15.30$, $p = 0.032$], and nicotine use [$\chi^2(1) = 15.67$, $p = 0.007$]. CBD+MJ users were younger, had less years of education and greater nicotine use than CBD only users. CBD+MJ users reported greater number of CBD self-administration methods [$F_{(1,180)} = 16.73$, $p < 0.001$, $\eta_p^2 = 0.09$]. Specifically, there were significant differences between CBD+MJ users and CBD only users in the following CBD self-administration methods: sublingual [$\chi^2(1) = 4.45$, $p = 0.035$, vaping $\chi^2(1) = 6.07$, $p = 0.014$], smoking [$\chi^2(1) = 21.49$, $p = 0.001$] and edible [$\chi^2(1) = 5.39$, $p = 0.020$] administration (**Table 2**).

Multiple Correspondence Analysis (MCA)

MCA identified four significant dimensions accounting for a combined total of 89% of the variance (see **Figure 1**). Dimensions 1 and 2 survived the Kaiser line test and were retained for further analyses. Together these two dimensions accounted for 77% of the variance. Dimension 1 accounted for 57%, while dimension 2 accounted for 20% of the variance. 95% mean confidence intervals via bootstrap resampling showed that dimension 2 best separated CBD+MJ respondents from CBD only respondents (see **Figure 2**). Based on the variable factor score map (see **Figure 3**), dimension 1 separated respondents primarily based on ailments indicated for the use of CBD. CBD+MJ use was associated with endorsement of ailments (anxiety, depression, physical pain, arthritis, migraines, and sleep disorders), high school level of education, being female, administration of CBD via topical, edible, and vaping, and using CBD more than once a day for longer than 2 years (see top right quadrant of **Figure 3** and **Table 3**). CBD only use was associated with absence of ailments related to CBD use, possession of advanced graduate degrees (i.e., master's degree), fewer types of CBD administration, and use of CBD less than once a day and <3 months (see lower left quadrant of **Figure 2** and **Table 3**).

Dimension 2 primarily separated respondents based on CBD and nicotine smoking behaviors. CBD+MJ use was associated with smoking and vaping CBD, use of CBD for more than 2 years at a rate of less than once day, smoking nicotine, <2 years of college level education, being male and between the ages of 18–24. CBD only use was associated with using CBD sublingually daily for <6 months, possession of a college education, being between the ages of 25–64, and self-reported anxiety, sleep disorders, MS (**Figure 4**).

DISCUSSION

The present study sought to elucidate the factors that contribute to co-use of CBD and MJ. MCA was used to explore multivariate relationships within the data, yielding two MCA dimensions, which accounted for the majority of variance. Dimension one separated the CBD only users from CBD+MJ users primarily on ailments for which CBD was used for—anxiety, depression, physical pain, arthritis, migraines, and sleep disturbances. Dimension two separated the groups based on smoking CBD and nicotine.

MCA Dimension 1

Our results suggest that co-use of MJ in CBD users is associated with indication of CBD use for medical ailments, use of CBD

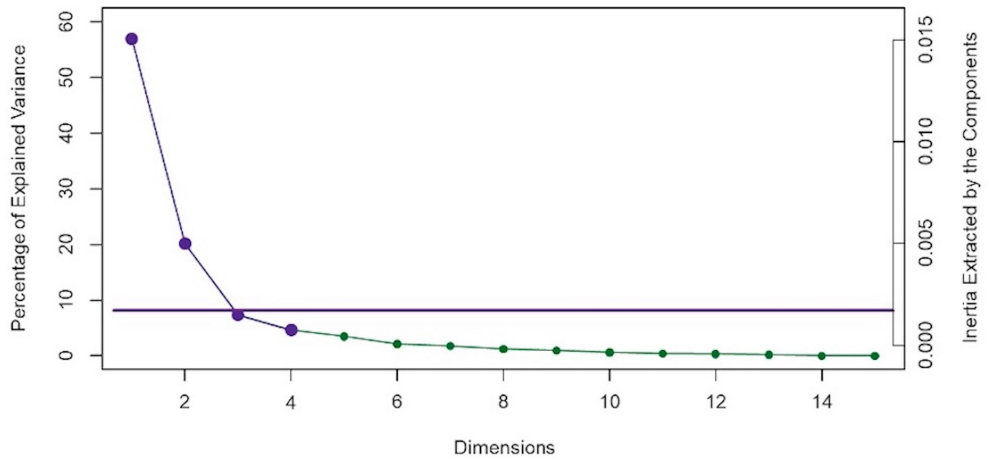

FIGURE 1 | Multiple correspondence analysis (MCA) screeplot. MCA identified four significant dimensions accounting for a combined total of 89% of the variance. The screeplot shows two statistically significant dimensions (dimensions 1 and 2) that survived the Kaiser line test and accounted for 77% of the variance. The purple Kaiser line is a visual representation of the "screetest."

TABLE 1 | Respondents' demographic information.

	Total all (*N* = 182)	CBD+MJ (*N* = 105)	CBD only (*N* = 77)	*p*-value
Biological Sex				0.669[a]
Male	112 (61.5%)	66 (62.9%)	46 (59.7%)	
Female	70 (38.5%)	39 (37.1%)	31 (40.3%)	
Age group				0.008[a]
18–24	53 (29.1%)	41 (39.0%)	12 (15.6%)	
25–34	74 (40.7%)	42 (40.0%)	32 (41.6%)	
35–44	34 (18.7%)	14 (13.3%)	20 (26.0%)	
45–54	16 (8.8%)	6 (5.7%)	10 (13.0%)	
55–64	3 (1.6%)	1 (1.0%)	2 (2.6%)	
65 or Over	2 (1.1%)	1 (1.0%)	1 (1.3%)	
Education				0.032[a]
No high school	3 (1.6%)	3 (2.9%)	0 (0.0%)	
High school/GED	17 (9.3%)	14 (13.3%)	3 (3.9%)	
Some college	60 (33.0%)	35 (33.3%)	25 (32.5%)	
Associate degree	19 (10.4%)	14 (13.3%)	5 (6.5%)	
Bachelor's degree	58 (31.9%)	28 (26.7%)	30 (39.0%)	
Master's degree	20 (11.0%)	8 (7.6%)	12 (15.6%)	
Doctoral degree	3 (1.6%)	1 (1.0%)	2 (2.6%)	
Professional	2 (1.1%)	2 (1.9%)	0 (0.0%)	

[a]*Pearson's Chi-squared test.*

CBD, cannabidiol; MJ, marijuana; CBD+MJ, respondents with CBD and marijuana use.

for more than once a day for longer than 2 years, applying CBD topically or consuming it via vaping or edibles, being female, and having lower educational attainment. Regarding the medical ailments found in MCA dimension 1—anxiety, depression, physical pain, arthritis, migraines, and sleep disorders -, we found that the presence of one ailment was associated with the possible presence of other ailments. Given high co-morbidity between psychiatric disorders, it isn't surprising that anxiety and depression were associated in CBD+MJ users. For example, anxiety has been linked with both depression and substance use (48, 49) and is particularly prevalent in marijuana users (50, 51). Although CBD is more widely considered to provide relief from symptoms related to pain, arthritis and sleep disturbances, we found that MJ use in CBD users was associated with presence of these conditions. It is possible that these individuals either experience or have expectancies that MJ use in addition to CBD provides greater relief for these ailments. There is existing literature that describes the "entourage effect" in cannabis where full spectrum cannabis products that maintain the full profile of the cannabis plant leads to increased endogenous cannabinoid levels that are above and beyond that of the individual phytocannabinoid's isolated components, making them more efficacious for a variety of medical ailments (52). Indeed, medical MJ that contain a variety of cannabinoids including THC, CBD, as well as other cannabinoids and terpenes is often indicated for relief of epilepsy, movement disorders, and pain (53–55). In pain studies, 1:1 THC:CBD (Sativex) combinations have been shown to be more efficacious for cancer-related, arthritis, and other chronic pain compared to both placebo and THC isolate (56–58). In studies involving MS patients, THC (2.7 mg Tetranabinex) and CBD (2.5 mg Nabidiolex) dominant medications were shown to produce pain relief, but a 1:1 THC:CBD combination drug (Sativex) significantly improved sleep symptoms and pain above the other two (59). These initial studies demonstrate that 1:1 THC:CBD combination drugs provide greater symptom relief than isolates in clinical populations. It is also possible that this association could be due to known associations of

TABLE 2 | CBD use in the study sample.

CBD use measure	All (*N* = 182)	MJ+CBD (*N* = 105)	CBD only (*N* = 77)	*p*-value
How often do you use CBD?				0.243[a]
Less than once a day	77 (42.3%)	48 (45.7%)	29 (37.7%)	
Daily	84 (46.2%)	43 (41.0%)	41 (53.2%)	
More than once a day	21 (11.5%)	14 (13.3%)	7 (9.1%)	
CBD use history				0.065[a]
Less than one month	11 (6.0%)	4 (3.8%)	7 (9.1%)	
Less than three months	13 (7.1%)	6 (5.7%)	7 (9.1%)	
<6 months	44 (24.2%)	25 (23.8%)	19 (24.7%)	
<1year	39 (21.4%)	22 (21.0%)	17 (22.1%)	
1–2 years	53 (29.1%)	29 (27.6%)	24 (31.2%)	
More than 2 years	22 (12.1%)	19 (18.1%)	3 (3.9%)	
Sublingual administration				0.023[a]
No	134 (73.6%)	84 (80.0%)	50 (64.9%)	
Yes	48 (26.4%)	21 (20.0%)	27 (35.1%)	
Vaping Administration				0.009[a]
No	125 (68.7%)	64 (61.0%)	61 (79.2%)	
Yes	57 (31.3%)	41 (39.0%)	16 (20.8%)	
Capsule administration				0.985[a]
No	163 (89.6%)	94 (89.5%)	69 (89.6%)	
Yes	19 (10.4%)	11 (10.5%)	8 (10.4%)	
Liquid administration				0.656[a]
No	151 (83.0%)	86 (81.9%)	65 (84.4%)	
Yes	31 (17.0%)	19 (18.1%)	12 (15.6%)	
Smoking administration				<0.001[a]
No	123 (67.6%)	56 (53.3%)	67 (87.0%)	
Yes	59 (32.4%)	49 (46.7%)	10 (13.0%)	
Edible administration				0.013[a]
No	121 (66.5%)	62 (59.0%)	59 (76.6%)	
Yes	61 (33.5%)	43 (41.0%)	18 (23.4%)	
Topical administration				0.518[a]
No	135 (74.2%)	76 (72.4%)	59 (76.6%)	
Yes	47 (25.8%)	29 (27.6%)	18 (23.4%)	
Number of CBD use methods	1.77 (1.04)	2.03 (1.17)	1.42 (0.69)	<0.001[b]
FTND scored	0.64 (1.80)	0.88 (2.09)	0.31 (1.24)	0.036[b]
AUDIT scored	5.89 (5.55)	7.01 (6.44)	4.36 (3.52)	0.001[b]
CUDIT scored	-	7.68 (5.17)	-	-

[a] *Pearson's Chi-squared test.*

[b] *Linear Model MANOVA.*

CBD, cannabidiol; MJ, marijuana; CBD+MJ, respondents with CBD and marijuana use; FTND, the Fagerstrom Test for Nicotine Dependence—Revised; CUDIT, the Cannabis Use Disorders Identification Test—Revised; AUDIT, the Alcohol Use Disorder Identification Test.

mood disorders with medical conditions such as chronic pain, arthritis, sleep disturbances (60–62) and may play a mediating role between pain and sleep disturbances in arthritis patients (61). In this instance, pain may contribute to exacerbated depression symptoms in the long-term which, in turn, can result in sleep disturbances. Given the large literature on the associations between marijuana use and mood disorders, we speculate that this may also explain why mood disorders and medical conditions were associated with CBD+MJ users.

Previous results demonstrating that the use of both MJ and CBD is associated with a need for pain relief are consistent with our findings, as the bootstrap ratios indicated that both physical pain and endorsement of MJ co-use were related. The underlying mechanisms for the analgesic effect of CBD are subject to debate. However, previous studies have proposed CBD's interaction with the glycine and serotonergic systems as possible vehicles (63). In animal models of arthritis, locally applied CBD has been found to lessen joint pain and inflammation (64–66). This finding may explain why the endorsement of administering CBD topically was associated with the indication of CBD use for ailments such as chronic pain and arthritis.

We also found that CBD+MJ users are more likely to be female, which is concordant with results showing that female MJ users were more likely to report MJ use for the treatment of pain compared to male MJ users (67). Previous studies have shown using CBD more than once a day is associated with medicinal use (22). The perceived medicinal benefits could be a contributing factor to high rates of CBD use, despite a likelihood of a deep overestimation about the efficacy of CBD has been demonstrated (22, 23). Nevertheless, the literature corroborates our finding that co-use of CBD and MJ is more related to co-existing medical ailments than CBD use alone.

MCA Dimension 2

Our results for dimension 2 from the MCA suggest that being young (18–24 years old), male, having an associate degree or less, and the use of nicotine products is associated with the endorsement of MJ co-use. The findings are in accordance with previous research showing that 18–25-year-olds have the highest rate of MJ use (68), and that MJ users tend to have lower levels of education compared to non-users (69, 70). Previous studies have found that earlier initiation of MJ use was associated with lower academic and career attainment (71, 72), suggesting that CBD use may not mitigate the detrimental effects of MJ use.

Nicotine use was found to be a significant a variable associated with MJ co-use. The co-use of nicotine with MJ has been shown in previous research, with data suggesting that greater exposure to one, is associated with greater exposure to the other (73). When examining the CBD history variables, it was found that using CBD less than once a day for longer than 2 years was associated with the endorsement of MJ co-use. The sporadic use history of CBD seen in MJ users could be due to CBD exerting a non-effect on the subjective rewarding effects of THC (24). From the bootstrap ratios, smoking CBD seemed to have the highest association with the endorsement of MJ co-use. This finding makes sense pharmacologically speaking, as smoking has been found to yield the highest plasma concentration in the shortest amount time in both CBD (74) and MJ use (75, 76). In this instance, smoking and vaping methods of administration could be associated with MJ and CBD co-use due to increased familiarity with these methods in MJ users. This is in line with previous studies showing that both vaping and smoking are popular methods of administration in experienced MJ users (77, 78).

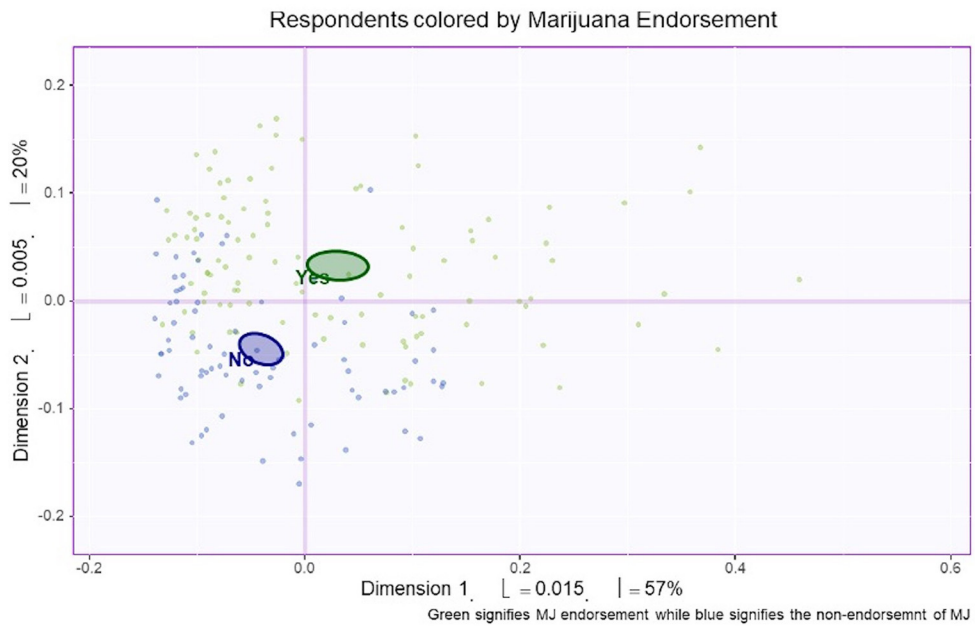

FIGURE 2 | Bootstrap confidence interval comparisons between CBD users with and without marijuana co-use. Mean confidence intervals were created from the bootstrap resampling. Respondents were classified according to endorsement of marijuana use. Based on this figure, dimension 1 (the horizontal line) and dimension 2 (the vertical line) separated CBD users with (green) and without (purple) concurrent marijuana use.

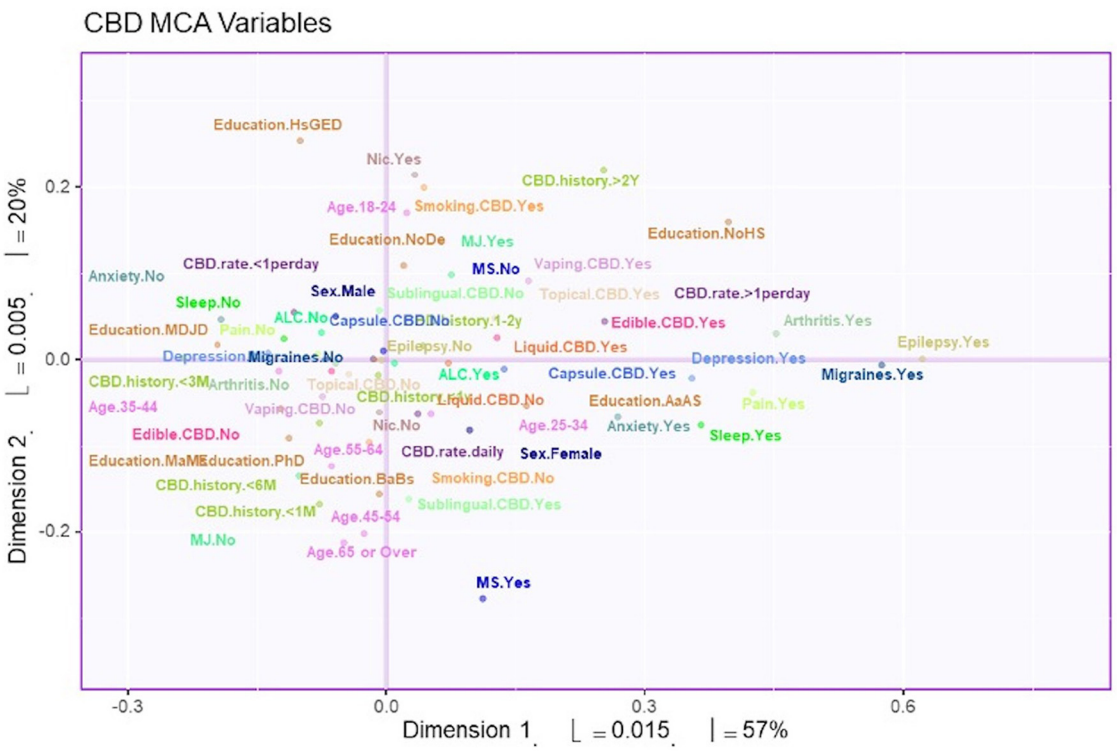

FIGURE 3 | Survey variables plotted on dimensions 1 and 2. The variable factor scores plotted to show dimensions 1 and 2. These two dimensions account for 77% of the total variance. Distance from the axis indicates the association of the variable to the dimension. In addition, two points that are close to each other have greater association with each other.

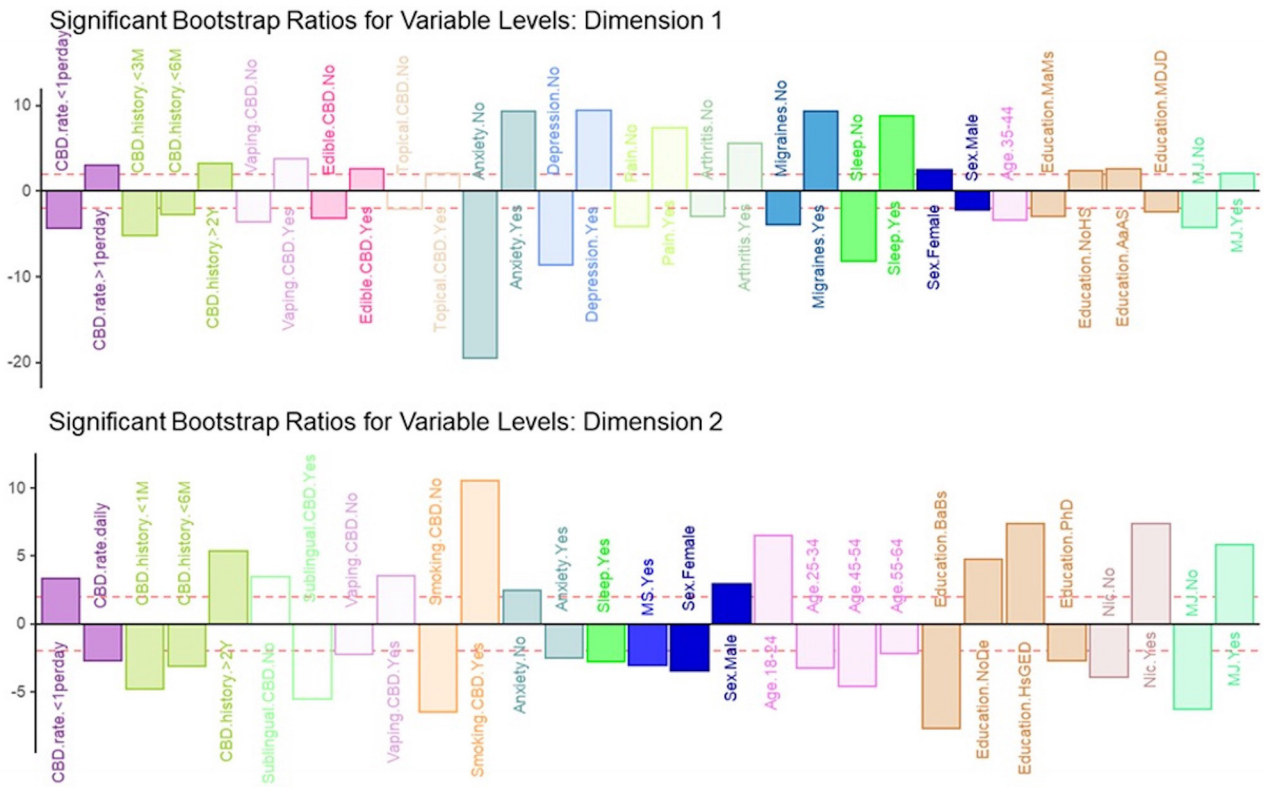

FIGURE 4 | Significant bootstrap ratios for dimensions 1 & 2. Illustration of the significant bootstrap ratios for the variables for dimensions 1 and 2. Bars that are filled-in represent variables with a bootstrap ratio >2. Variables in the same side of the y-axis are positively associated with each other.

TABLE 3 | Ailments attributed to CBD use.

Disorder	Total (*N* = 182)	MJ+CBD (*N* = 105)	CBD only (*N* = 77)	*p*-value
Anxiety	76 (41.8%)	48 (45.7%)	28 (36.4%)	0.206[a]
Depression	51 (28.0%)	35 (33.3%)	16 (20.8%)	0.062[a]
Pain	29 (15.9%)	19 (18.1%)	10 (13.0%)	0.352[a]
Arthritis	21 (11.5%)	16 (15.2%)	5 (6.5%)	0.068[a]
Migraines	20 (11.0%)	14 (13.3%)	6 (7.8%)	0.238[a]
Sleep disorders	45 (24.7%)	32 (30.5%)	13 (16.9%)	0.036[a]
Epilepsy	2 (1.1%)	1 (1.0%)	1 (1.3%)	0.825[a]
Multiple sclerosis	7 (3.8%)	2 (1.9%)	5 (6.5%)	0.112[a]

[a]*Pearson's Chi-squared test.*

CBD, cannabidiol; MJ, marijuana; CBD+MJ, respondents with CBD and marijuana use.

Previous findings have suggested that even though the effects of THC and CBD do not physiologically influence each other, the high rate of MJ co-use in the CBD using population may in part be due to MJ users having greater familiarity with CBD (22). The results of the present study support this claim as co-use was associated with using CBD longer but infrequently. Additionally, the methods of CBD administration that were associated with MJ use were methods that are most commonly seen in MJ use (e.g., edibles, vaping, and smoking) (79, 80).

CONCLUSIONS AND LIMITATIONS

Our findings suggest that co-use of MJ in CBD users may be influenced by several factors, with medical ailments and smoking behavior being primary factors. Although the co-use of MJ in CBD users is associated with factors that have been widely reported to be associated with MJ use, it is surprising to note that the presence of both psychological and medical conditions is more associated with CBD+MJ use than CBD use alone. This suggests that the use of these substances for symptom relief should be an important consideration for future studies.

Limitations

Due to the cross-sectional nature of the present study, the temporal relationship between CBD use and MJ use cannot be established. The present study also relied on self-reported measures and must take into account issues with reliability. Several studies have explored the reliability and validity of survey measures, including those performed online via similar platforms such as those used in this study. These studies have found that respondents tend to use satisficing or choosing "good enough" answers which increases consistency, reliability, and convergent validity of measures but decreases discriminant validity (81). This, along with our quality control procedures and our use of previously validated questionnaires

may mitigate some of the potential limitations of the survey approach. Furthermore, we followed recommendations from previous studies such as: designing the questionnaire in such a way to improve response rates, piloting the survey prior to distribution, and only asking questions that are applicable toward our research goal (82). Based on these recommendations and guidance provided by previous research on using survey approaches to measure substance use (83), we constructed our measurements and analytic approach to avoid common pitfalls. For example, in the survey we emphasized the confidentiality of all information provided by respondents and only used validated measures to minimize measurement error.

Additionally, there is no certainty that the survey respondents truly were diagnosed with the psychiatric conditions they endorsed. In this instance, we assume respondents are taking CBD for symptoms related to endorsed ailments, but these statements cannot be confirmed without professional diagnoses. Moreover, it is likely that due to the nature of the study respondents may have under-estimated their frequency of self-administration, tolerance, and other dependence 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 Internal Review Board, University of Texas at Dallas. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JV developed the study concept and design, conducted the acquisition, analyses and interpretation of the data, and drafted the manuscript. MT contributed to the data analyses and interpretation, and drafted the manuscript. FF contributed to the concept and design of the study and critical revisions and approval of the submitted manuscript. All authors contributed to the article and approved the submitted version.

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Acute Effects of Cannabis Concentrate on Motor Control and Speed: Smartphone-Based Mobile Assessment

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Background: The use of cannabis concentrate is dramatically rising and sparking major safety concerns. Cannabis concentrate contains tetrahydrocannabinol (THC) potencies up to 90%, yet there has been little research on motor impairment after concentrate use (commonly referred to as "dabbing"). This study measured postural control and motor speed after the use of high potency concentrates in males and females.

Methods: Experienced concentrate users ($N = 65$, Female: 46%, 17 ± 11 days/month of concentrate use) were assessed for motor performance in a mobile laboratory before, immediately after, and 1 h after *ad-libitum* cannabis concentrate use. Plasma levels of THC were obtained via venipuncture at each timepoint. We used a remotely deployable motor performance battery to assess arm and leg movement speed, index finger tapping rate, and balance. The sensors on a smart device (iPod Touch) attached to the participant provided quantitative measures of movement.

Results: Arm speed slowed immediately after concentrate use and remained impaired after 1 h ($p < 0.001$), leg speed slowed 1 h after use ($p = 0.033$), and balance decreased immediately after concentrate use (eyes open: $p = 0.017$, eyes closed: $p = 0.013$) but not at 1 h post-use. These effects were not different between sexes and there was no effect of concentrate use on finger tapping speed. Acute changes in THC plasma levels after use of concentrates were minimally correlated with acute changes in balance performance.

Conclusions: Use of cannabis concentrates in frequent users impairs movement speed and balance similarly in men and women. The motor impairment is largely uncorrelated with the change in THC plasma levels. These results warrant further refinement of cannabis impairment testing and encourage caution related to use of cannabis concentrates in work and driving settings.

Keywords: cannabis (marijuana), dab, tapping, acceleration, speed

INTRODUCTION

The use of concentrated forms of cannabis, often referred to as "dabbing," has become increasingly popular (1–4). Advances in production technology have allowed wax or resin dabs (5–7) to contain much greater concentrations of cannabinoids than more typical flower cannabis products. These concentrates often contain high levels of tetrahydrocannabinol (THC), the main cannabinoid associated with psychoactive effects from cannabis. Concentrates, with up to 70–90% THC potencies, are perceived by heavy concentrate users to be more dangerous than flower products, now averaging 10–30% THC (7–11), increase blood levels of THC (12), are associated with illicit drug use (1), higher rates of cannabis use disorder (2) and decreased mental and physical wellness (4, 13). However, the only report of acute physical effects of high-potency cannabis concentrate use that we know of is with a sample of flower and concentrate users in our prior publication (12).

The last two decades of research demonstrate that low-potency cannabis [i.e., up to 7% THC; (14) or 12 ng/ml plasma THC (15)] can impair executive function (16) as well as complex psychomotor performance. This includes maintenance of driving speed, reaction time, joystick errors (17), and simulator driving ability (15, 18–20). Complex psychomotor tasks like these can be sensitive enough to detect acute cannabis intoxication in chronic users (16). For example, low-potency THC was shown to acutely impair visuomotor arm tracking (in participants with a range of histories) (17). Low-potency cannabis effects have also been observed to be dose-dependent (21, 22), which has contributed to the rationale for current legal limits for THC whole blood or plasma levels of 5 or 7–10 ng/ml, respectively (23, 24). For instance, low-potency cannabis use modestly increased the risk of accident involvement in a driving simulator, but this was highly dose- and task-dependent (15). Complex psychomotor impairments from cannabis can therefore be observed in frequent users but are often dependent on dose and task complexity.

Psychomotor tasks that require high cognitive loads and controlled settings (i.e., driving simulations) often lack the precision to detect basic motor impairment [i.e., without enhanced intoxication from combining drug use (25–27)] and so far lack the external validity for use after naturalistic administration of concentrates (containing such high THC potencies). Greater understanding of driving capability after concentrate intoxication requires assessment of basic motor performance, such as the rapid movements necessary for safe driving behavior. In past research, administration of low-potency THC in cannabis users ($\geq$30 total uses) produced subjective intoxication and decreased a common measure of basic motor performance (finger tapping speed), but was uncorrelated with THC plasma levels (28). Similarly, we recently demonstrated that unperturbed balance is acutely impaired after naturalistic use of higher potency cannabis (12). These findings suggest that concentrates may impair other basic motor tasks necessary for successful driving.

To better understand the effects of concentrated cannabis on basic motor performance, potential sex differences should be considered. With few exceptions, sex differences have been poorly characterized in frequent or heavy cannabis users (16), even though men typically consume cannabis more often and in greater quantities than women (29, 30). Medical marijuana laws have led to decreases in automotive fatalities for both men and women, but decriminalization of cannabis led to increases in fatal crashes for men only (31). After legalization, the changing patterns of use and the greater THC plasma levels that arise from concentrate use suggests the need for more detailed information on the basic motor effects after acute intoxication from concentrates (21, 26, 30–33). Low-potency THC administration decreased tapping speed of the non-dominant hand in women more than men (34), yet dominant-hand speed, especially after concentrate use, remains untested between sexes. Another measure of basic motor performance, balance, is similar between healthy men and women in most conditions (35, 36), yet the potential sex effect after cannabis use has not been investigated. Additionally, low-potency cannabis has been shown to decrease complex psychomotor speed more for men than women (37), but the effect of high-potency cannabis on basic motor performance alone has not been assessed.

Using a portable, smart-device based protocol in a mobile laboratory, we previously documented acute cannabis-induced balance impairment in a large sample of flower and concentrate users (12). Here, we examined the use of cannabis concentrate on our complete portable battery of motor tasks in only the concentrate user sample from our previous study (12). Measures were taken before, immediately after, and 1 h after use. The presentation of the balance data here, as compared with our previous paper, allowed us to examine: (1) sex differences in motor impairment, (2) repeated testing effects by trial, (3) correlations between THC plasma levels and motor performance, and (4) inter-task correlations for the entire battery of motor measures: balance under three different conditions and speed of arm extension, leg withdrawal, and finger tapping.

METHODS

Participants

Methodological details pertaining to this sample population, baseline surveys, mobile lab procedures, cannabis potency, cannabinoid analysis, and the balance task are previously published (12) and are summarized below. Participants were recruited from the Boulder-Denver area in Colorado using social media and mailed flyers that summarized study criteria. Trained research staff screened potential participants via telephone. Study participants were oriented to the procedures and provided written informed consent. All procedures were approved by the University of Colorado-Boulder Institutional Review Board in accordance with the standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975 as revised in 2008.

Criteria for enrollment included: (1) aged 21–70, (2) cannabis concentrate use $\geq$4 times in the past month and general cannabis use $\geq$1 year, (3) experience with 90% THC (highest potency cannabis that could be assigned for the study), (4) no non-prescription drug use in the past 60 days, except cannabis,

(5) no daily tobacco use, (6) drinking ≤2 times per week with ≤3 (women) or 4 (men) drinks per occasion, (7) no pregnancy or intention to become pregnant, and (8) no current or history of psychosis or bipolar disorder. The age criteria (range: 21–69 years) were formulated to include a wide range of healthy cannabis users in the community in order to provide generalizable data on motor effects after concentrate use across various age groups.

A total of 75 concentrate users consented to undergo phlebotomy for plasma cannabinoid levels and smartphone-based testing of motor performance in the mobile laboratory vehicle at Pre-Use, Acute Post-Use, and 1 h Post-Use timepoints. Participants that did not complete key motor outcomes and/or did not have plasma data collected that conformed to our criteria (i.e., THC threshold of ≥20 ng/ml at the Acute Post-Use timepoint) were omitted from analysis ($n = 10$). Therefore, the sample of concentrate users studied for this report ($N = 65$) is nearly identical to a previous report of ours [$N = 66$ (12)], however, seven subjects differ between the study samples. Three participants did not complete key neurobehavioral outcomes and were omitted in our previous report. However, those three completed key motor outcomes and were therefore included in this report. Similarly, four participants completed key neurobehavioral outcomes and were included in our previous report, however, those four did not complete key motor outcomes and were omitted from this report.

Study Visits

Baseline Session (Campus Visit)

The Campus appointment included a 1.5-h visit (**Figure 1**). Participants were asked to refrain from alcohol or other recreational drug use for 24 h, cannabis use the day of testing, and tobacco or caffeine products for 1 h prior to the baseline appointment. Upon arrival, participants reviewed and completed the informed consent, a breathalyzer assay (Alcosensor IV, Intoximeter, Inc.; St. Louis, MO), a urine toxicology screen (SafeCup III Clia Waived, Germaine Laboratories; San Antonio, TX), and (for female participants) a pregnancy test (Sure-vue, Fisher Healthcare; Tulane, CA) to ensure that recent drug use or pregnancy were not present. Participants completed a blood draw, neurocognitive tests, and questionnaires.

At the appointment, participants were assigned to a concentrate potency condition (based on a random number table generated by the study statistician) and asked to purchase the assigned product at a local dispensary (The Farm; https://thefarmco.com/). Two concentrate products (70 or 90% THC potency) were set aside for participants to purchase. Federal regulations require that researchers not handle or blind the legal market products for participants. Differences between the two concentrate potencies (70 vs. 90%) were not observed with prior biological or psychomotor outcomes (12) and thus were not directly tested in current data analysis.

Experimental Session (Mobile Visit)

After the baseline appointment there was a 5-day *ad libitum* period for subjects to become familiar with the cannabis concentrate product. After this period, the second and final visit took place in a mobile laboratory (**Figure 1**). Before the mobile laboratory visit participants were asked to refrain from using alcohol or other recreational drugs for 24 h, cannabis use the day of testing, and tobacco or caffeine products for 1 h in preparation for three blood draws over 3-h. The mobile laboratory setting necessitated the use of portable technology to assess self-report surveys, plasma cannabinoid levels, and motor performance.

The experimental session (mobile visit) included three testing timepoints: before (Pre-Use), immediately after (Acute Post-Use), and 1 h after (1 h Post-Use) cannabis concentrate use. Assessments at each timepoint were performed identically and involved a blood draw, neurocognitive tests, questionnaires, and the motor battery. Participants completed the Pre-Use assessments, returned to their residence to weigh and use their desired amount of concentrate product, and were asked to immediately return to the mobile lab for Acute Post-Use and 1 h Post-Use testing.

Demographics and Cannabis Use Questionnaires

During the baseline visit, participants reported their age, sex, race, height and weight for body mass index (calculated), and age of regular cannabis use onset via questionnaire. The Marijuana Dependence Scale [MDS (38)] measured dependency symptoms. The calendar-assisted Timeline Follow Back [TLFB (39)] interview queried participants drug use over the past 30 days. During the experimental mobile laboratory session, the mode of administration [i.e., glass dab rig/tube used primarily (12)], the amount of time participants administered concentrate (in their home), and the amount of concentrate participants reported using was recorded.

Plasma Cannabinoids

A certified phlebotomist collected 32 mL of blood at each timepoint through venipuncture of a peripheral arm vein using standard, sterile phlebotomy techniques to assess plasma cannabinoid levels. Plasma was separated from erythrocytes, stored at −80°C, and sent to the Department of Anesthesiology at the University of Colorado Denver. Two plasma cannabinoids were quantified, THC and 11-OH-THC [the active metabolite with pharmacological activity (40)] using validated high-performance liquid chromatography/mass-spectrometry (41). Less than 5% of all cannabinoid values (22/450 data points) were below the quantifiable limit (<0.32 ng/ml), therefore 0.00 was replaced for those absolute values. Notably, no values less than that lower limit of quantification were observed at the Acute Post-Use timepoint. To ensure that participants followed study instructions and should be included in this analysis, the following cannabinoid criteria were set: (1) a THC measurement was obtained at Acute Post-Use, (2) THC value ≥20 ng/ml at Acute Post-Use, and (3) THC must have increased from Pre-Use levels.

Motor Battery

Materials, Setup and Data Processing

A smart device (iPod Touch 5th generation, iOS 12.11, Apple Inc., CA) and data logging App (Sensor Data, Wavefront Labs) recorded the outcomes for the motor battery tasks. Research

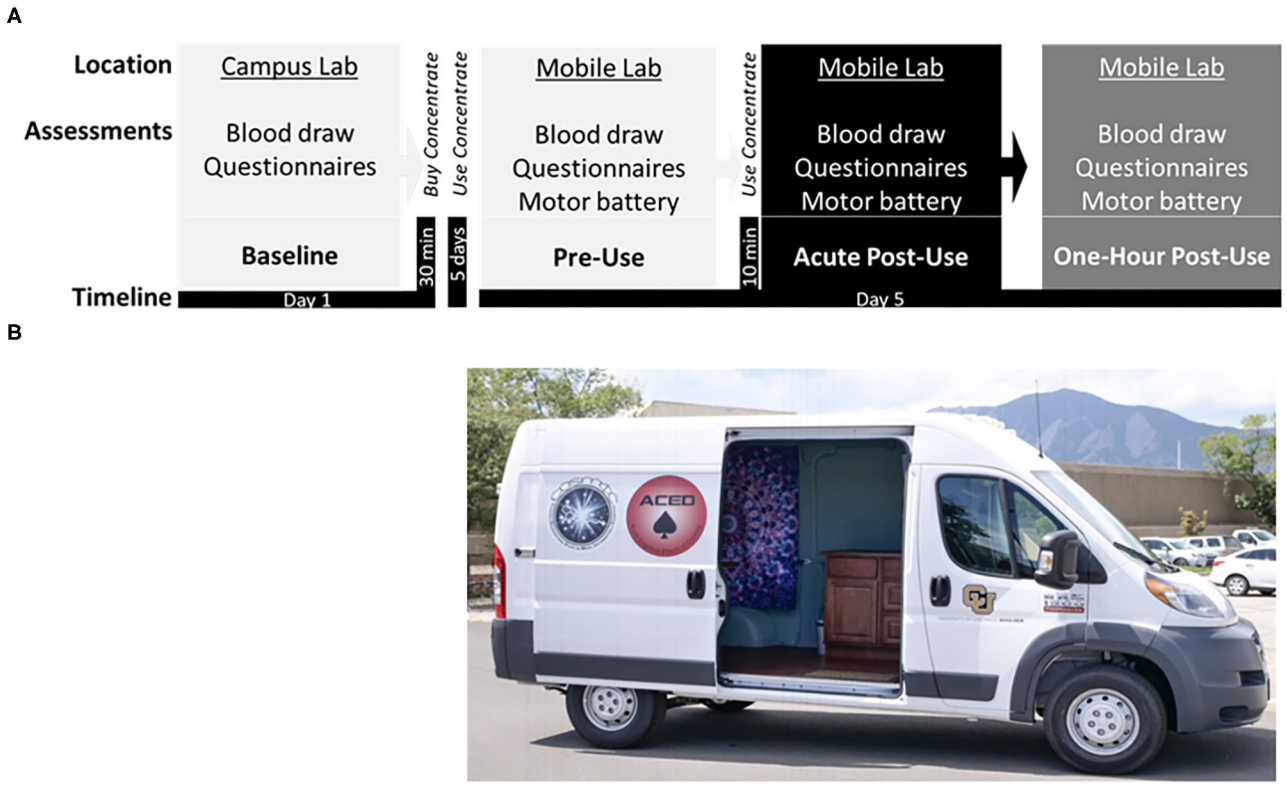

FIGURE 1 | (A) Study timeline displaying the: Baseline session at the campus lab, followed by purchase of cannabis concentrate (70 or 90% THC) at a local dispensary, ∼5 days of *ad libitum* use, and the subsequent Experimental session in the mobile lab, including the pre-concentrate use (Pre-Use) timepoint followed by in-home participant *ad libitum* use of concentrate, and two post-concentrate use timepoints (Acute Post-Use and 1 h Post-Use). **(B)** Photograph of the Mobile Lab, a high-top cargo van retrofitted with a Wi-Fi hotspot, hand rail and stair step, ice cooler, electrical outlets, a reclining phlebotomy chair, sterile equipment, and a chair/table for motor testing.

assistants described and demonstrated each task briefly and provided reminders of technique between tasks. Each task was completed twice, with a rest period of 30s between trials. Data were transferred to a lab computer and imported into the Spike 2 software program (Spike 2, v. 7.14, Cambridge Electronic Design, Cambridge, UK) for visual inspection and analysis. *Motor Battery* **Supplementary Material** provide materials, setup, and processing details for all tasks.

Tasks

Arm Extension

The goal of this task was to assess the ability to use a ballistic contraction to rapidly accelerate the arm over a small distance as is sometimes required during driving. The task was a standardized, abbreviated horizontal punch movement (a "jab").

Setup: An iPod was firmly attached to the distal side of the participants forearm (above the wrist) with the arm at a right-hand angle, while in a seated position.

Directions: Participants were instructed as follows: "*Every time you feel a tap on the iPod, punch your arm straight out as fast as possible and bring your arm back to the starting position*". Ten trials of the rapid arm movement were performed. A pseudo-random, investigator chosen, inter-trial interval of 2–5 s was employed to minimize the ability of the participant to predict the next tap stimulus and reduce confounding anticipatory movements. During this task participants kept their eyes closed, feet on the ground, and non-dominant hand in their lap. Two trials of ten repetitions were performed.

Processing: The identifiable peak in Y-axis acceleration (peak acceleration) that immediately followed the beginning of the movement in the outward direction was taken as the dependent variable (measured in G's, the output unit of the app). The average of the ten trials was taken as the outcome for each measure. Slower arm speeds (smaller peak acceleration values) were taken to indicate worse motor performance.

Leg Withdrawal

The purpose of this task was to create a standardized, iPod-measurable outcome that would simulate the ability to ballistically withdraw the leg in an upward direction as is required in rapid transition from the accelerator to brake pedal during driving. The focus was on the upward phase of the movement.

Setup: An iPod was firmly attached to the distal side of the participants lower leg (above the ankle) while in a seated position.

Directions: Instructions were as follows: "*Every time you feel a tap on the iPod, lift your leg and foot vertically about 6 inches as*

fast as possible, and then return your heel to the ground, keeping your ankle flexed and toes off the ground." During this task participants kept their eyes closed, their hands clasped together at the waist, not resting on the legs. Two trials of ten repetitions were performed (each with a pseudorandom interval of 2–5 s after the leg came to rest).

Processing: As with the arm movement task, the peak in Y-axis acceleration (peak acceleration) that immediately followed the beginning of the leg movement was taken as the dependent variable (measured in G's) with an average calculated from ten trials. Slower leg speeds (smaller peak acceleration values) were taken to indicate worse motor performance.

Index Finger Tapping

The goal of this task was to assess finger tapping speed, a validated measure of general motor function that has been used to assess fine motor control and simple motor speed after intoxication (42–46).

Setup: Participants were seated in a chair with their dominant forearm and palm resting on the corner of the iPod placed on a table.

Directions: The participants were instructed to: "*Tap the corner of the iPod with your index finger forcefully and consistently, as fast as possible, for 20 s, making sure to keep your hand flat while tapping.*"

Processing: The average number of taps per second (tapping rate) was calculated as the dependent variable. Slower tapping speeds (smaller tapping rate values) were taken to indicate worse general motor performance.

Postural Sway (Balance)

This task assesses changes in sway across three conditions, eyes open (EO), eyes closed (EC), and head tilted backwards with eyes closed (HBEC), as was described previously to assess proprioception and intoxication (12).

Setup: A Velcro-compatible elastic belt was wrapped tightly around the hips with an iPod firmly attached to the belt. Across trials and timepoints, the feet were placed 10% of body height apart. The hands were crossed in front of the chest.

Directions: Participants were directed to "*Stand as still as possible for 30 s with your eyes open, followed by 30 s with your eyes closed, followed by a final 30 s with your eyes closed and your head tilted slightly backwards, about 45°.*"

Processing: The order of conditions was the same for all subjects and time points. For each separate condition (EO, EC, HBEC) the standard deviation of acceleration (SD of Acceleration) was calculated as the dependent variable for the last 25s of each 30s trial. Greater SD of Acceleration values per condition were taken to indicate greater postural fluctuations (worsened balance). Methodological details can be found in Bidwell et al. (12).

Primary Statistical Analysis

All statistical analysis was completed using SPSS (IBM Statistics v. 26). Motor performance was first assessed for systematic differences between the two trials at each timepoint, using a General Linear Model Repeated Measures Analysis of Variance (RMANOVA). In the absence of a significant Trial effect, the average values of the two trials were used as the dependent variable at each of the three timepoints. If the Trial effect was significant, the best value of two trials was used as the dependent variable (see *Task Trial Analysis* in **Supplementary Material**).

For each dependent variable, significant main and interaction effects of Time (Pre-Use, Acute Post-Use, 1 h Post-Use) and Sex (Female, Male) are reported. *A priori* contrasts were employed based on the design and goals of the study. The contrasts assessed the significance of changes between timepoints and interactions between independent variables (e.g., sex) and time. Therefore, there was no correction of the $P < 0.05$ significance level within each family of comparisons (e.g., arm, leg, index finger, and balance tasks). The change in cannabinoid levels over the three concentrate use timepoints are reported elsewhere (12).

Demographics and Cannabis Use

Prior to the main analyses, female vs. male concentrate users were compared on relevant demographic characteristics. To test sex differences on race a χ^2-test was used, while *t*-tests were utilized to test sex differences in continuous measures (age, body mass index, and cannabis use measures).

Motor Performance Effects

For the arm, leg, index finger, and whole-body balance tasks a separate RMANOVA, one per task, was used to assess changes in motor performance after concentrate use and whether changes in performance across time were different between men and women. Extending previous balance findings (12), we completed a priori contrasts for each balance Condition (Eyes open, Eyes closed, Head back eyes closed) by Sex. The within-participant independent variable of Time and the between-participants independent variable of Sex were tested as main effects and the Time X Sex interaction was also tested.

Motor Performance and Cannabinoid Correlations

To determine whether a cannabis-related change in performance on one motor task was related to a cannabis-related change on another task, change scores between cannabis timepoints were computed for each significant motor outcome [(Acute Post-Use)–(Pre-Use), (1 h Post-Use)–(Pre-Use)]. Pearson correlations between the change in task performance acutely or 1 h after cannabis use was determined. Only tasks that demonstrated a significant change over time on performance in the primary repeated measure models were tested for associations.

Pearson correlations were also used to determine the relation between an acute change in motor task performance and an acute change in cannabinoid levels immediately after concentrate use. The acute change [(Acute Post-Use)–(Pre-Use)] in motor performance and the acute change in THC or 11-OH-THC levels [(Acute Post-Use)–(Pre-Use) were utilized in these analyses.

RESULTS

Sample Characteristics

Participant ($N = 65$) characteristics are summarized in **Table 1**. Males reported initiating cannabis use at an earlier age and spent less time inside their home between the mobile Pre-Use and Acute Post-Use timepoints compared to females. Other

TABLE 1 | Demographic and cannabis use history by sex.

Measure	Total overall	Sex group	
		Female	Male
Demographics			
N (% of total)	65	30 (47%)	35 (53%)
Age (years)	27.88 ± 9.49	26.63 ± 9.08	28.94 ± 9.83
Race (% White)	69%	73%	66%
Body mass index (kg/m^2)	24.13 ± 3.82	23.65 ± 4.66	24.54 ± 2.92
Cannabis use (Baseline)			
Regular Cannabis Use Onset (age in years)	17.13 ± 2.86	18.02 ± 3.15	*16.35 ± 2.36
[a]Marijuana dependence (0–11)	3.17 ± 2.20	3.37 ± 2.30	3.00 ± 2.13
[b]Overall cannabis use (days/month)	25.83 ± 5.33	25.50 ± 4.91	26.11 ± 5.72
[b]Concentrate use (days/month)	17.02 ± 11.04	15.37 ± 9.55	18.43 ± 12.12
[b]Dabs of concentrate (times/day)	5.13 ± 5.15	4.24 ± 3.70	5.96 ± 6.16
[b]Flower use (days/month)	14.94 ± 10.77	16.90 ± 9.66	13.26 ± 11.52
[b]Drags of flower (times/day)	10.84 ± 7.90	9.91 ± 7.35	11.71 ± 8.41
Cannabis use (acute post-use)			
[c]Concentrate amount used (grams)	0.13 ± 0.19	0.15 ± 0.22	0.12 ± 0.15
Time out of van/spent dabbing (min)	13.18 ± 6.19	15.23 ± 7.17	*11.40 ± 4.61

*Participant [N (% of total sample)] demographics and the average (mean ± SD) value is reported for each measure (units). [a]Marijuana Dependence Composite Score. [b]Timeline Follow-Back (30-day). [c]Amount of study cannabis participant weighed by scale in their home and self-administered during the mobile appointment. Similar Total Overall data previously reported (12). *Significant difference (t-test, *p < 0.05) by sex (male vs. female) denoted. Comparisons were conducted separately for each outcome measure.*

demographic and cannabis use measures were not significantly different by sex.

Motor Performance After Concentrate Use

Table 2 reports the mean % change in motor performance and the repeated measure and within-participant *post-hoc* contrast results between cannabis concentrate timepoints.

Arm Extension Task

For the arm task, there was a main effect of Time [$F_{(1.69,\ 103.12)} = 26.6$, $p < 0.001$] on arm speed and a main effect of Sex [$F_{(1,\ 61)} = 22.2$, $p < 0.001$]. *Post-hoc* pairwise comparisons showed that arm speed was slowed by 15% from Pre-Use to Acute Post-Use ($p < 0.001$) and by 16% from Pre-Use to 1 h Post-Use ($p < 0.001$) (**Table 2**, **Figure 2**). There was no difference between Acute and 1 h Post-Use timepoints ($p = 0.52$). Men extended their arm faster than women, however the changes over time were not different between sexes (Time x Sex $p = 0.097$; **Figure 2**).

Leg Withdrawal Task

For the leg task, there was a main effect of Time [$F_{(1.78,109)} = 3.24$, $p = 0.049$] and Sex [$F_{(1,\ 61)} = 4.33$, $p = 0.042$]. *Post-hoc* pairwise comparisons demonstrated a significant slowing from the Pre-Use timepoint to 1 h Post-Use ($p = 0.033$) and between the Acute and 1 h Post-Use ($p = 0.026$) timepoints (**Table 2**, **Figure 3**) with no difference between the Pre-Use and Acute-Post-Use timepoint ($p = 0.58$). As with arm speed, men moved the leg faster than women but there was no Time x Sex interaction ($p = 0.86$; **Figure 3**).

Index Finger Tapping Task

There was no main effect of Time ($p = 0.10$, **Table 2**) but a main effect of Sex [$F_{(1,\ 61)} = 5.79$, $p = 0.019$] on index finger tapping rate. Index finger tapping was significantly faster for men than women, but the responses over time were not different between sex (Time x Sex interaction $p = 0.64$).

Postural Sway Balance Tasks

These results extend our previous findings of a significant decrease in postural stability, across increasingly difficult balance tasks (Condition: EO, EC, and HBEC) as well as a significant quadratic effect of Time found only for the EC condition in a sample of flower and concentrate users. To determine: (1) overall balance differences between Sex and (2) differences across Time based on Sex from only the sample of concentrate users we assessed each balance condition (EO, EC, and HBEC) over Time (between individual timepoints) and by Sex.

EO Balance

There was a main effect of Time [$F_{(2,124)} = 3.41$, $p = 0.036$, **Table 2**], and neither a main effect of Sex ($p = 0.88$), nor an interaction of Time x Sex ($p = 0.52$). After using cannabis concentrate, EO postural sway increased at the Acute Post-Use timepoint ($p = 0.017$) but 1 h Post-Use did not differ from Pre-Use ($p = 0.11$) or Acute Post-Use ($p = 0.32$; **Table 2**).

EC Balance

There was also a main effect of Time [$F_{(1.74,107.64)} = 4.23$, $p = 0.022$], with postural sway increasing acutely from Pre-Use to Acute Post-Use ($p = 0.013$) with no difference between Pre-Use and 1 h Post-Use ($p = 0.36$) or between Acute- and 1 h Post-Use ($p = 0.062$; **Table 2**). Like EO, there was neither a main effect of Sex ($p = 0.88$) nor an interaction of Time x Sex ($p = 0.99$).

TABLE 2 | Effects of concentrate use over time on motor performance.

Measure	[a]Main effect of Time	Stat	[b]Pairwise effects by timepoint			Summary
			Pre vs. Acute	Acute vs 1 h	Pre vs. 1 h	
Arm speed	$F_{(1.692,103.197)} = 26.605$, $p < 0.001$	% Δ:	−15	−1	−16	Acute & 1 h impairment
		p:	*0.000	0.52	*0.000	
Leg speed	$F_{(1.782,108.724)} = 3.238$, $p = 0.049$	% Δ:	−2	−6	−7	1 h impairment
		p:	0.58	*0.026	*0.033	
Tap speed	$F_{(2,122)} = 2.350$, $p = 0.100$			No main effect of time		
Postural sway						
Eyes Open	$F_{(2,124)} = 3.411$,	% Δ:	14	−4	8	Acute impairment
	$p = 0.036$	*p:*	*0.017	0.32	0.11	
Eyes Closed	$F_{(1.74,107.64)} = 4.227$,	% Δ:	11	−7	3	Acute impairment
	$p = 0.022$	*p:*	*0.013	0.062	0.36	
Head Back/Eyes Closed	$F_{(2,124)} = 0.053$, $p = 0.95$			No main effect of time		

*[a]Repeated measure main effect of Time and [b]Pairwise differences reported between timepoints: before (Pre-Use) and after (Acute Post-Use and 1 h Post-Use) cannabis concentrate use, by mean % change (% Δ) and p-value (*p < 0.05).*

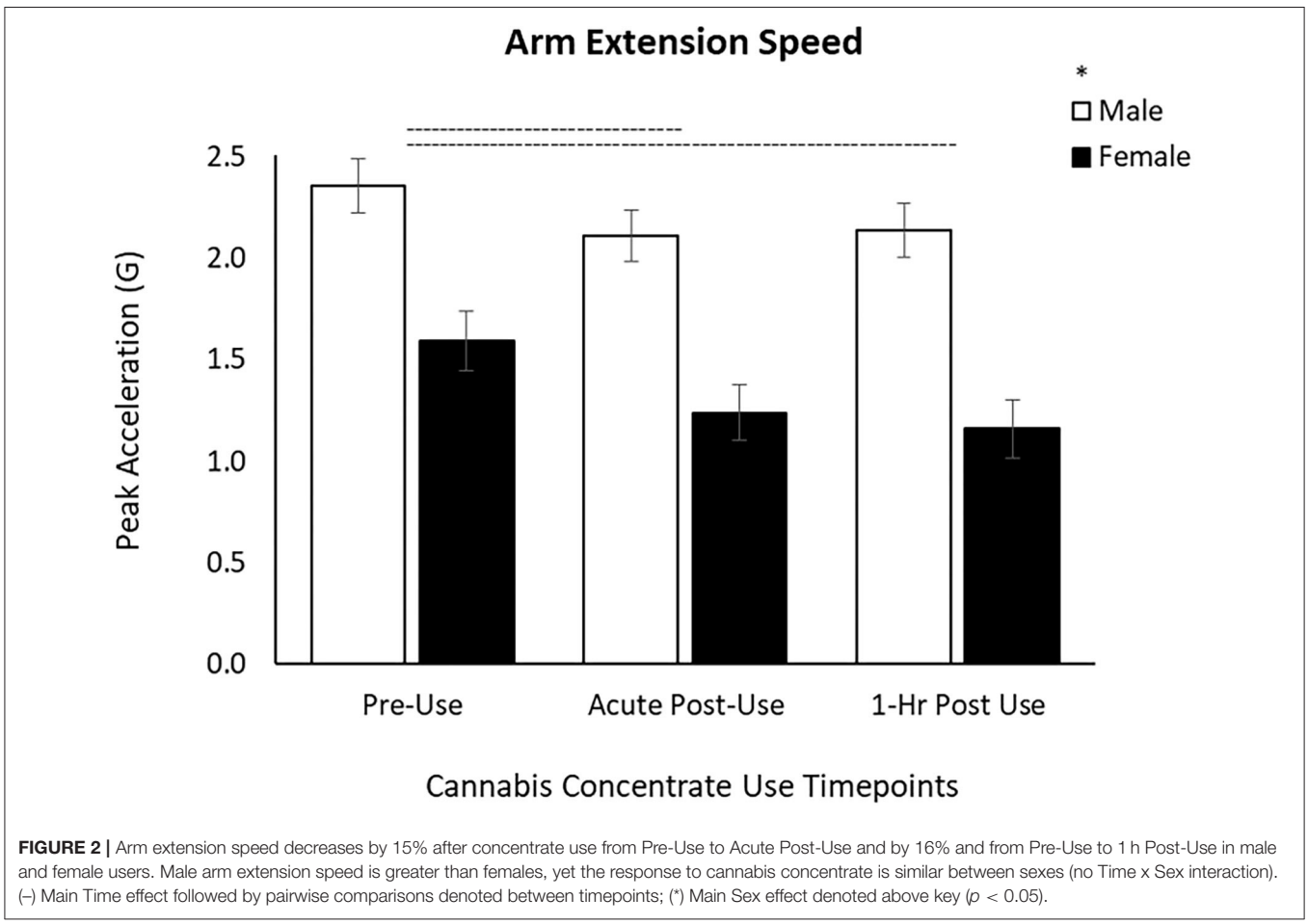

FIGURE 2 | Arm extension speed decreases by 15% after concentrate use from Pre-Use to Acute Post-Use and by 16% and from Pre-Use to 1 h Post-Use in male and female users. Male arm extension speed is greater than females, yet the response to cannabis concentrate is similar between sexes (no Time x Sex interaction). (–) Main Time effect followed by pairwise comparisons denoted between timepoints; (*) Main Sex effect denoted above key ($p < 0.05$).

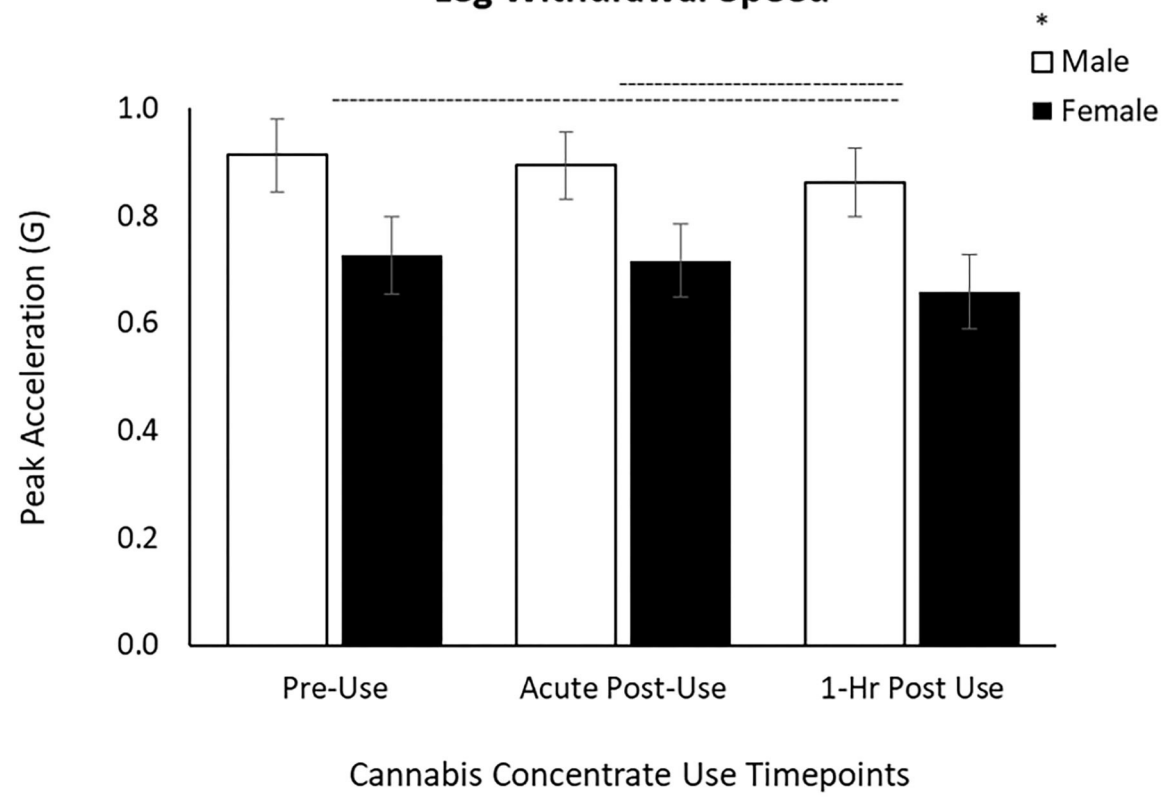

FIGURE 3 | Leg withdrawal speed decreased by 6% between Acute and 1 h Post cannabis concentrate use and by 7% from Pre-Use to 1 h Post-Use in male and female users. Male leg withdrawal speed is greater than females, yet the response to cannabis concentrate is similar between sexes (no Time x Sex interaction). (–) Main Time effect followed by pairwise comparisons denoted between timepoints; (*) Main Sex effect denoted above key ($p < 0.05$).

HBEC Balance

There was no main effect of Time ($p = 0.95$, **Table 2**), Sex ($p = 0.85$), or Time x Sex ($p = 0.33$).

Motor and Cannabinoid Correlations After Concentrate Use

Motor × Motor Correlations

To determine whether a change in performance on one motor tasks was related to a change in another motor task after concentrate use, change scores were computed between Pre and Acute and between Pre and 1 h timepoints, for each motor outcome. The change in performance from Pre-Use to Acute Post-Use was positively correlated between EO and EC postural sway ($r_{64} = 0.381$, $p = 0.002$), and between arm and leg speed ($r_{63} = 0.348$, $p = 0.005$). However, the change in performance from Pre-Use to Acute Post-Use was not associated between arm speed and EO sway ($p = 0.88$) or between arm speed and EC sway ($p = 0.70$). A modest positive association was shown between the arm speed and leg speed change scores from Pre-Use to 1 h Post-Use ($r_{63} = 0.289$, $p = 0.022$) but no other significant between-task correlations were found.

Motor × Plasma Correlations

For the motor tasks that changed significantly after acute concentrate use (arm speed, EO balance, and EC balance), we determined whether this change was correlated to acute changes (12) in plasma cannabinoid levels. Change scores were computed between Pre-Use and Acute-Use for each motor and cannabinoid outcome. To determine if a significant acute change in performance on motor tasks (arm, EO, and EC) is related to an acute change in THC-related plasma levels (plasma THC or 11-OH-THC) after concentrate use, change scores were computed between Pre-Use to Acute Post-Use timepoints for those three motor and two plasma outcomes. In total, there were only two weak positive associations, between the Pre-Use to Acute Post-Use change in EO postural sway and the change in plasma levels of THC ($r_{64} = 0.247$, $p = 0.049$) and 11-OH-THC ($r_{64} = 0.296$, $p = 0.017$).

DISCUSSION

This report on basic motor impairment after the acute use of cannabis concentrates shows altered performance on a battery of motor tasks in frequent users. Cannabis concentrate decreased limb speed with arm and leg peak acceleration

slowing 1 h after use (16 and 7%, respectively). Although men were faster overall for the motor speed tasks, cannabis-induced impairment was not different between women and men. Balance was acutely impaired after concentrate use, both with eyes open and closed (by 14 and 11%, respectively), yet there was no difference in impairment between men and women. In general, cannabis concentrate-induced motor impairments were correlated between arm and leg speed tasks and between balance conditions. However, the rise in acute post-use plasma THC levels (12) was not correlated with acute impairments of speed or balance. The results can inform researchers about future investigational targets on basic motor performance and allow more precise risk assessments to be made by policy makers regarding the impact of cannabis concentrate use on motor impairment.

Arm and Leg Speed Are Impaired After Cannabis Concentrate Use in Frequent Users

This is the first study to investigate movement speed after naturalistic use of cannabis concentrates. The tasks were simple in that they measured the pure ability to generate a rapid, discrete, large-amplitude descending motor command to accelerate an unloaded limb rapidly–with little contribution from sophisticated cognitive processing. There is little previous research assessing cannabis intoxication with simpler motor tasks. Despite no directly comparable findings in the literature, these results can be contextualized by comparing our conclusions with prior work in more complex psychomotor tasks after low-potency cannabis use. Two reports were conducted in small samples of users who were administered low-potency THC in a lab setting and used complex tasks that required a combination of reaction time, cognitive demand, and gross motor speed. The most comparable previous measure to our arm extension task was a target reaching task in response to a choice visual stimulus (47). In that study there was no effect in response speed or accuracy 30-min after THC administration. In a driving simulator study, significant increases in steering variability, decreases in driving speed, and increases in choice reaction time suggests an acute cannabis-induced decrease in motor processing and complex motor speed (15). The present results indirectly expand this conflicting literature in complex arm-related tasks, by confirming an acute and 1 h cannabis concentrate impairment in simple ballistic arm speed.

In the lower limb, the results of Liguori et al. were conflicting in that there was no cannabis effect on braking latency but a decreased ability to maintain a set driving speed in driving simulations (27). Notably, this driving simulation was completed 20–30 min after smoking a low-potency flower cannabis cigarette (up to 3% THC). This begs the question of whether leg movement latency and driving speed (both requiring multiple domains) contain a contribution from raw leg speed impairment, and of whether the timing of impairment is different with concentrated THC products, in that our data shows stronger evidence of impairment at the 1 h timepoint. While past psychomotor and driving simulator studies were necessarily more complex and required multiple domains and movements to be tested simultaneously, our battery of tasks was focused on the production of simple movements isolated to one limb. The reporting of isolated arm and leg speed impairment provides new information on subtle domain-, movement-, and time-specific effects in frequent concentrate users.

Balance With and Without Visual Feedback Is Acutely Impaired After Cannabis Concentrate Use

As with the acute impairments in arm speed, balance ability both with and without the benefit of visual feedback was acutely impaired after concentrate use but normalized after 1 h. In agreement, early research with low-potency cannabis (48) showed impaired balance (wobble board) that worsened as the dose of THC increased. Similarly, Hosko et al. (49) found decreased one-legged balance ability with eyes closed after administration of edible low-potency cannabis, consistent with our finding of impaired balance after high-potency cannabis use. Additionally, a study in experienced cannabis users also supports our findings with a general equilibrium score (as measured by body sway) increasing by ∼11% after smoking the highest dose of flower cannabis tested (3% THC) (27). A cannabis cigarette with 3% THC is modest in potency compared with the typical concentrated product, yet the magnitude of effect was similar with 14 and 11% impairment found in our eyes open and closed tasks after concentrate use in frequent users. This suggests that tolerance to THC has increased with current market trends or that balance ability under these conditions has a ceiling of impairment. Future research needs to determine whether motor performance can be used as a consistent marker of cannabis impairment, especially as it becomes more evident that neither tolerance nor acute plasma THC levels can predict the extent of balance impairment.

Extending prior findings on balance ability (12), the current report has examined balance performance in relation to concentrate use specifically and in more detail. We consider potential sex effects, correlations with plasma THC levels, and the relationship of cannabis-induced changes in balance with changes in other features of motor performance. Postural sway increased acutely after concentrate use but recovered to Pre-Use levels by 1 h, with and without vision. This suggests responsiveness in the balance task and an effect of cannabis concentrates on the neural processing necessary for postural stability. Visual feedback is known to be a dominant source of sensory feedback during postural control. Accordingly, the availability of vision typically reduces postural fluctuations compared with eyes closed (50), suggesting that impairment was robust in concentrate users if detectable even with the benefit of visual feedback. This within-subject design and the relatively large number of participants made it possible to detect small but significant differences in balance after concentrate use in a brief, remotely deployable smart

device-based motor battery. There was no effect of cannabis concentrate on head-back balance, a condition designed to disturb vestibular feedback and challenge balance control. This could be further explored with different types of users, cannabis administration paradigms, or increased task complexity, to provide more precise information on cannabis and proprioception-challenged balance.

Motor Impairment Is Similar Between Men and Women

An overall difference in motor performance between sexes has been well-established, especially for ballistic speed (51, 52). The observed sex differences are therefore expected and indicate that such differences are detectable with a smart device-based, portable movement battery deployed in a mobile, vehicular lab setting. Notably, our large sample and nearly equal number of males and females is a departure from most existing cannabis literature [e.g., (53–55)] and is a strength of this report focused on cannabis and sex effects. To report that cannabis concentrate alters balance, arm speed, and leg speed similarly between males and females, despite documented sex differences in general cannabis use patterns and effects (33, 56–59) fills a critical gap in the cannabis literature (16, 60). The similarity of cannabis effects between males and females may allow for more effective application of impairment testing in future prevention and policy efforts as cannabis use prevalence has begun to converge between women and men (61).

Motor Impairment Is Largely Uncorrelated With Plasma THC Levels

A lack of correlation between plasma cannabinoid levels (THC and 11-OH-THC) and psychomotor effects is in line with most of the cannabis intoxication literature to date (18, 21, 26). For example, Boggs et al. (47) demonstrated that increases in THC plasma levels (5-min after smoking low-potency THC cannabis) were not correlated with either impairment in complex upper and lower limb psychomotor measures, or with subjective intoxication. This agrees with our findings. However, the ability of the present dataset to provide information on potential correlations between impairment in domain-specific basic motor performance (limb speed, whole-body balance, finger movement) at quite high blood cannabinoid levels is largely novel and represents a substantive addition to the cannabis field.

With only a minor correlation found between the change in eyes open balance and cannabinoid levels, no potential effect of sex on balance, and no correlation between the acute change in arm or leg speed and the acute change in cannabinoids, the data suggests that blood cannabinoid levels do not predict the severity of acute physical impairment, at least on these tasks. This means that plasma THC level is limited in precision to predict functionally relevant movement impairment. Although this idea remains under-investigated, with little comparable research on basic motor performance after concentrate use, these findings at least suggest that plasma cannabinoid levels may not be the best measure of physical impairment. This also suggests that public policy needs to be better informed by basic, observational, clinical, and potentially industry research (to better access current market products that are federally regulated). Lastly, this highlights the need to remain critical of our common sobriety measures and to be open to novel investigational methods and devices.

Limitations and Significance for Cannabis Policy

To exclude a potential contribution of time related factors (e.g., boredom, fatigue, learning/testing effects) other than acute cannabis effects, it would be optimal to compare all results in the cannabis-use participants to a non-concentrate use control session in the same participants or to a non-concentrate use control group. We considered the possibility that the time between trials and timepoints could alter performance in a similar manner (fatigue within or between cannabis timepoints) and thus we reported any trial by time effects on performance in the supplemental report and calculated our dependent outcomes accordingly. However, if the time between timepoints (∼60 min) contributed largely to effects, one might expect all tasks would have a similar pattern of impairment over time, which was not the case. This does not entirely rule out these or other potential contributors to the performance declines but does lend support for acute cannabis being a primary contributor to impairments.

These movement speed and balance impairments reported in highly experienced users indirectly support survey-based association studies that positively linked frequency of cannabis use and THC with injuries (i.e., culpability of road traffic accidents, injuries inside and outside of work, minor injuries/accidents, etc.) (62–64). Since recreational cannabis and cannabis use research is legal only for those 21 or older, our results cannot be directly translated to those younger than 21.

The generalizability of balance results to daily living, is high in the sense that adequate control of the body's upright stance is critical for function and safety in humans. Postural stability (balance) is a common component of sobriety assessment and is accepted as a generalized measure of motor control. The ballistic arm and leg measures and finger tapping task were designed to assess raw movement speed, as opposed to the ability to perform a complete functional movement or series of movements as might be required in activities of daily living, driving, and work. A limitation of this approach is that our measure of standardized, abbreviated movement of the isolated limb is only part of a more complex movement that would be required in real life (brake pedal operation, reactive steering during driving, operating machinery etc.). The advantage is the ability to capture precise measures of speed and motor control that contribute to more complex movements in daily living, all using a smartphone-based app in a community-based sample. We believe these to be the first mobile assessments of motor performance in the context of cannabis intoxication.

Methodologically, this report tested within-subject effects before and after using high potency THC in frequent users. These results may therefore not reflect effects that might be observed in novice cannabis users. It is also possible that a much larger sample overall could increase the power to detect effects that in the present data are either borderline significant (i.e., a decrease in tapping rate over time) or non-existent (i.e., an interaction between sex and cannabis use over time). This experimentally derived report balances internal and external validity, using a within subjects design and *ad-libitum* administration of dispensary-grade cannabis concentrate to test effects of high potency cannabis on motor outcomes. The findings may be particularly useful in states that see an increase in the number of frequent concentrate users after legalizing recreational cannabis (65). The results should aid assessment of occupational risk, longitudinal and between-user public health study design, and data-driven policy.

CONCLUSIONS

These findings demonstrate the feasibility of a multi-task, mobile motor performance battery and the utility of combining this with acute measures of plasma cannabinoid levels after naturalistic cannabis administration. The increasingly popular use of concentrated cannabis impairs some, but not all features of motor performance. These findings provide the first evidence that concentrated cannabis slows arm and leg speed. This confirms the importance of assessing basic features of motor performance (i.e., without cognitive demands) after concentrate use. The results also demonstrate that changes in plasma cannabinoid levels are not correlated with limb speed impairments and only weakly correlated with the degree of balance impairment. Additionally, the cannabis concentrate effect on limb speed and balance is not different between men and women. Notably, motor effects are largely without meaningful correlation with plasma cannabinoid levels, highlighting a critical issue in past and future research, clinical evaluations, professional/work settings, legal assessment of cannabis intoxication, and public health and policy.

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 University of Colorado Boulder Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LH: data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing–original draft, and writing–review and editing. BT: conceptualization, formal analysis, methodology, project administration, resources, software, supervision, validation, writing–original draft, and writing–review and editing. AB and KH: conceptualization, funding acquisition, methodology, and writing–review and editing. LB: conceptualization, funding acquisition, methodology, project administration, resources, software, supervision, and writing–review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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REVIEW
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When Cannabis Use Goes Wrong: Mental Health Side Effects of Cannabis Use That Present to Emergency Services

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Cannabis use is a modifiable risk factor for the development and exacerbation of mental illness. The strongest evidence of risk is for the development of a psychotic disorder, associated with early and consistent use in youth and young adults. Cannabis-related mental health adverse events precipitating Emergency Department (ED) or Emergency Medical Services presentations can include anxiety, suicidal thoughts, psychotic or attenuated psychotic symptoms, and can account for 25–30% of cannabis-related ED visits. Up to 50% of patients with cannabis-related psychotic symptoms presenting to the ED requiring hospitalization will go on to develop schizophrenia. With the legalization of cannabis in various jurisdiction and the subsequent emerging focus of research in this area, our understanding of who (e.g., age groups and risk factors) are presenting with cannabis-related adverse mental health events in an emergency situation is starting to become clearer. However, for years we have heard in popular culture that cannabis use is less harmful or no more harmful than alcohol use; however, this does not appear to be the case for everyone. It is evident that these ED presentations should be considered another aspect of potentially harmful outcomes that need to be included in knowledge mobilization. In the absence of a clear understanding of the risk factors for mental health adverse events with cannabis use it can be instructive to examine what characteristics are seen with new presentations of mental illness both in emergency departments (ED) and early intervention services for mental illness. In this narrative review, we will discuss what is currently known about cannabis-related mental illness presentations to the ED, discussing risk variables and outcomes both prior to and after legalization, including our experiences following cannabis legalization in Canada. We will also discuss what is known about cannabis-related ED adverse events based on gender or biological sex. We also touch on the differences in magnitude between the impact of alcohol and cannabis on emergency mental health services to fairly present the differences in service demand with the understanding that these two recreational substances may impact different populations of individuals at risk for adverse events.

Keywords: cannabis, adverse events, cannabis induced psychosis, acute intoxication, mental health, emergency department, emergency transport

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INTRODUCTION

Cannabis is one of the most frequently used recreational drugs in the world with the United Nations Office on Drugs and Crime estimating that 192 million of the global population used in the past year (1). Cannabis-related adverse events, such as those requiring presentation to an emergency department (ED) or Emergency Medical Services (EMS) presentations, have had limited research compared to some of the other potential longer term negative effects, and the limited research and knowledge translation in this whole area has not fully addressed the public perception that cannabis use is harmless, being as safe or safer than alcohol (2–4). However, there is a growing body of evidence showing that like all other drugs known to mankind, some individuals will indeed experience adverse outcomes with cannabis use.

Cannabis use is becoming recognized as a modifiable risk factor for several adverse effects on human health, including mental illness (5). While the literature indicates a strong association with the development of psychotic disorders; mood and anxiety disorders as well as suicidal ideation have also been reported (5–7). Although physical health is not the focus of this article, there are several reported medical adverse events that are of concern, such as cannabinoid hyperemesis syndrome, lung injury with vaping cannabis and arrhythmias (8–11). Additionally, the role of cannabis in trauma (e.g., motor vehicle collisions), injuries (e.g., falls), and in acute negative effects in conjunction with illicit drug use, are causes of ED admissions (12).

With respect to cannabis use as a modifiable risk factor for the development and exacerbation of mental illness, there are signals emerging from ongoing research that indicate that early (e.g., adolescent) and regular (daily or almost daily) use, as well as the use of high potency products [high in delta-9-tetrahydrocannabinol (THC)] may be particular risk variables (13–15). These risk factors appear to decrease the average age for developing a mental illness and are attributed to an increased incidence of mental illness and increase the risk for development of a cannabis use disorder [e.g., for psychosis (14, 16)]. Cannabis use is also associated with exacerbation of and possibly development of anxiety disorders and depressive disorders but the evidence is mixed and not yet as extensive as that for the association with psychosis (7, 17, 18). When gender is considered, women tend to use less cannabis, but what minimal evidence exists suggests that women may be at even greater risk of negative effects; further, data outside a binary gender spectrum with cannabis use are almost non-existent (19). It remains unclear why some individuals develop these conditions as an adverse reaction to cannabis use while others do not. Genetic factors are likely involved and research focusing on this interaction has been promising; however, work to date has suggested that most mental illness is polygenic in origin and thus our understanding of the genetic basis for both acute and long term adverse effects may take some time to unravel (20–22). Another avenue of research in this area is the study of epigenetic mechanisms (e.g., DNA methylation) which has also shown some promise (23). Ultimately, modifying cannabis risk behaviors and early identification of high risk individuals may be our best approach from a public health standpoint in reducing both acute and long term adverse events.

Early identification and treatment of illness is vital to maximize positive outcomes in both physical and mental health. Early intervention services (EIS) for mental illness have been shown to significantly alter disease trajectory, decreasing personal, family and health care burden (24). However, a significant number of index (first) referrals to mental health care are from the Emergency Department (ED), implying that mental health concerns have already reached a critical level such that emergency services are required. For example, between 50 and 55% of youth and young adults accepted to EIS for psychosis are being referred from ED pathways (19, 25). Importantly, there is also a significantly high level of cannabis use in the EIS for psychosis demographic (26, 27) both at entry to care, and after a diagnosis is subsequently made. Studies report up to 50% of cannabis users that have ED presentations with subsequent hospitalization for cannabis induced psychosis, will go on to develop schizophrenia (28, 29). A broad concern with cannabis use and psychosis is a recent study examining population attributable fractions and incidence of schizophrenia that concluded that first episodes of psychosis would be reduced by 12% if high THC content cannabis was not available (14). It is yet unclear if a similar pathway may exist from ED to development of an anxiety disorder or depressive disorder with cannabis use in youth despite studies of long term cannabis users and cross-sectional survey that show higher rates of these disorders in cannabis users (7, 17, 18).

With the legalization of cannabis in various jurisdictions, there is an emerging focus of research in the understanding of who (e.g., age groups, risk factors) are presenting with cannabis-related adverse mental health events, particularly in an emergency (i.e., ED) situation. The popular point of view that cannabis is relatively harmless to use, which may be increasing ED presentations associated with it, seems to be related to the legal transition from medical cannabis to recreational cannabis permitted use (30, 31). It is evident that ED presentations should be considered as potentially harmful outcomes that need to be examined and considered when discussing the impacts of cannabis legalization. In the absence of a clear understanding of the risk factors for mental health adverse events with cannabis use it can be instructive to examine what cannabis use characteristics are seen with new presentations of mental illness both in EDs.

In this narrative review, we will discuss what is currently known about cannabis-related ED and EMS presentations of mental presentations of mental illness, discussing risk variables and outcomes both prior to and after legalization, including our experiences following cannabis legalization in Canada. We will also discuss what is known about cannabis-related ED adverse events based on gender (including transgender individuals) and biological sex. Where possible, we will discuss the differences between alcohol and cannabis on impact on mental health services to fairly present the magnitude of the impact with the understanding that these two recreational substances may impact different populations of individuals at risk for adverse events.

APPROACH TO THIS REVIEW

This is not a systematic review. However, to inform the reader of the approach taken we supply this brief overview of the method. Searches of Pubmed/Medline were conducted from July, 2020 to October, 2020 for the terms cannabis or marijuana and emergency department and adverse events or mental health or prevalence. A similar series of searches were conducted substituting emergency transport, ambulance, emergency mobile units for emergency department. However, the addition of the mental health term to the emergency transport searches was found to be too restrictive so the search was done with emergency transport or ambulance or emergency mobile units (ambulance MeSH terms) and cannabis or marijuana. We did not include presentations due to synthetic cannabinoids in this article. Google scholar was also searched for the same terms. Papers found were then scanned for mentions of mental health impacts associated with confirmed cannabis use in the emergency department and emergency transport setting. The reference lists from the papers located were also hand searched for relevant articles. Published studies from case series to systematic reviews were included in this manuscript.

CANNABIS AND ED PRESENTATIONS FOR MENTAL HEALTH CONCERNS: THE STATS WE KNOW

Cannabis-related mental health adverse events precipitating Emergency Department (ED) presentations can include anxiety, suicidal thoughts, psychotic or attenuated psychotic symptoms, and can account for 25–30% of cannabis-related ED visits (32). While these presentations do not constitute a large number of cases overall, they are concerning for the longer term mental health of the presenting individuals. Cannabis-related complaints also account for a small but important proportion of EMS presentations (3.8%) (4). Depending on co-ingestion of alcohol or other substances, 19–37% of these will not be transported to ED as some presentations such as acute anxiety may be managed entirely by paramedics on scene, thus still requiring use of health resources (4). Cannabis-related ED presentations have begun to be explored in more depth recently, due in part to increasing numbers of jurisdictions that have cannabis legalization (medicinal and recreational). In this first section of this review we discuss what we know about the frequency of cannabis-related mental health presentations from a variety of geographic areas.

The literature on this topic is limited in scope, and what does exist is derived mainly from US data. One such example using the Nationwide Emergency Department Sample (NEDS), one of the largest all-payer ED datasets in the US, Shen et al. (33) reported a 7 % increase annually of ED visits associated with cannabis use from 2006 to 2014 (33). While not detailed for diagnoses, they reported that 30% of cannabis use ED presentations were associated with individuals who had a co-morbid mental health disorder. There are additional US studies focusing on state level data. Perhaps not surprisingly, there is a concentration of studies out of Colorado where cannabis was legalized for medical use in November 2012 and recreational use in January 2014. An overall increase in demand for emergent medical care is shown in Colorado state-wide and single site studies that have reported significant increases in ED visits with cannabis-related billing codes for similar time frames (34–36). Wang et al. (37) reported that of those ED visits with cannabis billing codes, mental illness was the most prevalent diagnostic code. Wang et al. (34) also examined an adolescent (>13 and <21 years of age) population in a Colorado tertiary care pediatric hospital system. They reported a statistically significant increase in adolescent cannabis-related ED and urgent cares visits from 2009 to 2015 (34). A Colorado statewide study using a sample size of over 4 million ED visits found a 5-fold greater prevalence of mental health diagnosis among ED visits with cannabis associated codes, compared to ED visits without cannabis associated codes (38). This study used administrative data from the Colorado Hospital Association ED discharge data and looked for a cannabis exposure combined with a mental-health related code as the outcome. It should be noted that the number of cannabis-related ED visits in this data set (0.8%) were dwarfed by the number of alcohol-related visits (36%) (38).

An inner city hospital ED in Flint, Michigan, USA was the site of a prospective study with an online screening survey administered to 14,557 individuals who were admitted to the ED in association with substance use for either medical or injury reasons (39). This survey captured information on substance use (including cannabis) and also used the Short form health survey (SF-12) to gauge a quick measure of the individuals overall physical and mental health. Though not comprehensive, the SF-12 is a good fit for the ED setting where survey time can be limited. In the SF-12's domain of mental health which is characterized as a measure of psychological distress and well-being, substance use was associated with being in the bottom quartile of this measure (40). This study excluded suicidal individuals and while 6% of the sample met criteria for cannabis abuse/dependence, the mental health component was not broken out by substance used (39). Similarly, in Nevada, legalization came into effect for medical cannabis in 2013 and recreational cannabis use in 2017. 40 used the Nevada State ED database and showed cannabis-related ED visits were up 23% from 2009 to 2017. The characteristics of the groups most contributing to this trend were individuals 21 to 29 years old and female sex and 26% of the sample had co-morbid mental health issues (41). Of note, the ages 21–29 demographic comprised 52% of ED visits for cannabis-related complaints in 2017 (41). It should be noted that much of the US data may be underestimating the effects of cannabis as the decision as to whether to go to an ED in the US can depend on medical insurance coverage, as shown by studies showing decreasing appearances by uninsured individuals (42). Interestingly, while it is unknown if this can be generalized outside of the US, there is data suggesting that in a state with legalized cannabis, alcohol is not commonly associated with concurrent cannabis use in either the recreational or medical context (43).

ED usage for mental health concerns after cannabis legalization in Canada has been less well-studied but there

is a small body of literature beginning to emerge in this area. Recreational cannabis was legalized for use on October 17, 2018 after cannabis use for medical purposes was regulated from 2001. A crude estimate of morbidity impact in Canada of several cannabis associated events reported an estimate of 106–186 cannabis-attributable incident cases of schizophrenia in Canada per year (44). Most of these individuals will first identify to the ED and while the number is not high, the burden from this chronic condition on a publically funded health care system is measurable. Even prior to legalization the demand for mental health care in conjunction with cannabis use was significant and one study at a small urban center in Ontario, Canada showed that 8% of cannabis-related ED cases required inpatient psychiatric care (45). Hospital admission was more likely for cannabis induced psychosis (45).

The legalization of cannabis for recreational use was in part tied to gatherings in support of the movement on April 20 each year (4, 6–21) so it may be of interest to note that there is a Canadian study examining the impact of cannabis use at mass gatherings of 4–20 celebrations on emergency service demand. A study conducted across 6 regional hospitals in British Columbia, Canada over a 10 year period (2009–2018) showed significant increases in admissions for substance induced mental health disorders and cannabis intoxication on 4–20, compared to control days (46). Studies suggest the need for advance planning for emergency mental health services in conjunction with cannabis mass gatherings.

There have been a small number of studies comparing cannabis outcomes before and after legalization in Canada. One pre-post legalization study found a 45% increase in cannabis related ED visits post-legalization compared to pre-legalization across 14 urban ED centers in Alberta, Canada. Though this is a large percentage increase, this only translated into 3 additional visits per ED per month (47). Interestingly there was a small decrease in visits related to what the authors call psychological co-diagnoses post-legalization, which included psychosis and anxiety related disorders. However, the authors also noted a significant increase in individuals leaving the ED with a cannabis-related complaint without receiving treatment, which may account for the "missing" individuals (47).

Interestingly, there have been reported increases in cannabis-related ED visits in countries where legalization has not occurred, thus reflecting a possible overall societal change in attitudes toward cannabis use. For example, in southern France, Noel et al. (48) reported between 2009 and 2014 a statistically significant increase of ED visits related to cannabis exposure overall and by age group, including rate changes of 12.6 to 24.3/10,000 for 15–20 year olds and 8.0 to 11.7/10,000 for 21–26 year olds. While they reported a higher proportion of males in the 15–26 age group, the F:M ratio in younger age groups was the same (48). In Switzerland, cannabis has been decriminalized for minor possession in 2012 but not legalized. A retrospective study from one center in Switzerland examined all ED visits over a 4 year period from 2012 to 2016 (49). This study found that while <1% of overall ED visits were due to acute illicit drug toxicity, 26% of these cases were related to cannabis, second only to cocaine. Unfortunately, despite mental health effects being reported for the whole dataset they were not divided by specific substances used, which has been a common finding during our literature search for this paper (49). Another large retrospective study from Switzerland was recently published on ED visits related to acute toxicity (50). In the cannabis only group (26% of the sample of 717 visits), the average age was 26, 77% of the sample was male, and 43% of the sample came to the ED by ambulance. Twenty three percentage of these "cannabis only" individuals reported anxiety as their primary symptom. The majority of the cohort was discharged from the ED and considered by the authors as having experienced minor toxicity; however, 7% experienced psychosis and 8% of the cannabis only group were referred to psychiatric care. The most common substance detected in conjunction with cannabis in the other cases studied was alcohol (50). The cannabis and alcohol group presented with more agitation and aggression than the cannabis alone group which had significantly more anxiety than the combination group. Interestingly, there was no difference in the rate of presentations of psychosis between the cannabis only and the cannabis/alcohol groups (50).

In Australia, where cannabis has been decriminalized in some states, one study examined the nursing triage notes of 263 937 ED admission records over a period from 2004 to 2006 from two hospitals in Sydney, Australia (51). Alcohol related presentations far outweighed cannabis ones at 5% for alcohol and 2% for all other illicit drugs combined. Within the 2% of illicit drugs, 14% were cannabis and cannabis had the highest odds ratio (7.6) of being associated with a mental health primary diagnosis code (51). The patients in the alcohol and drug ED visit categories were also more likely to be under 30, and require more ED resources such as arriving by ambulance, being triaged as urgent or be an after-hours visit. This study was interesting also for its design, comparing nursing triage notes to ICD codes, reporting that the nursing free text detected more of the drug related diagnoses (51).

A study from Turkey, where cannabis is illegal except as approved cannabinoid pharmaceutical preparations for medical purposes as per legislation passed in 2016, showed that 44% of ED admissions associated with street drug use were for cannabis (52). However, this only comprised 0.2% of total ED admissions for the urban low income ED under study at a tertiary care center (52). This study reported on the frequency of hallucinations (verbal or auditory); approximately 3% of the sample experienced these psychotic symptoms but the reporting was not categorized by drug used; however, it is worth noting that there were no amphetamines or opioids used by the cohort in this study (52). Again, this study illustrates the challenges on getting broad but detailed data on the impact of cannabis use on mental health.

The literature on the impact of cannabis use on ambulance transport to the ED is very sparse. Despite this, reporting on the existing literature compliments the cannabis related ED presentation studies. The assessment of first responders is the most contemporaneous and well-positioned to capture detailed information about drug use that may be obtained from multiple sources as opposed to the patient themselves. Additionally, we know from the ED studies that a significant number of patients who present with adverse events associated with cannabis use depart the ED either prior to receiving treatment or against doctor's orders. This raises the question as to whether there is

another group of patients receiving some EMS care but refusing transport to the ED at all. What we know about cannabis involved EMS attendances is primarily from studies done in Australia. Expanding our focus more broadly to encompass all mental health presentations to the ED, there is some evidence that ambulance transport to the ED is increasing including when substance use is involved, with one study showing an increase from 35.6% in 2004 to 45.1% in 2013 (53). If we look more closely at transport to the ED for cannabis associated events, a review of trends of EMS use over time in Australia showed increasing use of EMS over time, and interesting age-group trends. Patients using cannabis-only tended to be slightly younger (15–29 years of age). Cannabis only individuals also were less likely to be transported to hospital with the non-transportation rate being 37% for this group and an additional 20.7% being assessed as not requiring any further emergency treatment (4). This was significantly different from the cannabis and alcohol combined patients who had the greatest police involvement rate and were more likely to be encountered in public outdoor areas (4). This study also found that rates of cannabis-related ambulance attendances among the total population increased significantly over the study period and concerningly, attendance rates for young females (15–29 years old) associated with only cannabis showed the second highest rate of change in attendances (increasing from only 0.2 attendances per 100,000 population per year to 7.1). Alcohol was by far the most frequent co-intoxicant across the study period (4). One further study out of Norway reported 35% of injection drug overdose EMS contacts were in individuals who used cannabis 2 or more days a week, suggesting a troubling co-use concern (54). Unfortunately, the difficulty in conducting this type of research even in the setting of retrospective database searching is that intoxicated patients will often refuse transport and ambulance crews may not see the value in recording this information so a record of contact is lost (55).

Cannabis use harms are also present in users aged 50 and older. This demographic (ages 45 to 64) is showing significant increases in use levels in Canada post-legalization (3, 56). Cannabis related ED presentations in this population has been found to be associated with greater healthcare usage regardless of amount or frequency of use, and the likelihood of injury was increased with the presence of any mental health disorder in these individuals (57). A study in South Carolina examined what drugs if any were found in the system of patients admitted to the ED who had a pre-existing mental illness and were ultimately admitted into a psychiatric inpatient service from the ED. THC was most common, found in 40% ($n = 191$) of patients with alcohol being third at 15% ($n = 72$) (58). The mean age of this sample was 37 years but ranged from 18 to 97 years (58). Unfortunately, this retrospective study did not breakdown the admissions by mental health diagnosis.

Overall a picture emerges of cannabis-related ED visits with comorbid mental health presentations being not uncommon and may be on the rise. Additionally, while less common than alcohol related ED visits, cannabis-related ED visits may present a higher level of service demand including mental health admissions and follow up.

CANNABIS AND ACUTE MENTAL HEALTH PRESENTATIONS

There are fewer studies that have specifically examined cannabis toxicity ED presentations and associated mental health symptoms, and fewer still that directly connect EMS attendances to acute or future mental health symptoms. However, development of acute psychiatric symptoms can be the hallmark of cannabis poisoning or cannabis toxicity. Cannabis poisoning can be considered an accidental overdose resulting in a constellation of physical and mental health side effects, including psychosis, anxiety, and paranoia. When codes for cannabis poisoning were examined in the national emergency department sample in the United States, it was found that individuals who were experiencing cannabis toxicity were significantly more likely to present as having a psychotic, anxiety, mood, or behavioral/emotional disorder and that the association with this presentation was stronger for females than males (59). Shelton et al. (60) employed an administrative database coupled with a chart review for the period of 2012–2016 and found that of cannabis-related ED visits, 24.8% were for psychiatric reasons compared to GI causes at 30.9% and intoxication at 29%. Particularly concerning in this study was that among the acute psychiatric symptoms, 74% of these individuals presented with suicidal ideation, anxiety and psychotic symptoms. They also reported a statistically significant increase in the number of ED visits for each year examined ($p = 0.016$, 0.015, and 0.013 for psychiatric, gastrointestinal, and intoxication, respectively) (60). The Euro-DEN project has studied the acute toxic effects of cannabis. In a study across 10 European countries, 16.2% of ED presentations involved cannabis alone or in combination with alcohol or other illicit drugs. Of the cannabis only presentations that were considered cannabis poisoning/toxicity, the most common mental health presentations were agitation/aggression (22.9%), psychosis (20%), and anxiety (20%). This was not a large sample size (35 cases). However, from a health services demand perspective, it is interesting to note that 21 of the 35 cannabis only cases arrived by ambulance and four were admitted to an inpatient psychiatric unit (32).

New York, USA decriminalized possession of <25 g of cannabis in 1970; however, the law was not uniformly applied so clear legal use was not seen there until legalized medical cannabis use was signed into law in 2014. A 2016 study based on prospective data from two urban hospitals compared 87 patients attending the ED who reported exposure to any cannabinoid to 17 patients who used synthetic cannabinoid receptor agonists (SCRAs) (61). They concluded that SCRAs had significantly greater neurotoxicity than cannabis alone; however, the table of neurological profiles included in the paper shows very similar values between the two patient groups except for agitation which is worse with SCRAs at 41% but still present at 16% for cannabis alone and delirium was only reported for the cannabis group (61). A strength of this study was the confirmation of use within the previous 24 h but a potential weakness is that recruitment only occurred during business hours (61).

Cannabis is often referred to in marketing materials as being an anxiolytic. Though unproven, this assertion is often promoted by staff at cannabis dispensaries (62, 63). This is primarily based on studies in rodents as in humans cannabis is more frequently reported to have anxiogenic effects. There is little evidence to support the anxiolytic properties of cannabis when used by humans. High grade evidence is lacking as shown in a recent meta-analysis and systematic review (64). Acute anxiety can be a feature of cannabis poisoning or acute toxicity. Some naïve users will experience acute anxiety that does not abate quickly and present to the ED. The Nationwide Emergency Department Sample in the United States was used to examine factors associated with acute accidental cannabis poisoning based on ICD-10 codes (59). They found that the association between cannabis poisoning and meeting criteria for an anxiety disorder was significantly higher (adjusted odds ratio of 2.82) as well as criteria for a mood disorder (adjusted odds ratio 2.30) for females than males (59). Measuring anxiety symptom presentations to the emergency department may underestimate the number of cases associated with cannabis poisoning. This conjecture is based on EHS studies, paramedics may often be resolving these presentations without transport (4). This would suggest that acute anxiety presentations may be more prevalent than currently understood but are not sufficiently severe to require ED services. However, this aspect of is not well-studied.

In summary, cannabis use does seem to be directly related to the development of new mental health symptoms in a minority of users but the evidence grade is not high at this juncture and more work is needed.

CANNABIS USE AND EMERGENCY HEALTHCARE SERVICE UTILIZATION

The most thorough manner to study ED service utilization with mental health presentations would be to not only collect administrative data but also to attempt to further characterize the patients attending the service. A recent study that is a step toward comprehensively studying the association between cannabis use and emergent service needs prospectively enrolled ED patients with an average age of 45 years (range 18–88 years) who had ever used cannabis. Unfortunately, the majority of participants (60.8%) had not used any cannabis in the past 30 days and it was unclear when the individuals in the group had last used or what their lifetime use pattern was. However, within these limitations the study shows some profound results. The median age for first use was 16 years old. Cannabis motives were examined and the second reason given for use at 30% ($n = 89$) was to treat anxiety and the fourth most common at 17% was to treat depression (65). While this suggests self-medication for individuals enrolled in the study who had mental health conditions, it is important to note that the majority (77%) began using cannabis prior to the onset of their mental health condition (65). Additionally, 59% of patients reported anxiety in the previous 30 days and 46% reported serious depression in the same period. Most concerning, 9% of the sample reported suicidal thoughts in the past 30 days (65). A point in favor of the study, it was a fairly balanced dataset for sex (52% female and 48% male) as well as ethnicity 55% white, 42% African American, and 1.7% Hispanic. A limitation of this study could be considered the lack of clarity around lifetime use levels with the inclusion of those who had ever used cannabis, and similarly, the majority of the sample not having a recent use pattern to compare to outcomes.

The impact of cannabis use on emergency services in conjunction with mental health concerns may be affected by the route of administration. Cannabis edibles can be much more variable with regard to THC content and even exceed the dose delivered by inhalation in some cases (66). While only 0.32% total cannabis sales in Colorado between 2014 and 2016 were edibles, 10.7 % of cannabis-related ED visits were related to edibles (36). Significant levels of intoxication and even accidental coma and death have been reported with cannabis edible use as well as some evidence of increased psychosis risk with intoxication by this route and concerns about lowered age of initiation (67). This underscores the need to further study the various modes of cannabis use to elucidate the strength of these relationships and establish causality.

There have also been studies that focused on examining health care utilization for those individuals presenting with cannabis-related ED presentation. One example is a study examining healthcare utilization by persons with cannabis use disorder in the US using the 2005–2013 National Surveys on Drug Use and Health data that found 40% of their sample reported an ED admission in the past year. The subgroup of individuals who had cannabis use disorder and a major depressive episode in the past year had the second highest prevalence of ED visits at 50% of the group (68). This study also highlights the paucity of studies that examined depressive symptoms and disorders in the context of ED visits associated with cannabis use.

Victims of suicide and suicide attempts will often require EMS and ED services. Suicides are difficult to study in conjunction with cannabis use. Metabolism and circulation cease with death leading to some researchers who study motor vehicle fatalities to contend that THC levels seen in post-mortem samples to be more accurate measure of the amount of THC present at the time of the crash then studies then those sampled in the ED (69). A similar comparison could be made with victims of suicide; however, in both situations victims are not able to self-report cannabis use and the pharmacokinetics of cannabis is such that detectable levels of THC or THC-COOH can be found for 30 days post-last use in daily chronic users (70). This is in part due THC's lipophilic nature and to its resistance to degradation by enzymes used to modulate the endocannabinoid system (71, 72). Thus, it is difficult to make a temporal connection between death and intoxication or direct impact of cannabis in this situation. With this caveat in mind, there are some troubling statistics related to the toxicological detection of cannabis in confirmed suicides. In what is otherwise a review article, Roberts presents data from the Colorado Suicide Data Dashboard showing a 77.5% increase in cannabis positive toxicology for suicide victims pre-post legalization with the caveat that not all suicides had toxicology data available (9). Non-completers with cannabis in their system have also not been well-studied. There is a study using data from a Canadian injury surveillance system electronic

Canadian Hospitals Injury Reporting and Prevention Program (eCHIRPP) reporting on 11 pediatric and 6 general emergency departments (ED) across Canada which found that when intent was examined for excessive cannabis use that self-harm was the second most common reason for pediatric cases and third most common for adult ones (73).

The demands of cannabis users on emergency services both ED and EHS are one of the more unmet needs of research on how cannabis impacts healthcare systems and are of pressing importance as more jurisdictions move toward legalization.

WHAT HAPPENS AFTER LEAVING THE ED?

As mentioned previously, the Euro-DEN project studied the acute toxic effects of cannabis and though as noted this was not a large sample size (35 cases). What may be most concerning in this study is that 71% of these received no treatment and 86% were discharged/self-discharged (32). While the patient's immediate symptoms may have resolved, it is unclear what the long term outcomes are for these individuals. A limitation of some of the large database administrative studies is the inability to distinguish between unique visits and repeat visits by cannabis users which inhibits the ability to follow a patient's trajectory longitudinally.

There is some collateral cannabis information related to ED admissions for alcohol intoxication in 2006–2007 at a hospital in Switzerland who were followed up regarding their substance use 7 years later (74). While not focused on their cannabis use, this study did find that 7 years after their ED admission, 53% reported past year cannabis use and 87% reported lifetime cannabis use. Men reported significantly more cannabis use but women reported significantly more psychiatric disorders with anxiety disorders being the category leading the difference in the previous 12 months (74). Additionally, 74% remembered the admission that began their enrollment in the study 7 years prior (74).

The situation in Colorado is also interesting from an epidemiological point of view as the past month cannabis use level among native Coloradans has remained constant since recreational legalization but healthcare utilization associated with adverse events due to cannabis has increased (38, 75). Some authors have noted that this may be related to the current market forces being focused on sales with ever increasing concentrations of THC in cannabis products (38). This may suggest a cumulative dose dependency for at least certain types of adverse events associated with cannabis use as has been suggested by others for the development of psychosis (28, 29, 76).

WHERE DO WE GO FROM HERE?

It may be useful to contemplate what the emergency department primarily administrative data is suggesting for longer term implications for mental health. This is unfortunately a thought exercise as even less literature focuses on what the care pathway, if any, may be for individuals who present to the ED with a cannabis-related mental health issue especially if it is an index mental health presentation. It should be stressed that these presentations do not constitute a large number of cases. The majority of particularly occasional cannabis users will not experience these types of adverse events. However, the number of cases requiring intensive emergency care resources such as transport by ambulance and inpatient psychiatric care indicates that these minority of cases can be healthcare resource intensive. The presence of conditions such as cannabis induced psychosis should constitute a public health concern. While we are slowly seeing a growing body of literature for the impact of cannabis-induced psychosis on repeat ED visits, for other mental health conditions, such as anxiety disorder, we do not know very much about the frequency of repeat ED visits and the degree to which they are relying on a revolving door of ED services to fill a mental health service gap (28, 29). Given that we know that a significant percentage of individuals who experience a psychotic episode will go on to develop a psychotic disorder, a routine referral from the ED to psychiatric care to monitor the individual post-ED would seem a reasonable approach to consider. It is not clear if anxiety symptoms severe enough to warrant emergency care will eventually actuate into an anxiety disorder in a similar continuum to what is postulated for cannabis and psychosis. The situation in the literature is similarly lacking when one examines major depressive disorder or bipolar depression. The literature regarding ED outcomes with cannabis use specific to these populations is very limited. Though there is at least one report of major depression as an adverse event with medical cannabis use which is not the focus here (77). The lack of research in these areas is not surprising given the challenges of doing research in urgent care and across disciplines to obtain outcomes for longer term psychiatric care. This lack of information further impacts clinical care as if we knew the frequency of conversion from a severe adverse mental health event related to anxiety symptoms or depressive symptoms with cannabis use to a diagnosed disorder requiring ongoing care, clinical guidelines could be developed. As we move to greater cannabis use with greater acceptance of the product, the ED may be one of the sentinel locations to monitor any emerging mental health trends.

There are also opportunities for public education that may be possible in the ED setting. The effects we present here are, we suspect, more commonly associated with higher (often defined as 12% and greater) THC concentration strains of cannabis with little to no cannabidiol in the material as these are the most commonly sold strains in the marketplace in legalized settings (78, 79). The sale of these higher THC strains is based on consumer preference (80). However, there is evidence that consumers do not understand the significance of the percentages of THC and CBD in sales materials in the legal marketplace (81). As this research moves forward, some differentiation between strains of cannabis and the relative content of two of the most common cannabinoids in the plant by weight should probably be part of the discussion. Individuals who use recreationally and who have an adverse event may not be aware that their choice of strain may have impacted their medical outcome. Additionally, the popularity of edibles and their use by youth to help conceal use for a variety of reasons should be addressed as this formulation of cannabis is disproportionately associated

with adverse events (82). However, it is not clear how well-understood the risks of using edibles are by youth or how well strain differences are understood among consumers overall.

There are limitations to the literature cited in this review that need to be considered when we try to move forward with research in this field. A number of the studies cited here mention being hampered by inconsistently applied ICD-9 or ICD-10 codes when examining administrative databases. Additionally, some studies mention being unable to distinguish between unique and repeat visits (51). Some of the prospective studies were only conducted during business hours which does not coincide with the known profiles of greatest demand for services related to cannabis users (50, 83). Lack of cannabis strain information but also lack of route of administration data hamper our ability to translate ED findings into public health education materials on the risk of various forms of cannabis use.

Another common limitation in this field of study is illustrated by many of the ED studies that are focused on psychosis and psychotic symptoms as an outcome. An example of this type of study is a published abstract from Alberta, Canada specifically examined substance induced psychosis at one urban ED and examined the presentation and outcomes for these cases. The study was not large at 44 cases but had an interesting case presentation as they were more likely 15–20 years old (35%), experiencing persecutory delusions (65%), and unlikely to be experiencing isolated visual hallucinations (9%) or to have a previously diagnosed psychiatric condition (32.5%). These patients were admitted to inpatient psychiatric services and the average length of stay was 6 days (84). The study infers that if admitted in an emergent context, it is possible that complete resolution of symptoms will occur in these substance induced presentations. Indeed, the literature is consistent with acute use of cannabis inducing self-limiting psychotic episodes that are reflected in the rate at which individuals are released from the ED without treatment. However, like many of the papers that we found in this field, when patients are classified as "substance using" frequently this refers to all mind altering (also called illicit) substances lumped as a group. So while there is nothing wrong *per se* with this study, it is an example of a potential missed opportunity to parse the impact of cannabis use as it is not isolated from other substance use as a group. The work to examine the association with cannabis misuse is most clear in psychosis but anxiety disorders and depressive disorders are also potentially impacted by regular use and more study is needed in the emergency context.

An additional facet of the impacts of cannabis use and mental illness that could not be discussed here as we found very little directly addressing this issue, is the increased use in pregnancy and decrease in perceptions of cannabis harms for pregnant women (85). It is unclear if pregnant individuals are presenting to the emergency department with mental health concerns as none of the data presented here recorded the pregnancy status of the women presenting to the ED despite data showing that pregnant women with a history of depression and anxiety are more likely to use cannabis during pregnancy (86). The only conditions that we could find literature for were an association between cannabis use during pregnancy and preterm birth which conceivably could require emergency services and a suggestion of cannabis use during pregnancy leading to increased nausea and vomiting also potentially requiring emergency intervention (87, 88). Additionally, in the longer term, the reported increases in levels of cannabis use during pregnancy may also lead to increasing numbers of individuals who were exposed *in utero* with behavioral outcomes that may be associated with a further cycle of cannabis harms that end in ED use [reviewed in (89)].

A final point to consider is how we could comprehensively arrange the data to enable larger epidemiological studies with more depth. There is a mechanism for reporting adverse events from cannabis use to the FDA in the United States (90) and the Government of Canada through Health Canada runs a website for reporting cannabis recalls, and adverse reactions (91). These systems may also be a mechanism to track the prevalence of adverse mental health events associated with cannabis use (92). This may be especially important in a setting where mental health impacts of cannabis are not generally captured in the usual hospital injury databases (93). However, harmonization of the data collected would be required.

AUTHOR CONTRIBUTIONS

CC wrote the first draft. All other authors contributed edits and comments to the first draft. CC and PT prepared the final draft. All authors approved the submission.

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Personal Correlates of Support for Medical and Recreational Cannabis Legalization in Australia

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Introduction and Aims: Increasingly more Australians are in favor of legalizing medical and recreational cannabis use. This paper explored the personal characteristics of those who supported each of these policies in Australia.

Design: Cross-sectional national survey.

Methods: This study included 21,729 participants aged 18 years and above who responded to the 2016 National Drug Strategy Household Survey. Participants were provided the assurance of confidentiality for their participations. Logistic regression models were used to examine the relationships between personal characteristics and support for the legalization of medical and recreational cannabis.

Results: Overall, 77 and 40% of participants supported the legalization of medical and recreational cannabis respectively. People of older age were more likely to support medical cannabis legalization while those who supported legalization of recreational cannabis use were more likely to be younger. Medical cannabis supporters were more likely to report chronic pain (OR = 1.44, 95% CI: 1.04, 2.00) while recreational cannabis supporters were more likely to suffer high level of psychological distress (OR = 1.28, 95% CI: 1.14, 1.43). Experience with cannabis use was strongly associated with supportive attitudes, with recent cannabis users almost 14 times (OR = 14.13, 95% CI: 5.37, 37.20) and 34 times (OR = 33.74, 95% CI: 24.22, 47.01) more likely to support the legalization of medical and recreational cannabis use, respectively.

Discussion and Conclusions: The majority of Australians approve the legalization of cannabis for medicinal purposes but most remain cautious about legalizing recreational cannabis use. The sociodemographic and clinical profile of supporters of medical and recreational legalization suggests a potential interaction of self-interests and beliefs about the harms of cannabis use.

Keywords: cannabis (marijuana), opinion, attitudes, determinants, marijuana

INTRODUCTION

Australian support for the legalization of medical cannabis has been stable for a decade since the 2000s with 68.5–69% of persons supporting legalization between 2004 and 2013 (1, 2) despite substantial international policy changes over the period. The 2016 National Drug Strategy Household Survey (NDSHS) found an increase in support for legalizing the medicinal use of cannabis (3). This shift in attitude coincided with the Australian Federal and state governments legalized access to medicinal cannabis in the same year. So far, the growth in public support for legalization of medical cannabis use has not been accompanied by an increase in support for the legalization of recreational cannabis use, something that most Australians continue to oppose (3).

News media coverage of cannabis issues is potentially a factor that may have contributed to these shifts in public attitudes (4–6). The increased reporting of positive media stories on medical uses of cannabis may have portrayed cannabis in a more favorable light, differentiating "medical" from "recreational" cannabis despite the fact that some cannabis products are used for both purposes. The perceived health benefits of cannabis use have been highlighted by a number of studies, reporting that medical cannabis is a valid treatment for chronic pain, cancers and mood disorders (7–11). Beliefs about the medical benefits of cannabis seem more salient for supportive attitudes toward medical cannabis legalization than beliefs about its negative side effects (4). Self-medicating cannabis users are more likely to have positive views about cannabis and to describe cannabis as being less harmful than never-users (11). Individuals who have used cannabis also hold a more permissive view toward cannabis legalization (12). The official approval of medical cannabis use may be perceived as a validation of its medical value and may reduce the perceived harmfulness of cannabis use. In the United States, young adults from states that have implemented medical cannabis laws are more likely to believe that cannabis has no or low health risks than residents of states without medical cannabis laws. However, the passage of medical cannabis laws does not appear to have affected the perceived wrongfulness of recreational cannabis use (13).

There is limited information on the characteristics of Australians who support different cannabis policies. Our study contributes to the literature by analyzing correlates of support for different cannabis policies in a representative sample of the Australian general adult population. The present study used data from the 2016 National Drug Strategy Household Survey (NDSHS) to characterize the supporters of medical and recreational cannabis legalization.

METHODS

Data Source

The study utilized data from the latest NDSHS. These data were collected between 18 June and 29 November 2016, from all Australian states and territories. The cross-sectional population survey aimed to provide reliable estimates of public awareness, attitude, and behaviors related to alcohol, tobacco, and illicit drug use in Australians 14 years and older.

Sample Design

The NDSHS sample was selected using stratified, multistage random sampling. The sample was stratified by region (15 strata in total–capital city and rest of state for each state and territory, with the exception of the Australian Capital Territory, which operated as one stratum). To produce reliable estimates for the smaller states and territories, sample sizes were boosted in Tasmania, the Australian Capital Territory and the Northern Territory. Weighting was applied to adjust for imbalances arising from execution of the sampling and differential response rates, and thereby ensure that the results were representative of the Australian population.

Study Population

A total of 23,772 participants completed the survey (response rate 51.1%). Of these, 18,528 (77.9%) completed the survey on paper, 5,170 (21.8%) online and 74 (0.3%) via telephone interview. This study included 21,729 participants aged 18 years and above, who responded to the questions about their support for medical and recreational cannabis legalization (91.4% of the full sample).

Attitudes Toward Medical Cannabis Legalization

The items assessing attitudes toward medical and recreational cannabis legalization were taken from the NDSHS questions "Thinking now about the use of marijuana/cannabis for medical purposes, to what extent would you support or oppose measures such as a change in legislation permitting the use of marijuana for medical purposes?" and "Considering marijuana/cannabis, to what extent would you support or oppose the personal use of marijuana/cannabis being made legal?", respectively. The six-point Likert scale responses was collapsed into three levels: "support" (derived from "strongly support" and "support"), "neutral" (derived from "neither support nor oppose" and "don't know enough to say") or "oppose" (derived from "strongly oppose" and "oppose").

Personal Characteristics

Personal characteristics variables were chosen based on a review of studies of public attitudes toward cannabis use (7, 8, 11).

Sociodemographic characteristics included: age (age groups: "18–29 years old," "30–49 years old" or "50+ years old"), sex ("male" or "female"), marital status ("never married," "divorced, separated, or widowed" or "married"), education attainment ("below high school," "high school or post-high school" or "tertiary education"), employment status ("currently employed," "unemployed" or "not in labor force or looking for work") and personal income [weekly income matched with national census in 2016 (Australian Bureau of Statistics): "1st quartile: nil or negative income-$399," "2nd quartile: $400–799," "3rd quartile: $800–1,499" or "4th quartile: $1,500 and above" per week].

Clinical characteristics included a self-reported diagnosis or treatment for cancer ("no" or "yes") and chronic pain ("no" or "yes") in the past 12 months. Psychological distress in the past month was assessed with the 10-item Kessler Psychological Distress Scale (K10) (14). The total score was used to define "low"

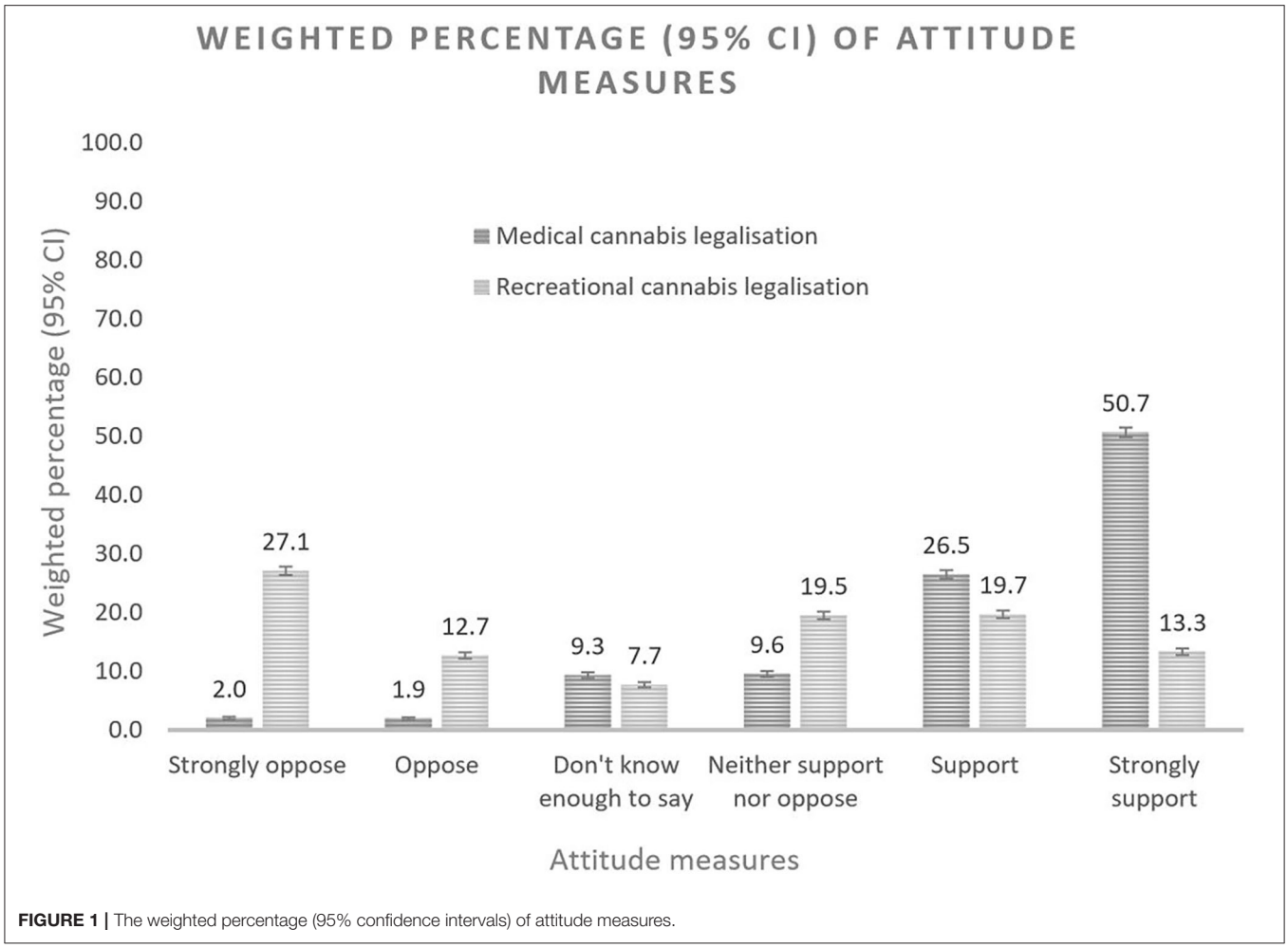

FIGURE 1 | The weighted percentage (95% confidence intervals) of attitude measures.

(K10 score <15), "moderate" (K10 score between 15 and 20) or "high or very high" levels of distress (K10 score >21).

Cannabis use status was classified into "never user" (those who never used cannabis), "past user" (those who used cannabis but not in the past 12 months) or "recent user" (those who used cannabis in the past 12 months). Alcohol use status was defined using the Alcohol Use Disorder Identification Test (AUDIT-Consumption). The AUDIT-C is a three-item alcohol screen that consists of a scoring system to estimate alcohol consumption in a standard manner. The total scores from these questions categorized the risk levels of hazardous drinking and alcohol use disorders. The questions and responses in NDSHS were structured slightly differently from the AUDIT-C questions. Using an approximation, a similar scoring system was created to classify alcohol use status for our participants: "non-drinker or low-risk drinker" (total score $\leq$3.99 for male and $\leq$2.99 for female) or "high-risk drinker" (total score $\geq$4 for male and $\geq$3 for female). Questions in the AUDIT-C and NDSHS, and the scoring system are documented in **Appendix A**. Smoking status was derived from several items that measured frequency and quantity of smoking: "non-smoker" (those who used <100 cigarettes in a lifetime), "ex-smoker" (those who used 100 or more cigarettes in a lifetime but not in the past 12 months) or "current smoker" (those who used cigarettes in the past 12 months).

Analysis

Cross-tabulations were used to compare the distributions of support for medical and recreational cannabis legalization by socio-demographics and health status. Design adjusted Rao-Scott Chi-Square tests were used to test the statistical significance of these sets of independent variables. Due to the large amount of missing responses for some independent variables, multiple imputation (30 iterations) was used to handle variables with missing values. Multiple imputation is an iterative form of stochastic imputation that leads to more accurate sets of estimates (15). It is considered as crucial in analysis of survey data with many non-monotone missing categorical variables. We included all independent variables as auxiliary variables (variables that may be correlated to the missing variable) in the imputation model.

The association between participants' characteristics and support for medical and recreational cannabis legalization were examined using multinomial logistic regression analyses. All analyses were conducted using SAS version 9.4 and were adjusted for weights and strata for differential selection, to match the

TABLE 1 | Distribution of opinions on medical cannabis legalization distinguished by individual characteristics.

Characteristics		Total (*N* = 21,582)	Support (*N* = 17,042)	Neutral (*N* = 3,727)	Oppose (*N* = 813)	χ^2	df	*p*-value
		Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)			
Sex	Males	49.3 (48.5, 50.1)	76.0 (75.0, 77.1)	19.5 (18.5, 20.5)	4.4 (3.9, 5.0)	13.9	2	0.001
	Females	50.7 (49.9, 51.5)	78.3 (77.4, 79.2)	18.3 (17.4, 19.1)	3.4 (3.0, 3.9)			
Age group	18–29 years old	21.7 (20.9, 22.5)	71.8 (69.9, 73.8)	23.7 (21.8, 25.6)	4.5 (3.6, 5.4)	68.8	4	<0.001
	30–49 years old	35.5 (34.7, 36.3)	77.3 (76.1, 78.4)	18.7 (17.6, 19.8)	4.0 (3.5, 4.6)			
	50+ years old	42.8 (42.0, 43.6)	79.8 (78.9, 80.7)	16.6 (15.8, 17.4)	3.6 (3.2, 4.0)			
Marital status	Never married	24.2 (23.4, 24.9)	75.3 (73.6, 77.0)	20.7 (19.1, 22.3)	4.0 (3.2, 4.8)	15.4	4	0.004
	Divorced/widowed/separated	12.1 (11.7, 12.6)	80.0 (78.4, 81.6)	16.6 (15.2, 18.1)	3.4 (2.6, 4.2)			
	Married	63.7 (62.9, 64.6)	77.4 (76.6, 78.3)	18.6 (17.8, 19.4)	4.0 (3.6, 4.4)			
Employment status	Not in labor force	36.2 (35.5, 37.0)	76.4 (75.2, 77.5)	19.9 (18.8, 21.0)	3.8 (3.3, 4.3)	37.0	4	<0.001
	Unemployed/looking for work	5.9 (5.5, 6.3)	70.5 (67.1, 74.0)	24.9 (21.6, 28.2)	4.6 (3.1, 6.0)			
	Currently employed	57.9 (57.1, 58.7)	78.9 (78.0, 79.8)	17.2 (16.3, 18.1)	3.9 (3.4, 4.3)			
Education attainment	Below high school	10.8 (10.2, 11.4)	81.1 (78.8, 83.5)	15.7 (13.5, 17.8)	3.2 (2.1, 4.3)	9.5	4	0.049
	High school/post-high school	43.9 (43.0, 44.9)	80.4 (79.1, 81.6)	16.1 (15.0, 17.3)	3.5 (3.0, 4.1)			
	Tertiary	45.2 (44.3, 46.2)	78.0 (76.8, 79.3)	18.3 (17.1, 19.5)	3.7 (3.1, 4.2)			
Personal income	Lowest quartile	27.0 (26.2, 27.8)	76.4 (74.9, 78.0)	18.8 (17.4, 20.2)	4.8 (4.0, 5.6)	39.0	6	<0.001
	Medium-lowest quartile	21.6 (20.8, 22.3)	80.5 (78.9, 82.1)	16.2 (14.7, 17.7)	3.3 (2.6, 4.0)			
	Medium-highest quartile	26.6 (25.8, 27.4)	80.1 (78.6, 81.6)	16.2 (14.9, 17.6)	3.7 (3.0, 4.4)			
	Highest quartile	24.8 (24.0, 25.6)	82.8 (81.4, 84.2)	13.8 (12.5, 15.0)	3.4 (2.7, 4.1)			
Cannabis use status	Never user	63.3 (62.5, 64.1)	69.2 (68.2, 70.1)	25.6 (24.6, 26.5)	5.3 (4.8, 5.7)	725.3	4	<0.001
	Past user	26.2 (25.5, 26.9)	89.1 (88.1, 90.1)	8.8 (8.0, 9.7)	2.1 (1.6, 2.6)			
	Recent user	10.6 (10.0, 11.1)	96.4 (95.3, 97.6)	3.1 (2.1, 4.1)	0.4 (0.0, 0.9)			
Alcohol use status	Non-drinker/Low-risk drinker	55.2 (54.3, 56.0)	70.9 (69.8, 71.9)	23.8 (22.8, 24.8)	5.4 (4.8, 5.9)	392.8	2	<0.001
	High-risk drinker	44.9 (44.0, 45.7)	85.0 (84.1, 85.9)	12.8 (12.0, 13.7)	2.2 (1.8, 2.5)			
Tobacco use status	Current smoker	15.4 (14.8, 16.0)	86.0 (84.5, 87.5)	11.6 (10.1, 13.0)	2.4 (1.8, 3.1)	335.7	4	<0.001
	Ex-smoker	24.6 (23.9, 25.2)	84.6 (83.5, 85.8)	12.7 (11.6, 13.7)	2.7 (2.2, 3.2)			
	Never smoker	60.1 (59.3, 60.9)	71.9 (70.9, 72.8)	23.3 (22.4, 24.2)	4.8 (4.4, 5.3)			

(Continued)

TABLE 1 | Continued

Characteristics		Total (*N* = 21,582)	Support (*N* = 17,042)	Neutral (*N* = 3,727)	Oppose (*N* = 813)	χ^2	df	*p*-value
		Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)			
Psychological distress[$]	Low level	67.8 (67.0, 68.6)	75.7 (74.8, 76.6)	20.2 (19.4, 21.0)	4.1 (3.7, 4.5)	38.3	4	<0.001
	Moderate level	20.7 (20.0, 21.3)	79.5 (78.0, 81.0)	16.6 (15.2, 18.0)	3.9 (3.2, 4.6)			
	High or very high level	11.6 (11.0, 12.1)	81.8 (79.8, 83.7)	15.0 (13.2, 16.9)	3.2 (2.3, 4.1)			
Cancer[%]	Yes	3.8 (3.5, 4.1)	81.9 (79.0, 84.9)	14.5 (11.8, 17.2)	3.6 (2.2, 4.9)	7.8	2	0.020
	No	96.3 (96.0, 96.5)	77.4 (76.6, 78.2)	18.7 (18.0, 19.5)	3.8 (3.5, 4.2)			
Chronic pain[§]	Yes	10.7 (10.2, 11.2)	85.2 (83.6, 86.9)	12.2 (10.6, 13.7)	2.6 (1.9, 3.3)	68.7	2	<0.001
	No	89.3 (88.8, 89.8)	76.6 (75.8, 77.4)	19.4 (18.7, 20.2)	4.0 (3.6, 4.3)			

All figures are rounded to one decimal place. P-values are rounded to three decimal places.

[$] *Personal experience of psychological distress in the past month, categorized by Kessler Psychological Distress Scale (K10).*

[%] *Being diagnosed or treated for cancer in the past 12 months.*

[§] *Self-reported chronic pain in the past 12 months.*

survey samples to population sociodemographic distributions. In the weighted sample of 21,729 participants, the average age was 51 years (median = 51, age range between 18 and 84) with more females (54.7%) than males (45.3%). A full description of the study population is presented in **Appendix B**.

Ethics

The access of the 2016 NDSHS data has been approved by the Australian Data Archive on behalf of the Australian Institute of Health and Welfare. This study has been exempted from ethics review under the National Statement on Ethical Conduct in Human Research and The University of Queensland policy (#2019001159).

RESULTS

Overall, 77% of survey participants supported the legalization of medical cannabis in 2016. In contrast, 19% of the participants were neutral and only 4% were opposed (**Figure 1**; **Table 1**). People of older age (50+ years old: OR = 1.78, 95% CI: 1.25, 2.54) and females (OR = 1.61, 95% CI: 1.33, 1.96) were more likely to support medical cannabis legalization. The association between other sociodemographic characteristics and supportive attitudes were not significant. Any personal experience with cannabis use was strongly associated with support for medical cannabis, with past users and recent users almost three times (OR = 2.78, 95% CI: 2.07, 3.73) and fourteen times (OR = 14.13, 95% CI: 5.37, 37.20) more likely to support medical use, respectively. High-risk drinking (OR = 2.12, 95% CI: 1.70, 2.65) was also associated with supportive attitudes but less so than cannabis use. Compared with participants of other health issues, people who reported having chronic pain (OR = 1.44, 95% CI: 1.04, 2.00) were more favorable to medical cannabis legalization (**Table 3**).

Opinions about legalizing recreational cannabis were more varied, with 40% percent of Australians opposed to the policy, 33% supporting it and 27% neutral (**Figure 1**; **Table 2**). The sociodemographic profiles of persons who supported the legalization of recreational cannabis use differed from those who supported medical cannabis use. They were more likely to be younger and never married. Male and female were basically alike in their support for recreational cannabis legalization. Personal experience with substances was associated with more support for legalization of recreational cannabis use, with recent cannabis use (OR = 33.74, 95% CI: 24.22, 47.01) more strongly associated than all characteristics combined. In contrast, support for recreational cannabis legalization was significantly reduced among past cannabis users who had not used cannabis in the past 12 months (OR = 4.16, 95% CI: 3.75, 4.63). High-risk drinking (OR = 1.57, 95% CI: 1.43, 1.72) and current use of tobacco (OR = 1.47, 95% CI: 1.27, 1.70) were moderately associated with supportive attitudes. Those reporting moderate (OR = 1.59, 95% CI: 1.36, 1.85) or higher level of stress (OR = 1.28, 95% CI: 1.14, 1.43) were more supportive of legalizing recreational cannabis than those reporting low levels of stress. The results, however, suggested no association with other health conditions (**Table 3**).

DISCUSSION

The majority of Australian adults supported the decision to approve the use of cannabis for medicinal purposes. This high level of support is consistent with surveys from other countries that have implemented medical cannabis policies, with percentages of support at 91% in the USA and 78% in Israel

TABLE 2 | Distribution of opinions on recreational cannabis legalization distinguished by individual characteristics.

Characteristics		Total (*N* = 20,607)	Support (*N* = 7,262)	Neutral (*N* = 6,204)	Oppose (*N* = 9,233)	χ^2	df	*p*-value
		Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)			
Sex	Males	49.3 (48.5, 50.1)	35.6 (34.4, 36.8)	26.4 (25.3, 27.5)	38.0 (36.8, 39.2)	41.7	2	<0.001
	Females	50.7 (49.9, 51.5)	30.5 (29.5, 31.5)	28.0 (27.0, 28.9)	41.5 (40.4, 42.6)			
Age group	18–29 years old	21.7 (21.0, 22.5)	41.5 (39.4, 43.6)	27.9 (25.9, 29.9)	30.6 (28.6, 32.5)	339.2	4	<0.001
	30–49 years old	35.5 (34.7, 36.3)	36.9 (35.7, 38.2)	27.1 (25.9, 28.3)	35.9 (34.6, 37.2)			
	50+ years old	42.8 (42.0, 43.5)	25.5 (24.5, 26.4)	26.9 (25.9, 27.9)	47.7 (46.6, 48.7)			
Marital status	Never married	24.1 (23.4, 24.9)	44.9 (43.0, 46.8)	27.0 (25.2, 28.8)	28.1 (26.3, 29.8)	361.4	4	<0.001
	Divorced/widowed/separated	12.1 (11.6, 12.5)	30.2 (28.5, 31.9)	29.1 (27.4, 30.8)	40.7 (38.8, 42.6)			
	Married	63.8 (63.0, 64.6)	29.1 (28.2, 30.0)	26.9 (26.0, 27.8)	44.0 (43.0, 45.0)			
Employment status	Not in labor force	36.2 (35.5, 37.0)	27.1 (25.9, 28.2)	27.8 (26.6, 29.0)	45.1 (43.8, 46.4)	133.0	4	<0.001
	Unemployed/looking for work	5.9 (5.5, 6.4)	35.8 (32.1, 39.4)	29.2 (25.5, 33.0)	35.0 (31.3, 38.7)			
	Currently employed	57.9 (57.0, 58.7)	36.7 (35.7, 37.8)	26.4 (25.4, 27.3)	36.9 (35.9, 38.0)			
Education attainment	Below high school	10.8 (10.2, 11.5)	32.9 (29.9, 35.8)	28.0 (25.3, 30.6)	39.2 (36.3, 42.1)	11.4	4	0.022
	High school/post-high school	44.0 (43.0, 44.9)	35.1 (33.7, 36.6)	27.2 (25.8, 28.5)	37.7 (36.2, 39.1)			
	Tertiary	45.2 (44.2, 46.2)	35.5 (34.1, 36.9)	24.6 (23.3, 25.9)	39.9 (38.4, 41.4)			
Personal income	Lowest quartile	27.0 (26.2, 27.8)	31.9 (30.2, 33.6)	25.7 (24.1, 27.3)	42.4 (40.7, 44.2)	49.0	6	<0.001
	Medium-lowest quartile	21.5 (20.8, 22.2)	34.9 (33.0, 36.7)	27.0 (25.3, 28.8)	38.1 (36.3, 39.9)			
	Medium-highest quartile	26.7 (25.9, 27.5)	36.3 (34.6, 38.0)	27.1 (25.5, 28.6)	36.6 (34.8, 38.3)			
	Highest quartile	24.8 (24.1, 25.6)	39.2 (37.4, 40.9)	23.7 (22.2, 25.2)	37.2 (35.4, 38.9)			
Cannabis use status	Never user	63.3 (62.5, 64.1)	18.8 (18.0, 19.7)	29.2 (28.3, 30.2)	51.9 (50.9, 53.0)	2763.6	4	<0.001
	Past user	26.2 (25.5, 26.9)	46.2 (44.6, 47.7)	29.0 (27.6, 30.4)	24.8 (23.5, 26.1)			
	Recent user	10.5 (10.0, 11.0)	85.5 (83.5, 87.5)	10.5 (8.8, 12.2)	4.0 (2.8, 5.2)			
Alcohol use status	Non-drinker/low-risk drinker	55.1 (54.3, 55.9)	23.9 (22.9, 24.8)	28.0 (27.0, 29.0)	48.1 (47.0, 49.2)	771.0	2	<0.001
	High-risk drinker	44.9 (44.1, 45.7)	44.3 (43.1, 45.5)	26.3 (25.2, 27.4)	29.4 (28.3, 30.5)			
Tobacco use status	Current smoker	15.3 (14.7, 15.9)	52.0 (49.9, 54.2)	25.8 (23.9, 27.7)	22.1 (20.5, 23.8)	646.7	4	<0.001
	Ex-smoker	24.6 (23.9, 25.2)	36.6 (35.1, 38.0)	26.9 (25.6, 28.3)	36.5 (35.0, 37.9)			
	Never smoker	60.1 (59.3, 60.9)	26.7 (25.8, 27.7)	27.6 (26.7, 28.6)	45.6 (44.6, 46.7)			

(Continued)

TABLE 2 | Continued

Characteristics		Total (*N* = 20,607)	Support (*N* = 7,262)	Neutral (*N* = 6,204)	Oppose (*N* = 9,233)	χ^2	df	*p*-value
		Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)	Weighted % (95% CI)			
Psychological distress[$]	Low level	67.8 (67.0, 68.6)	28.9 (28.0, 29.7)	27.8 (26.9, 28.7)	43.4 (42.4, 44.4)	289.0	4	<0.001
	Moderate level	20.7 (20.0, 21.4)	38.5 (36.7, 40.2)	27.0 (25.4, 28.6)	34.5 (32.8, 36.3)			
	High or very high level	11.5 (11.0, 12.1)	47.6 (45.1, 50.1)	24.5 (22.3, 26.6)	27.9 (25.7, 30.2)			
Cancer[%]	Yes	3.8 (3.5, 4.1)	27.5 (23.8, 31.1)	26.9 (23.3, 30.5)	45.6 (41.7, 49.6)	13.3	2	0.001
	No	96.2 (95.9, 96.5)	33.9 (33.0, 34.8)	27.1 (26.3, 28.0)	39.0 (38.1, 39.9)			
Chronic pain[§]	Yes	10.7 (10.2, 11.2)	36.5 (34.2, 38.8)	25.0 (22.9, 27.0)	38.6 (36.2, 40.9)	8.4	2	0.015
	No	89.3 (88.8, 89.8)	33.1 (32.3, 34.0)	27.4 (26.6, 28.2)	39.5 (38.6, 40.4)			

All figures are rounded to one decimal place. P-values are rounded to three decimal places.

[$] *Personal experience of psychological distress in the past month, categorized by Kessler Psychological Distress Scale (K10).*

[%] *Being diagnosed or treated for cancer in the past 12 months.*

[§] *Self-reported chronic pain in the past 12 months.*

(16). The high level of support agrees with a survey that found supporters generally believe the benefits of medical cannabis outweigh the potential side effects and so patients should have access to it (4). By contrast, only a third of Australians supported legalizing recreational cannabis. This supports the hypothesis that the public distinguishes between "medical cannabis" and "recreational cannabis" use, which affects public perceptions of the risks associated with these different reasons for uses and affects support for these different policies (5).

Females and persons over the age of 50 were more likely to support medical cannabis legalization, whereas, those who supported recreational cannabis use were more likely to be under the age of 30. The characteristics of Australian recreational cannabis supporters are similar to the supporters in other population, who are pre-dominantly younger (17). The different group of supporters for medical and recreational cannabis legalization perhaps partially reflect self-interest. Self-reported chronic pain was the strongest health factor associated with support for medical cannabis legalization in this study. Chronic pain was a common reason for medical use of cannabis as in previous studies (8, 9, 11). The sex and age correlates of support could reflect the fact that the prevalence of chronic pain is higher in females than males (18, 19) and increases with age. In contrast, persons suffering from moderate to very high level of psychological distress in the past month were more likely to support recreational cannabis. Although it is unclear whether the supporters would actually use cannabis if it became legal, using cannabis to cope with negative emotions is associated with elevated distress and cannabis use disorders (20). Therefore, assessment of cannabis related attitudes and motivation may be clinically important.

Personal experience with alcohol, tobacco and cannabis use were associated with supportive attitudes toward cannabis legalization and the association was especially strong with experience of cannabis use. Persons with recent cannabis experience were overwhelmingly more supportive of cannabis legalization than past users. Experience with cannabis may determine how a person perceives or interpret the benefits and risks associated with its use. The strong associations between recent cannabis use and support for legalization may have been driven by the reduced perception of risk and self-interest (21). Cannabis users would prefer cannabis use to no longer be a crime and to have easier access at lower prices. People who use cannabis by choice may also view the new medical cannabis policy as a validation for their beliefs about its benefits. Tobacco and excessive use of alcohol are widely recognized as harmful, with substantial public health and scientific efforts to reduce consumption and public harms over the years. The increased perception of medical cannabis as low in harm or beneficial may increase cannabis use. The epidemiology of cannabis use among cannabis users pre- and post-medical cannabis legalization warrants special attention.

There are several limitations in this study. As a cross-sectional survey, the study could only report associations. Data about history and frequencies of substance use were based on self-reports. Given the sensitive nature of these questions, there is a potential for social desirability bias despite the assurance of confidentiality given to survey participants. Also, views on legalization are likely to be shaped by a number of intersecting factors, such as views on criminal justice, personal liberty, and other aspects outside the scope of the survey, which should be considered when interpreting the results.

TABLE 3 | Results of multinomial logistic regression analysis on opinions on medical and recreational cannabis legalization, using response "oppose" as reference.

Characteristics		Medical cannabis legalization		Recreational cannabis legalization	
		Neutral	Support	Neutral	Support
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Sex	Male	1 (reference)		1 (reference)	
	Female	1.22 (0.99, 1.50)	1.61 (1.33, 1.96)**	1.02 (0.93, 1.11)	0.98 (0.89, 1.08)
Age group	18–29 years old	1 (reference)		1 (reference)	
	30–49 years old	0.92 (0.65, 1.32)	1.16 (0.82, 1.63)	0.90 (0.77, 1.05)	0.94 (0.79, 1.10)
	50+ years old	0.84 (0.58, 1.22)	1.78 (1.25, 2.54)*	0.76 (0.64, 0.89)*	0.84 (0.71, 1.00)*
Marital status	Never married	1 (reference)		1 (reference)	
	Divorced/widowed/separated	1.03 (0.67, 1.58)	0.90 (0.60, 1.36)	0.92 (0.78, 1.10)	0.70 (0.58, 0.85)**
	Married	1.00 (0.71, 1.40)	0.90 (0.65, 1.24)	0.75 (0.66, 0.87)**	0.58 (0.50, 0.67)**
Employment status	Unemployed/looking for work	1 (reference)		1 (reference)	
	Not in labor force	0.74 (0.48, 1.14)	1.04 (0.69, 1.58)	0.88 (0.70, 1.10)	1.09 (0.85, 1.39)
	Currently employed	0.96 (0.63, 1.45)	1.21 (0.81, 1.81)	0.91 (0.73, 1.14)	1.08 (0.85, 1.37)
Education attainment	Below high school	1 (reference)		1 (reference)	
	High school/post high school	0.99 (0.69, 1.43)	0.95 (0.66, 1.37)	0.98 (0.83, 1.14)	1.00 (0.85, 1.18)
	Tertiary	1.07 (0.72, 1.60)	1.02 (0.70, 1.49)	0.94 (0.79, 1.11)	1.11 (0.93, 1.32)
Personal income	Lowest quartile	1 (reference)		1 (reference)	
	Medium-lowest quartile	1.18 (0.88, 1.59)	1.27 (0.96, 1.67)	1.06 (0.93, 1.22)	1.09 (0.94, 1.27)
	Medium-highest quartile	1.11 (0.80, 1.53)	1.20 (0.88, 1.63)	1.07 (0.91, 1.24)	1.08 (0.92, 1.27)
	Highest quartile	1.10 (0.75, 1.60)	1.31 (0.93, 1.85)	0.95 (0.81, 1.13)	1.18 (1.00, 1.40)*
Cannabis use status	Never user	1 (reference)		1 (reference)	
	Past user	0.85 (0.62, 1.16)	2.78 (2.07, 3.73)**	1.87 (1.68, 2.08)**	4.16 (3.75, 4.63)**
	Recent user	1.29 (0.46, 3.59)	14.13 (5.37, 37.20)**	3.19 (2.20, 4.61)**	33.74 (24.22, 47.01)**
Alcohol use status	Non-drinker/Low-risk drinker	1 (reference)		1 (reference)	
	High-risk drinker	1.40 (1.11, 1.77)*	2.12 (1.70, 2.65)**	1.27 (1.16, 1.39)**	1.57 (1.43, 1.72)**
Tobacco use status	Never smoker	1 (reference)		1 (reference)	
	Current smoker	0.96 (0.69, 1.34)	1.15 (0.84, 1.57)	1.44 (1.25, 1.66)**	1.47 (1.27, 1.70)**
	Ex-smoker	1.00 (0.78, 1.29)	1.26 (0.99, 1.59)	1.09 (0.98, 1.20)	1.12 (1.01, 1.24)*
Psychological distress[$]	Low level	1 (reference)		1 (reference)	
	Moderate level	0.88 (0.62, 1.25)	1.03 (0.74, 1.44)	1.11 (0.95, 1.30)	1.59 (1.36, 1.85)**
	High or very high level	0.83 (0.65, 1.05)	0.95 (0.76, 1.19)	1.10 (0.98, 1.22)	1.28 (1.14, 1.43)**
Cancer[%]	No	1 (reference)		1 (reference)	
	Yes	0.84 (0.53, 1.31)	0.99 (0.64, 1.52)	1.02 (0.83, 1.24)	1.06 (0.85, 1.33)
Chronicpain[§]	No	1 (reference)		1 (reference)	
	Yes	1.02 (0.72, 1.44)	1.44 (1.04, 2.00)*	0.96 (0.83, 1.10)	1.14 (0.98, 1.32)

Odds ratios and 95% CIs are rounded to two decimal places.

***P-values < 0.001; *P-values < 0.05.*

[$] *Personal experience of psychological distress in the past month, categorized by Kessler Psychological Distress Scale (K10).*

[%] *Being diagnosed or treated for cancer in the past 12 months.*

[§] *Self-reported chronic pain in the past 12 months.*

Despite these weaknesses, this study provides an empirical examination of a wide range of factors that have shaped public opinion toward medical and recreational cannabis legalization in Australia.

In conclusion, the majority of Australians welcome the decision to legalize medical cannabis but many are cautious about legalizing recreational cannabis use. The different sociodemographic and clinical profile of supporters for medical and recreational cannabis policies suggests a potential interaction of self-interests and beliefs about cannabis. Perceptions of cannabis may be influenced by the subjective experience of cannabis or other substance use.

Future studies with data across different years is needed to verify the significance of these determinants consider the potential influence of age, period and cohort on the shifting attitude, and its association with the prevalence of cannabis use. The mechanism underlying the relationships between cannabis-related attitudes and cannabis legalization, and their links to the subjective intentions and decisions to use cannabis are not yet clear. Given that people are more inclined to support policies that work in favor of their personal interests, community-based surveillance of cannabis use may be needed as the liberalization of cannabis regulations increase access to and the availability of medicinal cannabis.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Permission to access the data is required by the data custodian. Requests to access these datasets should be directed to https://ada.edu.au.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

VC, WH, and JL conceptualized the study. VC, GC, WH, CL, and JL contributed to the methodology. VC compiled the data, conducted the analysis, and completed the original draft. All other authors contributed to reviewing and editing the draft.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.551661/full#supplementary-material

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SYSTEMATIC REVIEW
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Duration of Neurocognitive Impairment With Medical Cannabis Use: A Scoping Review

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While the recreational use of cannabis has well-established dose-dependent effects on neurocognitive and psychomotor functioning, there is little consensus on the degree and duration of impairment typically seen with medical marijuana use. Compared to recreational cannabis users, medical cannabis patients have distinct characteristics that may modify the presence and extent of impairment. The goal of this review was to determine the duration of acute neurocognitive impairment associated with medical cannabis use, and to identify differences between medical cannabis patients and recreational users. These findings are used to gain insight on how medical professionals can best advise medical cannabis patients with regards to automobile driving or safety-sensitive tasks at work. A systematic electronic search for English language randomized controlled trials (RCTs), clinical trials and systematic reviews (in order to capture any potentially missed RCTs) between 2000 and 2019 was conducted through Ovid MEDLINE and EMBASE electronic databases using MeSH terms. Articles were limited to medical cannabis patients using cannabis for chronic non-cancer pain or spasticity. After screening titles and abstracts, 37 relevant studies were subjected to full-text review. Overall, seven controlled trials met the inclusion/exclusion criteria and were included in the qualitative synthesis: six RCTs and one observational clinical trial. Neurocognitive testing varied significantly between all studies, including the specific tests administered and the timing of assessments post-cannabis consumption. In general, cognitive performance declined mostly in a THC dose-dependent manner, with steady resolution of impairment in the hours following THC administration. Doses of THC were lower than those typically reported in recreational cannabis studies. In all the studies, there was no difference between any of the THC groups and placebo on any neurocognitive measure after 4 h of recovery.

Variability in the dose-dependent relationship raises the consideration that there are other important factors contributing to the duration of neurocognitive impairment besides the dose of THC ingested. These modifiable and non-modifiable factors are individually discussed.

Keywords: cannabinoids, medical cannabis, tetrahydrocannabinol, cannabidiol, pain, impairment, intoxication, cognition

INTRODUCTION

The legalization and decriminalization of cannabis in multiple countries and states has contributed to a wealth of research on the potential therapeutic benefits of cannabis-based medicines (1–5). In 2014, cannabinoids were deemed appropriate as third-line treatment for neuropathic pain by the Canadian Pain Society (6). Cannabis has also been investigated as an adjuvant in refractory chronic non-cancer pain and in harm-reduction approaches for those tapering off high-dose opioid medications, with promising preliminary findings (7–11). As the indications for cannabis expand beyond neuropathic pain, seizures and multiple sclerosis (MS)-related spasticity, it is necessary to assess the risks associated with medicinal cannabis use, especially among those who regularly ingest THC-containing compounds.

Research on the effects of cannabis on humans has largely focused on recreational use, with smoking as the most common route of administration. This early work found strong associations between the dose of THC inhaled and resulting acute cognitive impairment (12). Specifically, THC and other cannabinoid receptor 1 (CB_1) agonists acutely impair psychomotor and neurocognitive domains including attention, manual dexterity, coordination, and reaction time, as CB_1 receptors are neuroanatomically expressed in regions responsible for cognitive and motor control (13, 14). Therefore, THC dose-dependently disrupts important cognitive and psychomotor functions needed for safety-sensitive work, including driving motorized vehicles (15, 16).

There is currently no standardized definition of impairment associated with medical cannabis use in the literature and therefore, no general consensus on how to measure or define this impairment. Unlike with alcohol, where blood alcohol levels directly correlate with the degree of intoxication, the relationship between cannabinoid and neurocognitive or functional impairment remains undetermined. While evidence supports a positive relationship between THC dose and impairment, an accurate blood concentration range has not been determined (17). Some studies have suggested THC blood concentrations between 2 and 5 ng/ml are associated with impairment (18–20). However, these measures do not consistently correlate with impairment across individuals (17, 21). This is likely due to the complex nature of THC pharmacokinetics and metabolism (17, 20) which is strongly impacted by individual factors such as genetics and tolerance to THC.

The two main metabolites of THC include the primary psychoactive metabolite "11-hydroxytetrahydrocannabinol" (11-OH-THC) and the second metabolite "11-nor-9-carboxy-tetrahydrocannabinol" (THC-COOH) (22). The latter is a non-psychoactive and non-intoxicating cannabis metabolite which is usually eliminated from the body within 5 days of consumption primarily via feces and urine (23). From recreational cannabis studies, the detectable half-life of THC-COOH is much longer than for THC and 11-OH-THC. For infrequent cannabis users the half-life of THC-COOH is around 1.3 days, while for frequent users it is in the range of 5–13 days (24). The practical implication for medical cannabis patients is that they would likely test positive for cannabis on urine drug tests (which typically detect THC-COOH) days after last using THC (22). As THC-COOH is not psychoactive, its prolonged presence in frequent users is not a valid biomarker of impairment.

There is evidence that medical cannabis patients who use THC regularly develop tolerance to many of the impairing effects of THC (25). Tolerance has also been found with recreational cannabis use, with experimental studies demonstrating that frequent recreational cannabis users, with use more than four times per week, developed psychological and behavioral tolerance, and showed no significant impairment in neurocognitive function or motor side effects compared to infrequent users at the same dose of THC (26, 27). Other research demonstrates that tolerance is incomplete, and people who use cannabis regularly still demonstrate some impairment, albeit blunted, after acute use (28).

Determining the duration of potential THC impairment, and what THC dose a medical cannabis patient should take to minimize neurocognitive impairment, proves to be challenging. There are some unique considerations when studying impairment in medical cannabis patients, defined here as someone who uses cannabis under the guidance of a medical practitioner, compared to recreational cannabis users. Medical cannabis patients often use THC to manage symptoms for a variety of conditions including chronic pain, insomnia, PTSD, autoimmune conditions, and neurological disorders, that induce a certain level of neurocognitive impairment by themselves. By treating these symptoms, their neurocognitive and psychomotor functioning may actually improve. Medical cannabis patients also have different patterns of use, including a more consistent and standardized dosing schedule, along with different expectations and goals (29). They often consume cannabis orally, which lengthens the time until onset and the duration of effect after use, and choose use chemovars high in cannabidiol (CBD), which

is non-impairing (30). If medical cannabis patients are starting THC, most start with low-dose THC products, with doses titrated to obtain symptomatic relief while purposely avoiding impairing side-effects.

The aim of the present scoping review was to identify and summarize studies that investigate the duration and degree of acute neurocognitive impairment with medical cannabis use, and to compare this literature with the body of research on neurocognitive impairment in recreational cannabis users (31–35). Impairment, for the purposes of this review, is considered as disruption in neurocognitive and motor tasks that, if present, could potentially cause harm to the subject or others (e.g., driving or workplace safety). To investigate this critical question, we performed a scoping review of clinical trials that used standardized neurocognitive and psychomotor tests to study medical cannabis patients preceding and following acute THC administration. These findings are then compared to similar research involving recreational cannabis users to explore unique features of the medical cannabis patient population. We conclude by proposing a provisional standardized neurocognitive and psychomotor assessment battery for studying acute THC impairment in medical cannabis patients, and by discussing how medical professionals can best advise patients with regards to safety-sensitive work, including driving.

TABLE 1 | PICOS breakdown of study eligibility criteria.

P (Problem or Patient or Population)	Adults living with chronic, non-cancer pain (pain of >3-month duration) and/or spasticity.
I (Intervention/indicator)	Medical cannabis use or cannabinoid-based medicines.
C (Comparison)	Chronic pain/spasticity controls (without cannabis use). Studies without comparators will also be included.
O (Outcome of interest)	Duration of acute neurocognitive and psychomotor impairment using objective standardized measures
S (Study types selected)	Randomized controlled trials and other clinical trials will be included.

TABLE 2 | Inclusion and exclusion criteria (for medical cannabis patients using cannabis for chronic non-cancer pain or spasticity).

Inclusion criteria	
	Cannabis and the management of chronic non-cancer pain and/or spasticity
	Efficacy, tolerability, and safety studies on the use of medical cannabis for chronic non-cancer pain and/or spasticity
Exclusion criteria	
	Studies in a language other than English
	Studies published before 2000
	Studies which focus on recreational cannabis use
	Studies focusing on cannabis use disorder
	Studies without any formal and objective/reproducible neurocognitive testing
	Studies investigating the non-acute use of cannabis (for example, impairment after using daily THC for 1 month, instead of 1 h-post consumption)
	Studies on animals

MATERIALS AND METHODS

This study is a scoping review and qualitative analysis of the literature on impairment in medical cannabis patients. A systematic electronic search for English language randomized controlled trials (RCTs), clinical trials and systematic reviews (in order to capture any potentially missed RCTs) between 2000 and 2019 was conducted through Ovid MEDLINE and EMBASE electronic databases using the following MeSH terms: (exp Cannabinoids/ OR cannabi* OR dronabinol OR marijuana OR tetrahydrocannabinol OR THC OR Sativex) AND (chronic non? cancer pain OR Chronic Pain/OR muscle spasticity/OR spasticity) AND (impair* OR cognition OR intoxication OR reaction time OR coordination OR neurocognitive OR psychomotor). This search strategy was developed with the assistance of a medical librarian, and was conducted as we have previously reported on prior studies of drug-associated psychological effects (36–38).

Titles and abstracts were reviewed and obviously irrelevant studies were excluded. Full text of the remaining studies was reviewed to determine eligibility. The review was performed by a single investigator. Input from a second investigator was sought as required. The current focus was on medical cannabis patients using cannabis for chronic non-cancer pain or spasticity. Studies were included if they documented dose, product type and method of THC administration in addition to having formal objective neurocognitive or psychomotor baseline and acute post-THC assessments. See **Table 1** for PICO statement. Abstracts were analyzed for inclusion based on PRISMA criteria. Studies were excluded if they focused solely on recreational cannabis use, did not have any objective neurocognitive or psychomotor testing, or if the testing was done following subacute exposure, such as after weeks or months of daily THC exposure (**Table 2**).

Systematic reviews on medical cannabis use were also evaluated. Three additional RCTs that met the inclusion criteria were found in the references of these systematic reviews and were added to the analysis. One newly published observational clinical trial discovered through exert recommendation was added to the final analysis that was not found in our original electronic search. A database was not created from our review.

Data extracted from the investigated studies included the type of study completed, the number of participants, the participant characteristics, such as their medical condition causing pain or spasticity and their previous experience with cannabis, (or presumed THC tolerance), the THC concentrations assessed, the THC dosing intervals, the neurocognitive tests utilized, the timing of the neurocognitive testing intervals and the results of these neurocognitive tests for each THC dose and timing interval. The data drawn from the included studies was interpreted and summarized to make a preliminary recommendation on the duration of neurocognitive and motor impairments in medical cannabis users.

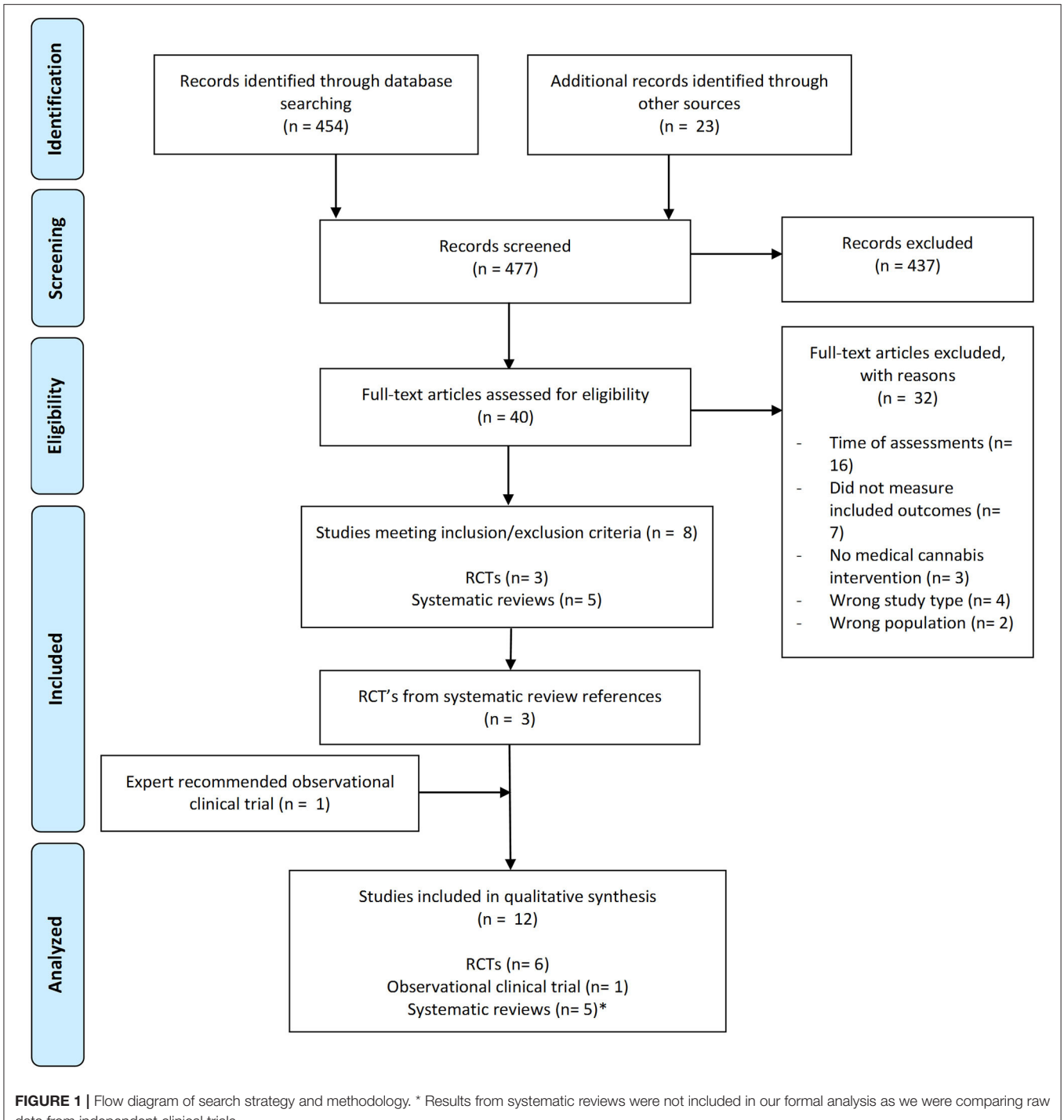

FIGURE 1 | Flow diagram of search strategy and methodology. * Results from systematic reviews were not included in our formal analysis as we were comparing raw data from independent clinical trials.

RESULTS

We identified 454 potentially eligible publications from the search strategy and twenty other potential articles from other resources. After screening titles and abstracts, 37 relevant studies were subjected to full-text review. One review article analyzed contained three additional RCTs which were independently reviewed for a total of 40 relevant studies reviewed. 32 studies were excluded for the following reasons: they measured subacute impairment of THC (days to weeks after ingestion), they did not have formal neurocognitive testing, there was no formal medical THC intervention completed, the study was not interventional, or they did not study adults living with chronic, non-cancer pain and/or spasticity. Eight studies met

our final criteria, five systematic reviews and three RCT's. From the systematic reviews, three RCT's were extracted for analysis. One newly published observational clinical trial discovered through expert recommendation was added that was not found in our original search. Overall, seven controlled trials met the inclusion/exclusion criteria and were included in the qualitative synthesis: six RCTs and one observational clinical trial. A flow diagram of our search strategy summarizes our methodology (**Figure 1**).

Study Characteristics

Study characteristics for the six RCTs and one observational trial are summarized in **Table 3** (39–45). A total of 234 medical cannabis patients were included in these studies: 175 patients with neuropathic pain, 37 patients with MS-associated spasticity and 22 patients prescribed medical cannabis pre-dominantly for chronic pain, anxiety or depression.

Route of cannabis administration varied: two studies required patients to smoke cannabis, three used vaporized cannabis, one allowed for smoking or vaporizing, and one study used sublingual THC, CBD, or THC: CBD spray. All three vaporization studies utilized the Foltin Puff Procedure, where participants are verbally signaled to "hold the vaporizer bag with one hand and put the vaporizer bag mouthpiece in their mouth" (30 s), "get ready" (5 s), "inhale" (5 s), "hold vapor in lungs" (10 s), "exhale and wait" before repeating the puff cycle (40 s) (39, 43, 44).

Four of the seven studies required participants to abstain from non-study cannabis use for at least 30 days prior to the start of the study (39, 40, 44). Two of the four verified abstinence through negative urine drug screens (39, 41). Several of the studies allowed medical cannabis use prior to the study initiation (42, 45), with less than half of the participants from one study reporting regular cannabis use (43).

There were a variety of testing protocols, with significant variability on the timing of THC or placebo administration and when the neurocognitive testing was completed. Some studies performed a single THC administration (39, 41, 45), where others had cumulative inhalation procedures (40, 42–44). Neurocognitive testing was either singular or repeated, with the most complete testing at baseline and every 30 min for 3 h total after THC ingestion (39).

Summary of Findings

Neurocognitive testing varied significantly between all studies, including the specific tests administered and the timing of assessments post-cannabis consumption. **Table 3** provides findings from individual studies, while **Table 4** provides details about the neurocognitive tests administered and the cognitive modalities examined with each test.

Two of the three studies using the Trails Making Test to assess visual attention and processing speed with switching tasks did not find significant differences between THC groups compared to placebo except for at two timepoints (39, 43). In one study, the low-dose THC group took longer than the high-dose THC group on the Trails A at 420 min, immediately after the second THC dosing interval (43). The second study found the high dose group took longer compared to placebo on the Trails B at 120 min post-dose (39). The third study assessing the Trails Making Test did not report their quantitative results in their findings (42).

Of the three studies using the Paced Auditory Serial Attention Test for auditory processing speed and working memory (39, 41, 43), one study found no significant differences between THC groups and placebo at any timepoint, but the high-dose THC group performed better than the low-dose THC group at 420 min (43). In the second study, the high- and medium-dose THC groups had worse performance than placebo at 15 min post-inhalation, but there was no difference in performance between low, medium, or high dose THC groups compared to placebo at the following 60-, 120- or 240-min post-inhalation testing (39). In the final study, the THC group had worse performance compared to placebo at 45 min post-inhalation with no further testing after this timepoint (41).

Results were mixed between the three studies using the Grooved Pegboard Test (GPT) (40, 43, 44) to assess dexterity and fine motor control. All three studies used cumulative cannabis inhalation protocols. One study found no significant effects across active doses compared to placebo on the dominant-hand GPT but observed decreased performance on the non-dominant GPT in the high-dose THC group compared to placebo. This occurred 1-h after the second THC dosing session and resolved after an additional 60 min (43). In the second study, the low-dose THC group had worse performance than the medium-dose THC and the placebo group on the dominant-hand GPT at 60 min, (immediately after the first dosing session), and 240 min, (60 min after the second dosing session) (44). This same study found that both the low-dose and medium-dose THC groups had decreased performance on the non-dominant GPT at the 120- and 180-min (60 min after first dosing session and immediately after the second dosing session) (44). There was no difference in performance between placebo and either THC group at the 300-min mark, 3 h after the last scheduled inhalation (44). The final study found a decrease in overall performance in the high-dose THC group compared to placebo on the dominant-hand GPT, but no difference between the low-dose THC group and placebo. In the non-dominant hand GPT, this study found that both THC groups had decreased performance compared to placebo. The study measured maximal recovery 2 h after the last inhalation session at 180 min where low-dose and high-dose THC groups had significant improvement on the GPT compared to their previous scores (40).

All three studies that administered the Hopkins Verbal Learning Test and Delayed Learning Test to assess learning, immediate and delayed recall found THC dose-dependent impairment on learning and recall compared to placebo (40, 43, 44). For two studies, performance following higher THC doses was worse than for lower doses of THC, which in turn, were worse than placebo (40, 44). Notably, one study found poor performance on this test even in the placebo group, hypothesized to be due to their underlying neuropathic pain condition (40). The second study found recovery of these differences 2 h after the last inhaled THC session (44). The final study found no difference in test scores between the low-dose THC group and placebo. In this study, the high-dose THC group had fewer true-positive responses and more false positives compared to

TABLE 3 | Study characteristics and results.

Study	Population	Intervention	Cannabis use	Outcome	Results
Wallace et al. (39) Randomized, double-blind, placebo-controlled crossover study	Painful Diabetic Neuropathy 16 participants	Placebo, 1, 4, and 7% THC vaporized 4 inhalations using the Foltin Puff Procedure in one single dosing session (equaling 0, 4, 16, or 28 mg THC)	No use of cannabis in past 30 days prior to study tested by urine drug screen	Trail Making Test Paced Auditory Serial Attention Test Testing at 5-min, 30-min and every 30- min for 3 h. Final measurement at 240-min.	Decline in neurocognitive performance with THC exposure which was dose dependent and improved with time. No difference in any groups at 240-min post-inhalation (4-h). *Trails*: 7% THC group took longer compared to placebo on Trails B at 120-min. No difference between 1 and 4% THC groups and placebo *Paced Auditory Serial Addition Test*: 7% THC and 4% THC groups had worse performance than placebo at 15-min post-THC dose. There was no difference in performance between 1, 4, or 7% THC groups compared to placebo at the following 60-, 120-, or 240-min testing.
Wilsey et al. (40) Double-blind, placebo-controlled, crossover study	Central and Peripheral Neuropathic Pain 38 participants	Placebo vs. 3.5% THC vs. 7% THC smoked 2 inhalations at 60-min, 3 inhalations at 120-min, and 4 inhalations at 180-min for a total of 9 cumulative inhalations (total estimate: 19 mg THC low dose, 34 mg THC high dose)	All had previous cannabis exposure No cannabis 30 days prior to study	Digit Symbol Test Hopkins Verbal Learning Test and Delayed Learning Grooved Pegboard Dominant and Non-Dominant tests Testing completed at baseline, 60-mins (after 2 puffs), 120-min (after 3 puffs), 180-mins (after 4 puffs), 240-min (after 1-h recovery).	Modest decline in cognitive performance with THC use, most significant in the 7% THC group. 76% of participants had cognitive impairment at baseline. *Digit Symbol Test:* no significant dose-effect differences *Hopkins:* 7% THC group had worse performed than the 3.5% THC group which performed worse than placebo. Poor performance even in placebo group *Dominant-hand Pegboard*: 7% THC group performed worse than placebo. No difference in performance between the 3.5% THC group and placebo. *Non-dominant hand pegboard:* Both THC groups had decreased performance compared to placebo. 2-h after the last inhalation session, both THC groups had significant improvement compared to their previous scores
Corey-Bloom et al. (41) Randomized placebo-controlled trial	Multiple Sclerosis Spasticity 37 participants	Placebo vs. 4% THC smoked 4 inhalations of 4% THC smoked in one dosing session (∼16 mg THC)	Cannabis naïve or negative toxicological screen for THC at study initiation	Timed walk score Paced Auditory Serial Addition Test Baseline and 45-min post-treatment	*Timed walk*: no difference *Paced Auditory Serial Addition Test*: 4% THC group had worse performance compared to placebo at 45-min. There was no neurocognitive testing beyond 45-min.
Notcutt et al. (42) Prospective, randomized, double-blind, placebo-controlled crossover study	Chronic mostly neuropathic pain 34 participants	Sublingual Spray 2.5 mg THC vs. 2.5 mg CBD vs. 2.5 mg THC and 2.5 mg CBD One spray every 15–30 min and individually stopped further dosing after response was achieved Total intake: 2–8 sprays over a 4-h period (∼5–20 mg THC)	Excluded if significant past or current recreational cannabis use, okay if medical cannabis use	Trail Making Tests A & B Adult Memory and Information Processing Battery Baseline and 3-h post-dose	Equivocal results, requiring a more detailed analysis than the study planned. Testing often improved after the initiation of cannabis-based medicine.

(Continued)

TABLE 3 | Continued

Study	Population	Intervention	Cannabis use	Outcome	Results
Wilsey et al. (43) Crossover, randomized, placebo-controlled human laboratory experiment	Patients with refractory neuropathic pain who have disease or injury to their spinal cord 48 participants	Placebo vs. 2.9% vs. 6.7% THC vaporized 4 puffs using the Foltin Puff Procedure at 60-min with a second dosing session at 240-min of 4–8 puffs (flexible dosing schedule: the participant chooses their second dose between 4–8 puffs)	17/42 participants used cannabis regularly Some were cannabis naïve or ex-users	Wechsler Adult Intelligence Scale Digit Symbol Test Trail Making Test Grooved Pegboard Test Paced Auditory Serial Addition Test Hopkins Verbal Learning Test Revised with 20-min delay Neurocognitive testing every hour (with variations to prevent learning)	Measurement of neurocognitive performance proved technically challenging due to the various disabilities in the population studied. THC showed dose-dependent neurocognitive impairment with resolution 2 h after inhalation of THC. *Dominant-hand Pegboard:* no significant dose-effect differences *Non-Dominant Hand Pegboard*: 6.7% THC group performed worse compared to placebo 1-h after the 2nd THC dosing session. Resolved 1-h later *Digit Symbol Test*: no significant dose-effect differences, with all groups improving scores over time, consistent with practice effects *Trail Making Test-A*: 2.9% THC group took longer than the 6.7% THC group on the Trails A at 420 min, immediately after the 2nd THC dosing interval *Hopkins*: no difference in test scores between the 2.9% THC group and placebo. 6.7% THC group had less true-positive and more false-positive responses compared to placebo. Resolved 2-h after the 2nd dosing session *Paced Auditory Serial Addition Test*: no significant differences between THC groups and placebo at any timepoint. 6.7% THC group performed better than the 2.9% THC group at 420 min, 3-h after the 2nd dosing interval
Wilsey et al. (44) Randomized double-blind placebo controlled cross-over trial	Central or peripheral neuropathic pain (Refractory) 39 participants	Placebo vs. 1.29%, vs. 3.53% THC vaporized 4 puffs at using the Foltin Puff Procedure at 60-mins with a second dosing session at 180-min of 4–8 more puffs (flexible dosing schedule: the participant chooses their second dose between 4 and 8 puffs)	All had previous cannabis exposure No cannabis 30 days prior to study	Wechsler Adult Intelligence Scale Digit Symbol Test Hopkins Verbal Learning Test Revised Grooved Pegboard Test Baseline, 60-, 120-, 180-, 240-, and 300-min after administration of THC	THC produced a short duration of neurocognitive impairment. No difference in performance between THC and placebo 2-h after the last dosing session *Digit Symbol Test*: 1.29 and 3.53% THC groups had worse performance at 60-min, (after 1st inhalation) and 180-min, (after the 2nd inhalation) compared to placebo. No difference in either THC group and placebo at 120- and 240-min (1-h after each dose) *Dominant Hand Pegboard*: 1.29% THC group had worse performance than the 3.53% THC and the placebo group at 60-min (after 1st inhalation) and 240-min, (60-min after 2nd inhalation) which resolved 60-min later *Non-dominant Hand Pegboard*: 1.29% THC and 3.53% THC groups had decreased performance at 120-min (60-min after 1st inhalation) and 180-min (after 2nd inhalation) which resolved 60-min later *Hopkins*: performance following higher THC doses was worse than for lower doses of THC, which in turn, were worse than placebo. There was recovery of these differences 2-h after the last THC inhalation session.

(Continued)

TABLE 3 | Continued

Study	Population	Intervention	Cannabis use	Outcome	Results
Olla et al. (45) Observational Clinical Trial	Medical Cannabis Patients 22 participants	One gram 20% THC in vapes, cannabis cigarettes (joints) and dabs for 10 min One dosing session with 10 min of THC intake	Regular cannabis use ≥6 month 3.2 g/day cannabis average)	Brief Neurocognitive Battery: Animal Fluency, Boston Naming Test-15, Coding, Digit Span, Stroop Color Naming/Word Reading/Interference, Trails Making Test A/B Baseline, 30 min and 2.5–3 h after intake Included Performance Validity Testing	There was no psychometric evidence for a decline in performance on cognitive testing following THC ingestion and some participants had improved performance after THC ingestion compared to the normative sample. Performance Validity Test: More failures in the THC group, which were the most affected parameters of the suppressing effects of THC on cognitive functioning.

placebo, a difference that resolved 2 h after the second dosing session (43).

Two of the three studies administering the Wechsler Adult Intelligence Scale Digit Symbol Test to assess concentration and graphomotor speed found no significant dose-effect differences throughout the duration of the study (40, 43) with one study noting improvement among all conditions (including placebo), consistent with a learning effect (43). The remaining study found a decrease in performance at 60-min, (immediately after first inhalation session), and 180-min, (immediately after the second inhalation session), in both the low dose and high dose THC groups compared to placebo, although there was no difference between placebo and either THC group 1 h after each dosing session (44).

One study used the Adult Memory and Information Processing Battery in addition to Trails Making Test, although the authors did not report their results (42). The final study utilized the Brief Neurocognitive Battery (**Table 4**), consisting of a comprehensive series of neurocognitive tests with combined Performance Validity Testing-additional tests that are robust to the effect of genuine impairment and allow for the determination of the impact of the patient's effort or engagement in testing (45). Cannabis patients were compared to the normative sample supplied with the Brief Neurocognitive Battery technical manual and were also compared to test results from 40 non-cannabis using Canadian UG students completing this test battery unimpaired. Medical cannabis patients either matched or outperformed both the normative data set and the Canadian UG students test results at 30 min and 150–180 min post-THC ingestion, showing no evidence of neurocognitive impairment following THC consumption. (45).

In summary, there is evidence that cognitive performance declined mostly in a THC dose-dependently manner, with steady resolution of impairment in the hours following THC administration. There is some variability in this dose-dependent relationship, bringing forward the consideration that there are other important factors contributing to the duration of neurocognitive impairment besides the dose of THC ingested. For example, one study found no neurocognitive impairment, and even higher neurocognitive test scores in the THC group compared to the normative data set (42, 43, 45). In all the studies, there was no difference between any of the THC groups and placebo on any neurocognitive measure after 4 h of recovery (39).

DISCUSSION

This scoping review provides evidence that cognitive performance in medical cannabis patients acutely declines after THC use, with steady resolution of impairment in the hours following THC administration. The degree of impairment is predominantly dose-dependent; higher doses of THC are generally more impairing than the lower doses. The duration of neurocognitive impairment varied between studies, partly due the heterogeneity in study designs. Nonetheless, there was no difference on any neurocognitive test between placebo and the active THC groups at 4-h of recovery, irrespective

TABLE 4 | Neurocognitive tests and cognitive domains.

Neurocognitive test	Neurocognitive correlate assessed
Paced Auditory Serial Attention Test	Auditory information processing speed and working memory
Wechsler Adult Intelligence Scale Digit Symbol Test	Concentration, psychomotor speed, and graphomotor abilities
Trail Making Test A and B	Processing speed, visual attention, and task-switching
Grooved Pegboard Test (Dominant and Non-Dominant)	Fine motor coordination and speed
Hopkins Verbal Learning Test Revised with 20-min delay	Learning/ability to retain, reproduce, and recognize information after a 20 min delay. Immediate and delayed recall of verbal information
Adult Memory and Information Processing Battery	*Spatial Recall Test*: Visuospatial memory *Symbol Digit Modalities Test*: Concentration, psychomotor speed, and graphomotor abilities *Paced Auditory Serial Addition Test*: Auditory information processing speed and working memory *Word Generation List*: Lexical fluency *Selective Reminding Test*: Verbal learning and memory
Brief Neurocognitive Battery	*Animal Fluency*: Semantic fluency and executive control *Boston Naming Test-15*: Expressive language *Coding*: Attention and visuomotor processing *Digit Span*: Auditory attention and working memory *Stroop Color Naming*: Attention and speed of information processing *Stroop Word Reading*: Attention and speed of word reading *Stroop Interference*: Inhibition and cognitive flexibility *Trails Making Test-A*: Simple attention, visual scanning and processing speed *Trails Making Test-B*: Visual scanning, divided attention and cognitive flexibility

of the THC dose inhaled (39–45). Importantly, none of the studies collected blood to measure plasma levels of THC and its metabolites. It would have been informative to have been able to directly relate objectively measured cognitive impairment across specific domains to plasma levels of cannabinoids in these subjects.

Several observations from this review draw important comparisons with the recreational cannabis literature. As we have already discussed in detail the results of the scoping review and the seven studies in the Summary of Findings above, the focus on the present Discussion is to highlight and discuss important considerations when reviewing the current literature in addition to a variety of modifiable and non-modifiable factors that were found to influence the duration and degree of neurocognitive impairment in medical cannabis patients (see **Figure 2**).

There are several non-modifiable factors, intrinsic to the patient, that influence both the degree and duration of impairment (**Figures 2A–C**). These important factors are sometimes overlooked within the larger body of literature, particularly within recreational studies.

Genetics and Metabolism

Genetic and metabolic profiles or predispositions influence how an individual responds to cannabis, and thus the side effects experienced. Genetics, such as variations in the COMT/AKT genotype (46, 47), individual endocannabinoid system "tone" [endogenous endocannabinoid levels, receptor sensitivity and abundance, which may be altered in psychiatric conditions such as depression (48, 49)], as well as hypo- or hypermetabolizers can influence how THC is metabolized (50) and thus the degree and duration of impairment experienced by an individual (**Figure 2B**). This may influence study outcomes, particularly when smaller sample sizes are used.

Personal or Family Mental Health History

It is important to consider personal or family mental health history when assessing factors of impairment. Experienced or known pre-dispositions to some mental health conditions may increase the risk of impairment for some individuals (**Figure 2B**) (51, 52). The use of high THC chemovars may exacerbate this risk.

Comorbidities

Studies that assess the therapeutic effects of THC based on ability to manage symptoms, predominantly pain or spasticity, should acknowledge that these symptoms may contribute to impairment (**Figure 2C**). Patients with certain medical conditions, such as multiple sclerosis, epilepsy, insomnia, anxiety, and depression, have twice the risk of motor vehicle accidents than healthy controls (53–55). Chronic pain syndromes can manifest with comorbid fatigue, weakness, dizziness, or cognitive slowing, which may compound the impairment produced by THC. However, by managing these symptoms with medical cannabis, baseline neurocognitive and psychomotor functioning may improve, as was reported in a driving simulation study with patients who have multiple sclerosis (56). Co-morbidities with additive impairing effects should be carefully considered clinically and in future research. In addition to non-modifiable factors, this review identified several modifiable factors that were found to influence the duration and degree of impairment. These are now discussed in more detail below (**Figures 2D–K**).

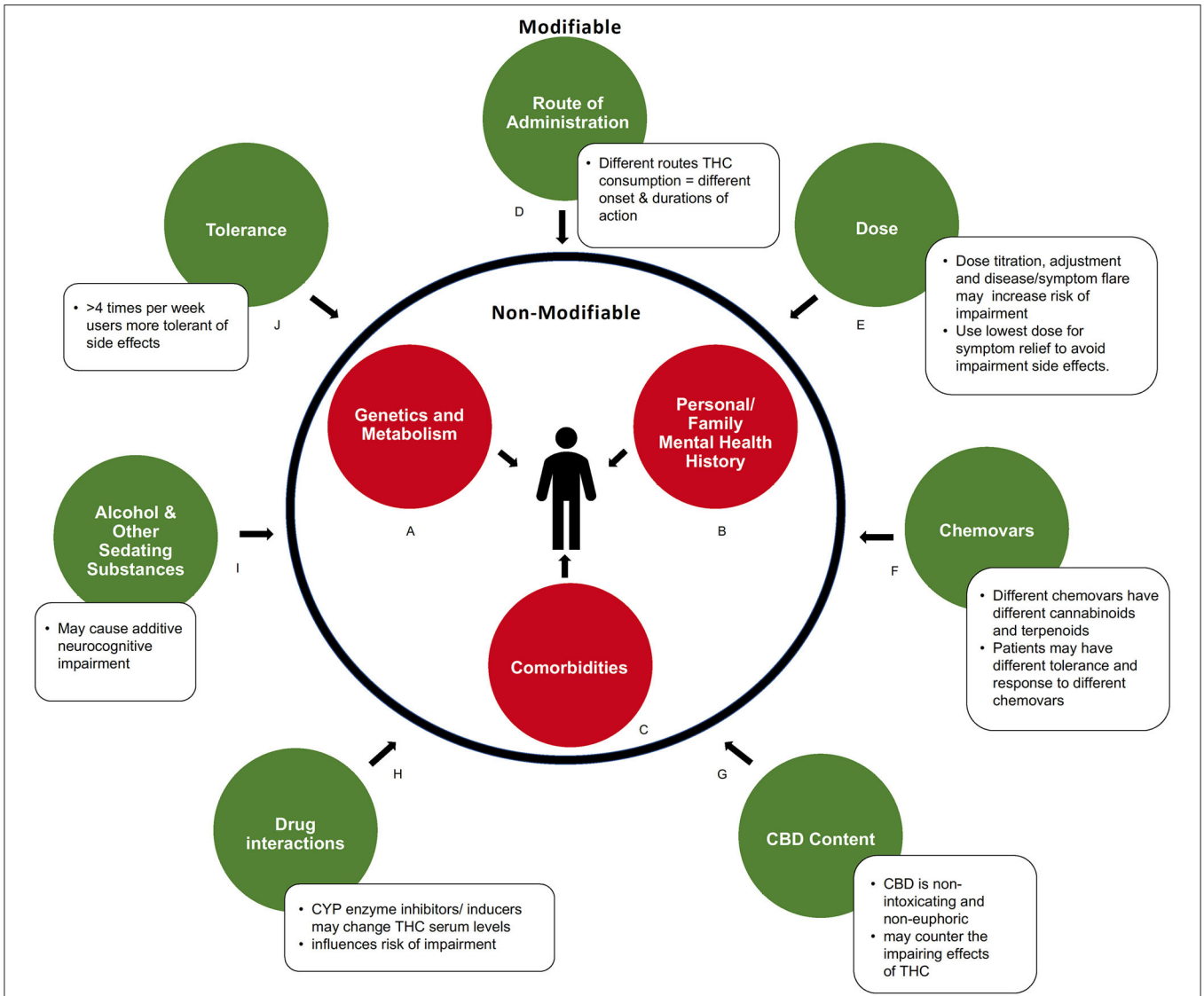

FIGURE 2 | Modifiable and non-modifiable factors influencing acute neurocognitive impairment in medical cannabis users. **(A)** Genetic and metabolic profiles can influence response to cannabinoids. **(B)** Predisposition to or history of mental health conditions may increase risk of impairment. **(C)** Comorbidities that produce symptoms like fatigue, dizziness, or cognitive slowing may compound impairment. **(D)** How cannabis is consumed influences the duration of impairments via differences in absorption and metabolism. **(E)** Severity of impairment is THC dose-dependent. **(F)** Chemical composition (level of various cannabinoids and metabolites) of a cannabis product influences degree of impairment **(G)** Amount of CBD contained in product may balance side effects of THC. **(H)** Drug interactions can alter serum THC levels. **(I)** Use of other sedating recreational or prescribed substances may cause additive impairment. **(J)** Pattern of regular consumption in medical cannabis users decreases drug response, and side effects, to cannabinoids.

Route of Administration

As represented in **Figure 2D**, there is a clear difference in the duration of neurocognitive impairment depending on the route of administration (smoked vs. sublingual spray vs. oils). Due to differences in absorption and metabolism, THC has a different onset and duration of action depending on where in the body it is administered (57–59). Cannabis oils may provide up to 8 h of symptom relief due to gradual absorption of THC from the gut combined with first pass metabolism conversion of THC to 11-OH-THC, another active compound, in the liver (30, 58). The longer duration of therapeutic action also gives ingested formulations a greater period of potential impairment. Inhaled or vaporized THC produces a shorter period of impairment compared to oral formulations, with typical onset with 5–10 min and duration for 3–4 h. This is due to rapid absorption of THC from the lungs into the bloodstream, with minimal conversion to 11-OH-THC by the liver via first-pass metabolism (30, 60–62). Although none of the studies above utilized oil ingestible THC formulations, clinically this is a common method of intake for patients using medical cannabis, to limit the negative effects of smoking. We would recommend that future studies administer cannabis oils, providing doses similar to those that

are prescribed in practice, in order to appropriately represent the medical cannabis population. Further, new formulations are being manufactured with different carrier oils, extraction techniques, and cannabinoid content which may lead to different levels and duration of impairment. Future pharmacokinetic studies assessing these formulations are needed.

Dose

The degree and duration of neurocognitive impairment is dose-dependent, with higher THC doses being more impairing than lower doses. The dose of THC used among the medical cannabis studies reviewed were substantially lower compared to typical recreational studies (**Figure 2E**). Recreational studies often measure neurocognitive functioning in heavy cannabis users and follow the participants usual cannabis regimen, with a reported average of two cannabis "joints" per dosing session (63–66). If one "joint" contains ∼750 mg of cannabis with a THC concentration of 15%, one dosing session would contain 225 mg of THC. Some of these high-dose THC recreational studies have shown subtle defects in cognitive tasks up to 24-h after THC inhalation (65). However, recreational studies using doses similar to this medical cannabis review, [with the highest dose administered being 34 mg of THC (40)], do not note any neurocognitive impairment 24-h after THC ingestion (67).

Rather than using data from studies with medical cannabis users and with doses typically used by medical cannabis patients, Health Canada's "Cannabis Impairment" report based its conclusions on data from studies of recreational cannabis, where doses are substantially higher. The report notes: "(s)ome effects of cannabis use, for example drowsiness, can last up to 24 h, well after other effects may have faded…(T)here is no standard waiting time to drive after using cannabis. If you are using cannabis, do not drive." (68). If they followed these recommendations, many daily medical cannabis patients would be unable to drive or attend work, even if they only utilize THC at night before going to sleep.

This review of the literature found no reports of neurocognitive deficits with THC use 4-h after inhalation using modest THC-dosing strategies. We would recommend using lower-THC doses, (as were seen in the studies in this review), for daily symptom management, as higher doses may prolong the duration of impairment.

Chemovars and CBD Content

The addition of other cannabinoids, such as CBD, may have an impact on the severity of neurocognitive impairment (**Figures 2F,G**) (69). One of the studies in this review, compared oromucosal spray formulations of THC vs. THC: CBD 1:1 vs. CBD vs. placebo and noted that participants in the THC: CBD group had less drowsiness, dysphoria, and euphoria (**Figure 2F**) (42). In addition to CBD, cannabis contains many other cannabinoids and terpenes that may affect neurocognitive impairment (**Figure 2F**). For example, myrcene may potentiate the sedating effects of THC (70, 71). Importantly, this could mean that patients who develop tolerance to the unwanted neurocognitive side effects of one chemovar of cannabis may not have the same tolerance to other chemovars with different concentrations of cannabinoids and terpenoids (70). Thus, another informative avenue for future studies would be to monitor and record in detail the quantities and concentrations of the other constituents of the cannabis being studied, as the individual or "entourage" effects of these on cognitive impairment is largely unknown.

Drug Interactions and Sedating Substances

Medical cannabis patients often utilize other impairing substances to manage their conditions. The interaction of these substances with THC may further the duration and severity of neurocognitive impairment (**Figures 2H,I**). For example, there is the potential for additive impairment due to interactions with other intoxicants (e.g., alcohol) or sedating medications such as benzodiazepines, opioids, tricyclic antidepressants, and anti-epileptics (**Figure 2I**) (58). All studies in the current review required patients to stay on their normal routine medications (39–45), and only one study excluded participants who were on opioid medications or used any other medication deemed to interact with cannabis (45). The articles in this review did not list which medications were routinely consumed by patients, which would have been useful information. Most of the articles provide a brief summary of the major medical conditions that were associated with medical cannabis use, so some inferences can be drawn, but detailed information is missing. In clinical practice, it has been commonly noted that many patients reduce their use of prescription medications if they achieve greater symptom relief with marijuana, which can actually reduce overall sedation. Further, polypharmacy may result in drug interactions (**Figure 2H**). THC is metabolized by the CYP family of enzymes, therefore, CYP inducers or inhibitors may alter serum levels of THC, influencing risk of impairment (58, 72). It will therefore be important for future studies to report any relevant patient medications as potential confounding factors.

Tolerance

One of the important differences between the medical cannabis patient and those who use recreational cannabis is the pattern of THC use (e.g., intermittent vs. daily consumption). Medical cannabis patients typically manage symptoms using THC on a daily basis, which can lead to pharmacological tolerance, including tolerance to possible side effects (**Figure 2J**) (73–77). For example, a study of patients with multiple sclerosis did not demonstrate impairment in driving-related tasks after 4–6 weeks of daily medical cannabis treatment (when compared to their baseline without medical cannabis) (78). Notably, the one study where all participants used their daily medical cannabis up until testing day found improved performance compared to normative data (45). This suggests that patients who take medical cannabis every day may not develop the same amount of neurocognitive impairment as those who previously abstained or use infrequently.

Some of the studies evaluated in this review enrolled participants with a previous history of cannabis use (44, 45), while others enrolled cannabis naïve participants (41, 43), which may contribute to the significant heterogeneity between study results.

Even within medical cannabis patients, those who use medical cannabis for persistent, chronic daily symptoms vary significantly in their use patterns from those who use to control acute and intermittent symptoms. Future clinical studies should consider THC tolerance and ensure that the duration and amount of previous THC use is specified in the eligibility criteria and evaluated when interpreting results. A standardized definition for chronic, daily medical cannabis use should be implemented in future studies. For most patients, titration and monitoring of cannabis intake typically takes 4–12 weeks to achieve an optimal therapeutic effect. The titration period depends on a number of factors (**Figures 2A–C,I**) including comorbidities, polypharmacy, genetics, and age (30). A research definition should account for this titration period and consider stabilization to have occurred when no further dose adjustments are required over a 2 week period. This will ultimately increase the validity and applicability to research findings. Further reviews and commentary on factors that influence impairment (**Figure 2**) are greatly needed.

Limitations

Findings from this review were constrained by the limitations of the current literature. Due to the heterogeneity of the study populations, study designs and protocols, and variability in the objective testing measures between studies, we were unable to complete a meta-analysis. The lack of cognitive and motor test standardization and the inconsistent methods between studies, including the type and time of testing post-THC ingestion, precluded statistical pooling of the data. There were no standardized medical cannabis products used across studies, with each study exploring varying concentrations of THC and CBD in either smoked, vaporized, or sublingual formulations, including cannabis-based medicines such as THC:CBD oromucosal spray (**Figures 2F,G**). Combining findings between the included studies and coming to definitive conclusions would be premature.

An additional limitation in the literature was lack of research assessing oral THC products, including cannabis oils. Due to the known pharmacokinetic differences between ingested and inhaled THC and given that many medical cannabis patients use oral formulations, it will be important for future studies to incorporate these products in their trials. An important confounder in studies on impairment are the participants underlying medical conditions (which in these studies often included illnesses that are detrimental to neurocognitive performance). Patients baseline cognitive functioning was only described and controlled for in three of the six studies (39, 40, 43), and is important to document for future studies. Blood levels of THC and its metabolites were also not assessed in any of these studies. This was a missed opportunity to obtain a better understanding of how drug levels relate to cognitive impairment in medical cannabis users with medical doses. It would also have better enabled comparison of effects between medical and recreational cannabis users.

Finally, the literature on this topic is limited by the relatively small sample sizes of included studies. Small sample sizes may overestimate treatment effects or be insufficiently powered to detect a true difference, although some studies stated they were sufficiently powered to detect differences. Future trials would provide more robust information if they had larger sample sizes and captured data on a wider range of medical cannabis patients. Nevertheless, the trends that emerged among these medical cannabis impairment studies compared to the recreational data supports that medical cannabis patients do not have the same duration or degree of neurocognitive impairment as recreational users.

TABLE 5 | Summary of findings.

Summary of findings
Neurocognitive impairment following cannabis inhalation is less than or equal to 4 h in medical cannabis patients, independent of their dosing regimen (e.g., daily, intermittent, or infrequent)
Impairment is THC dose-dependent
Acute impairment was found to be statistically significant in the following neurocognitive and psychomotor domains: • Immediate and delayed verbal recall • Processing speed • Task switching • Visual attention • Fine motor coordination • Working memory
There are several non-modifiable factors that influence duration and degree of impairment: • Comorbidities • Personal/ Family Mental Health History • Genetics and metabolism
Medical cannabis patients consume cannabis to manage symptoms and improve quality of life by optimizing the following modifiable domains: • Intent of use • Route of administration • Chemovar selection • CBD content • Dose • Tolerance • Alcohol & other sedating substances • Drug interactions
We cannot extrapolate the conclusions found in this review to recreational cannabis populations or those "medical cannabis" patients not under the guidance of a health care practitioner.

CONCLUSIONS

This review suggests that the duration of neurocognitive impairment following inhalation or sublingual absorption of THC containing products is 4 h or less in medical cannabis patients. The results of this review are consistent with the College of Family Physicians of Canada's 2014 statement that medical cannabis patients should err on the side of caution, and delay safety sensitive activities for 3–4 h if cannabis (THC) is inhaled, 6–8 h if ingested orally, and 8 h if any euphoria is experienced (79). There are important differences between medical and recreational cannabis users that may not allow for the same conclusions to be drawn about the duration or degree

of impairment within the recreational cannabis population. These differences pertain to factors including the dose of THC, method of intake, patient tolerance and intent, additional chemovars added (such as CBD) and concurrent sedative or hypnotic medication intake (**Figure 2**). This review suggests that neurocognitive impairment in medical cannabis patients can involve multiple neurocognitive and psychomotor domains. A summary of the main conclusions and recommendations from this review can be found in **Table 5**.

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

LE was primarily responsible for the review of published abstracts, with additional support from LL, and wrote the first draft. CM supervised the project and provided the overall intellectual leadership. All other authors contributed to revising the manuscript with additional intellectual input.

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Cannabis-Induced Hypodopaminergic Anhedonia and Cognitive Decline in Humans: Embracing Putative Induction of Dopamine Homeostasis

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Over years, the regular use of cannabis has substantially increased among young adults, as indicated by the rise in cannabis use disorder (CUD), with an estimated prevalence of 8. 3% in the United States. Research shows that exposure to cannabis is associated with hypodopaminergic anhedonia (depression), cognitive decline, poor memory, inattention, impaired learning performance, reduced dopamine brain response-associated emotionality, and increased addiction severity in young adults. The addiction medicine community is increasing concern because of the high content of delta-9-tetrahydrocannabinol (THC) currently found in oral and vaping cannabis products, the cognitive effects of cannabis may become more pronounced in young adults who use these cannabis products. Preliminary research suggests that it is possible to induce 'dopamine homeostasis,' that is, restore dopamine function with dopamine upregulation with the proposed compound and normalize behavior in chronic cannabis users with cannabis-induced hypodopaminergic anhedonia (depression) and cognitive decline. This psychological, neurobiological, anatomical, genetic, and epigenetic research also could provide evidence to use for the development of an appropriate policy regarding the decriminalization of cannabis for recreational use.

Keywords: cannabis use disorder, depression, anhedonia, neuroanatomic alterations, reward deficiency syndrome, genetic testing, pro-dopamine regulation, dopamine homeostasis

PREVALENCE

Cannabis is regarded as the most abused illicit drug in the world today. An estimated 150–200 million people use cannabis regularly, and a relatively common disorder, known as cannabis use disorder (CUD), has an estimated prevalence of 8.3% in young adults in the United States (1, 2). A recent survey of 482 young college students, ∼19–20 years, found that 29% of students vaped cannabis. From this survey, men from high socioeconomic status (SES) vaped higher cannabis amounts than men 13–14 years from lower SES status and women (3). Between 2000 and 2016, the lifetime and daily use of cannabis among 12th graders was 44 and 6%, respectively. In 2019, 8th graders' ∼13–14 years, past-year use was 11.8%, and past-month use was 6.6%, 28.8% of 10th graders had used marijuana in the past year and 18.4% in the past month. Among 12th graders, ∼17–18 years, rates of cannabis use grew to 35.7% during the previous year and 22.3% in the previous month. Reports of daily and near-daily use were 6.4%. Almost 4% of 12th grader teens vape cannabis products daily (NIH What is the scope of marijuana use in the United States? Marijuana Research Report, https://www.drugabuse.gov/ [accessed October 28, 2020]).

More importantly, there is increasing concern by the addiction medicine community that because of the high content of delta-9-tetrahydrocannabinol (Δ9-THC), (the chemical that causes the high) currently found in edibles and vaping cannabis vaping products [up to 90%; https://www.marijuanabreak.com/90-percent-thc-weed, (accessed January 20, 2020)], the chronic cannabis users may develop more severe hypodopaminergic-anhedonia (depression) and cognitive decline. Incidentally, other serious respiratory and pulmonary consequences, including chronic obstructive pulmonary disorder (COPD), have also been reported among those who use e-vaping devices (4).

CANNABIS AND NEUROANATOMIC ALTERATIONS AND COGNITION

Cannabidiol (CBD) can ameliorate the effects of THC and protect the brain from damages, possibly through CB1 antagonism (5). These psychophysiological damages include dose-dependent psychotic cognitive and behavioral symptoms (6) and observed from several human structural neuroimaging studies frequency of use dependent reductions in gray matter volumes. The reductions occur in the medial temporal cortex, orbitofrontal cortex, temporal poles, parahippocampal gyrus, and insula. Chronic cannabis users also display significant neuroanatomic alterations in the medial temporal, frontal cortex, cerebellum (7), and the fusiform gyrus, temporal pole, superior temporal gyrus, and occipital cortex (8).

A top area of concern, especially in young developing adults, is the damaging effect of high doses of Δ9-THC and consequent cognitive impairment. According to Floresco et al. (9) and Lorenzetti et al. (8), the neuroanatomic alterations in the prefrontal-hippocampal function and subsequent down-regulation of CB1 receptors may result in cognitive decline/working memory, decision-making, and inhibitory control in chronic cannabis users. Cannabinoid type 1 receptors (CB1) associated with motivational, emotional, and affective processing (10) are usually abundant in these areas, so upregulation of CBD1 receptors may positively affect THC-induced brain damage. Notably, these cognitive effects may return to normal after 4–6 weeks of abstinence from cannabis (11, 12).

THE SYNAPTIC MECHANISMS UNDERLYING THC-INDUCED ANHEDONIA AND COGNITIVE DEFICITS

In adult cannabis users, brain activation decreases in the middle temporal gyrus, insula, and striate area and increases in the superior and posterior transverse temporal and inferior frontal gyri and middle temporal gyrus. While activation in adolescents increases in the inferior parietal gyrus and putamen compared to healthy controls (13). Research suggests that functional alterations in these areas are neuroadaptive changes in cannabis users and may be compensatory (13).

CANNABIS AND DOPAMINERGIC FUNCTION

Chronic cannabis usage, including in adolescents, has also significantly reduced striatal dopamine release causing (hypodopaminergia) and associated poor memory, inattention, and impaired learning performance (14). Chronic use of cannabis observed with [18F]-DOPA PET found reduced brain dopamine synthesis and subsequently attenuated reward sensitivity, motivation, and induced apathy. It is noteworthy that the 9/9 allele polymorphism carriers have high D2/D3 receptor availability (due to higher dopamine re-absorption rates) compared to carriers of the 10/10 alleles in early-onset heavy cannabis users (15). The carriers of the 7R DRD4 polymorphism are likely to experiment with cannabis more than the non-carriers. According to Volkow et al. (16), among cannabis users, there is a reduced dopamine brain response linked to the emotionality and severity of the addiction. Cannabis users also show inversely correlated dopamine reactivity with higher negative emotionality scores relative to controls (17). There is some evidence that suggests large doses of Δ9-THC increase dopamine release by inhibiting VTA GABAergic activity (18). This effect may translate to an increased fear reaction in cannabis users. In animal experiments (19), the repeated administration of Δ9-THC induced depressive-like symptoms, including prolonged anhedonia due to CB1 type receptors' impairment and dopaminergic alterations in the mesolimbic region. This Δ9-THC induced dysfunction in animals associates with attenuated anandamide signaling. Interestingly, the subjects with CUD diagnosis and no baseline depressive symptoms were at the follow-up, four times more likely (age-adjusted) to have depressive symptoms than those with no CUD diagnosis (20).

In the past, the chronic use of cannabis of low potency (2–4% Δ9-THC) did not associate with significant neuroanatomic alterations, psychosis, or even depression. However, as the

mean Δ9-THC concentration has increased substantially over the last 10 years, from 8.9 to 17.1% by 2017 (21), the use of cannabis products such as pastes, gummies, and e-vaping devices with still higher concentrations of Δ9-THC, reported as high as 90%, may result in a higher degree of hypodopaminergia, associated poor memory, inattention, and impaired learning performance in chronic cannabis users, especially among adolescents with cannabis use disorder. Thus, the brain changes and symptomatology that signify chronicity depend on potency and duration, frequency of use; smoking cannabis daily multiple times per day.

BALANCING DOPAMINE FUNCTION WITH PRECISION PRO-DOPAMINE REGULATION

The functional neuroimaging techniques, such as resting-state functional magnetic resonance imaging (rsfMRI), have shown that acute exposure to cannabis reduces the neuronal activity in the nucleus accumbens (NAc) and prefrontal cortex (PFC), anterior cingulate gyrus (ACG), striatum, and thalamus. In contrast, chronic cannabis exposure increases the rsfMRI in these brain regions, and in adolescents' chronic use of high Δ9-THC content cannabis results in impaired motivation with depression, anhedonia, low academic achievement, and reduced functional connectivity in the brain reward circuitry (22, 23). The primary neurochemical insult is an altered dopaminergic function across mesolimbic pathways requiring neurotransmitter balance across the brain reward system. Nestor et al. (24) found that in chronic cannabis users (with an average of 6.1 [range = 2.5–17] lifetime years of cannabis use and with the consumption of 7,258-lifetime cannabis joints), there is an increased ventral striatal (VS) blood-oxygen-level-dependent (BOLD) response to stimuli predicted potential non-drug rewards. Importantly, VS hyperactivity is seen during reward anticipation associated with years of cannabis use and the lifetime estimation of numbers of cannabis joints consumed. Another known impairment related to chronic cannabis use relates to compulsive drug use with NMDA receptor-dependent synaptic depression located at the ventral tegmental area (VTA) linked to dopamine circuitry. Chronic cannabis exposure also activates VTA cannabinoid CB1 receptors and reduces transient neurotransmission at VTA local Glu-DA synapses by activating NMDA receptors and subsequent endocytosis of AMPA receptor GluR2 subunits (25).

This evidence provides possible new targets in obviating chronic addiction learning, specifically with chronic cannabis use in humans. Dopamine augmentation is difficult to achieve, especially after the development of a substance use disorder (SUD). Vigorous physical exercise, like Eminem, TMS, and nutraceuticals, have been proposed as viable options. Our proposal herein of incorporating genetic risk allelic testing related to reward pathways along with potential induction of dopamine homeostasis seems logical. This concept takes on even more importance when we consider that the onset and peak use of cannabis occur during brain development in teenagers and, as such, represents an unwanted window of liability (26, 27). The onset of cannabis use begins in the mid-teens and peaks by the age of 25, with the development of cannabis use disorder between 15 and 20. In order to either prevent or treat the high dose Δ9-THC-induced hypodopaminergic anhedonia and cognitive decline, it may be possible to combine the non-invasive testing for the genetic addiction risk score (GARS) with pro-dopamine regulation and restore the dopamine function (26–58). A novel model (**Figure 1**) espouses a reasonable biphasic approach; a short-term blockade followed by long-term dopaminergic upregulation with KB220Z* primarily for reward deficiency syndrome (RDS) behaviors (29–38).

*"*KB220Z Components, The most recent variant of KB220Z (powdered form), is composed of the following ingredients: Vitamin B6, 10 mg (500%); Thiamine, 15 mg (1,033% of Daily Value); and Chromium poly nicotinate, 200 mcg (166%). A fixed-dose of synaptose is included as well, which is a combination of amino acids and herbs that contains DL-Phenylalanine, L-Tyrosine, Passion-Flower Extract; a Complex containing Arabinogalactans, N-Acetylglucosamine, Astragalus, Aloe Vera, Frankincense Resin, White Pine Bark Extract, and Spirulina; Rhodiola; L-Glutamine; 5-Hydroxytryptophan (5-HTP); Thiamine Hydrochloride; Pyroxidal-5-phosphate and Pyridoxine HCl, CoQ10, NADH, and N-Acetyl Cysteine (NAC);* (59). *The powder was manufactured by Cephram, Inc. (New Jersey)".*

However, in chronic cannabis-using adolescents, the goal would be to enhance brain reward functional connectivity [measures the degree of synchrony of the BOLD time-series between different brain regions] and connectivity volume [Voxel-based morphology (VBM)], attenuate depression-like symptoms (anhedonia), and target stress-like anti-reward drug dependence symptoms. Using fMRI of both naïve animals (60) and heroin abstinent subjects (61), we confirmed blood-oxygen-level-dependent (BOLD) activation of dopaminergic reward pathways and recruitment of dopamine neuronal firing with KB220Z. These types of fMRI results provide some evidence for dopaminergic activation.

Millions of individuals worldwide struggle to combat their frustrating and even fatal romance with getting high daily. The neuroscience community conducts and funds incredible research using sophisticated molecular-genetic applied technology in animal experiments and humans using neuroimaging to advance our understanding of brain reward circuitry's complex functions that play a vital role in the expressed symptoms found in addictions. Although dopamine is known as a major neurotransmitter involved in addictions, many disagree about how to deal with dopamine dysregulation clinically to prevent and treat addictive disorders, including cannabis use disorder (CUD). An alternative approach could include two phases; a brief blockade followed by stable dopaminergic upregulation. The treatment goal would be to augment brain reward functional connectivity volume by targeting reward deficiency and the stress-like anti reward symptomatology of addiction. These phenotypes can be characterized using the Genetic Addiction Risk Score (GARS). Dopamine homeostasis may thus be achieved via "Precision Addiction Management" (PAM)®, the customization of neuronutrient supplementation based on the GARS test result, along with a behavioral intervention (29).

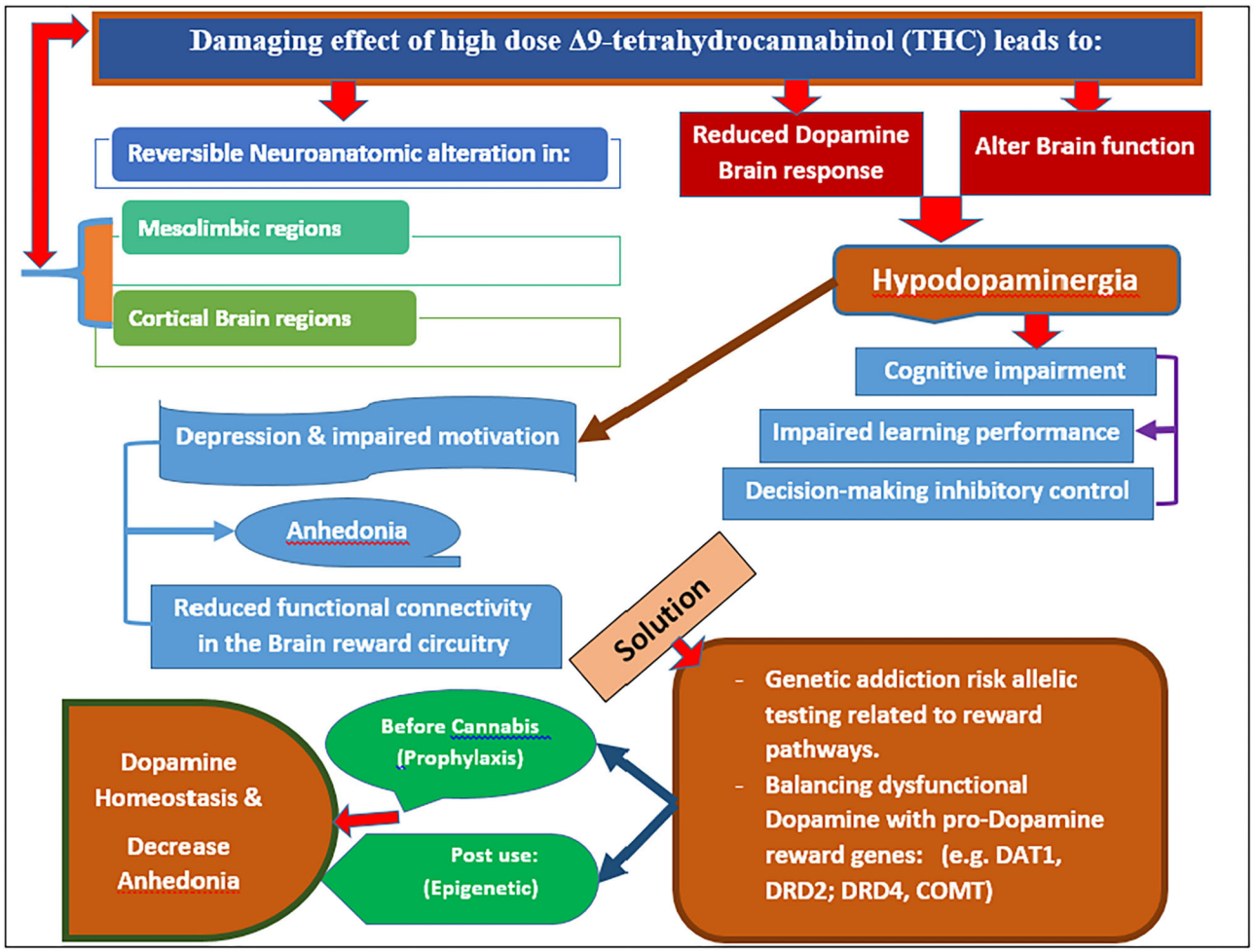

FIGURE 1 | It is a Model proposed for combatting chronic use of potent cannabis and anhedonia (Original figure Blum 2020). Note: Potency of cannabis may be as high as 90% THC in gummies and vaping products.

Dopaminergic homeostasis could be achieved by genetic testing for addiction risk and administering precursor amino acid and enkephalinase inhibitory, non-addictive, natural complex pro-dopamine regulator (KB220), matching to one's neurotransmitter pathways associated reward gene polymorphisms, as previously proposed. Fried et al. (59) reported a case series about the novel treatment of screening with GARS and utilizing a customized pro-dopamine regulator matched to polymorphic reward genes with a hypodopaminergic risk. The proband was a female of 34 years with a history of cannabis abuse and alcoholism. She voluntarily entered treatment after experiencing a car accident while driving under the influence. Following an assessment, she was genotyped using the GARS and given a polymorphic matched neuro-nutrient with a KB220Z base. She successfully recovered from Substance Use Disorder (SUD) and experienced improved socialization, family, economic status, well-being, and attenuation of major depression. She tested urine negative over the first 2 months in treatment and a recent screening. Following ∼2 months into the program, her parents also decided to take the GARS and started taking the recommended variants. The proband's father (a binge drinker) and mother (no SUD) showed improvement in various behaviors. Finally, the proband's biological children were also GARS tested, showing a high risk for SUD. This three-generation case series represents an example of the impact of genetic information coupled with an appropriate DNA guided "Pro-Dopamine Regulator" to recover and enhance life.

Over the many years of the development of the putative pro-dopamine regulator, with the research ID code of KB220Z, there have been a plethora of studies showing remarkable benefits related to reward deficiency behaviors and associated drug and non-drug phenotypes (26, 27, 29, 51, 55, 56, 59, 60, 62–93).

This KB220Z variant has been the subject of at least 43 clinical and pre-clinical studies showing anti-RDS addictive behaviors via dopaminergic mechanisms [see Annotated Bibliography and review by Blum et al. (30)] and **Figure 2**.

Manza et al. (94) suggest that chronic cannabis abuse is associated with resting-state brain function changes, particularly

FIGURE 2 | It is a schematic showing list of RDS benefits of KB220 variants Original figure Blum 2020.

in dopaminergic nuclei implicated in psychosis, habit formation, and reward processing. Is it possible that by utilizing GARS-guided precision, KB220Z could help restore the normal functioning of reward processing and connectivity in cannabis-using subjects, especially in our youth and high-risk populations?

ISSUES OF CANNABIS LEGALIZATION

Even though extensive research shows that chronic use of cannabis is associated with significant adverse health effects (16, 95–97), there is a disturbing trend of many states in the United States (US), and other countries legalize cannabis for unregulated recreational and medicinal use. Colorado was one of the first two U.S. states to legalize cannabis for recreational use for adults 21 and older. There are serious concerns regarding physical and mental health risks, particularly among adolescents who may use cannabis of high THC content. According to Parnes et al. (98), two hypotheses have been studied. First, cannabis use among college students 21 years old and older would increase after recreational legalization. Second, there would be a positive correlation between the new cannabis legislation and out-of-state students' decision to attend a Colorado university as well as their cannabis use after that. However, the opposite was found. Data from a survey of 5,241 undergraduate students showed that cannabis use increased since recreational legalization for all students, particularly for those over 21 years. For past-month use frequency, no differences were found between pre-legalization and post-legalization (98).

Moreover, out-of-state students reported higher past 30-day use than in-state students. Indeed, one real concern relates to the post-legalization opening of retail cannabis stores and adult cannabis use throughout the country. Specifically, Everson et al. (99) evaluated this issue in Washington and found that frequent cannabis use grew significantly between 2009 and 2016 with greater access to cannabis retailers. Frequent use

increased among adults living within 0.8 miles of a retailer. Moreover, Klimer (100) developed a 14-point policy as follows: (1) Production, (2) Profit motive, (3) Power to regulate, (4) Promotion, (5) Prevention and treatment, (6) Policing and enforcement, (7) Penalties, (8) Prior criminal records, (9) Product types, (10) Potency, (11) Purity, (12) Price, (13) Preferences for licenses, and (14) Permanency. A crucial aspect of moving forward in terms of legalization must address the high content of THC in waxes and other products, as well as statewide inconsistencies (101).

On the other hand, the American Society of Addiction Medicine (ASAM) issued a policy statement (102) on marijuana and cannabinoids, recommending *decriminalization* instead of legalization of cannabis and cannabinoids. Furthermore, the legalization of the commercial sale and promotion of cannabis with high THC content for recreational use in many states (Alaska, California, Colorado, Illinois, Maine, Massachusetts, Michigan, Nevada, Oregon, Vermont, and Washington) may lead to significant increases THC intoxication, dependence, and addiction because of the euphoria. Consequently, the neurochemical impact on reward systems in the brain that can lead to neurological reward system deficits may also be significant and of great concern to clinicians.

Thus, until an FDA-approved therapy for treating cannabis use disorder and any of its adverse health components, developing a safe and responsible strategy toward decriminalizing cannabis and cannabis products seems paramount in the United States. As such, consideration of using KB220Z, a dopamine up-regulator discussed above, for restoring balanced neurotransmission and alleviating hypodopaminergia and its consequences like anhedonia (depression), cognitive decline, and other mental health effects due to chronic cannabis use. Similarly, the supplement N-acetylcysteine (NAC) to treat substance use disorders, including CUD, could be useful. In a double-blind, randomized control trial of a cohort of cannabis-dependent adolescents, Gray et al. (103) demonstrated that NAC is an effective treatment for cannabis use disorder, and Tomko et al. (104) revied NAC as a potential treatment for substance use disorders, including cannabis.

CONCLUSION

Although the prevalence of recreational cannabis users at high risk for developing anhedonia and depression is unknown, the amount of cannabis used (dose of THC) seems to be an important factor. Chronic use of high THC content cannabis, either by oral ingestion or vaping, results in reversible neuroanatomic alterations in the mesolimbic and cortical brain regions with subsequent hypodopaminergia and associated depression/anhedonia. Cannabis use among young adults causes these neuroanatomical and psychological changes, magnified by DNA polymorphisms in pro-dopamine reward genes (like DAT1, DRD2, DRD4, COMT). These DNA polymorphisms can be measured either before cannabis use (prophylaxis) or post-use (epigenetic). Treatment should involve the induction of dopamine homeostasis via pro-dopamine regulation and thereby ameliorate anhedonia. No FDA-approved therapies are currently available to treat CUD or any comorbidities, such as depression or cognitive decline (23, 58, 71, 94, 105–112). Using a dopamine up-regulator such as KB220Z to restore brain dopamine in hypodopaminergia until an FDA-approved therapy is available could be considered for chronic cannabis users with CUD. The development of an appropriate policy regarding the legalization of cannabis and cannabis products and decriminalization is needed.

AUTHOR CONTRIBUTIONS

AB developed the schematic. The original manuscript was developed by KB and JK, and all authors commented and equally contributed.

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MINI REVIEW
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A Mini-Review of Relationships Between Cannabis Use and Neural Foundations of Reward Processing, Inhibitory Control and Working Memory

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Cannabis is commonly used, and use may be increasing in the setting of increasing legalization and social acceptance. The scope of the effects of cannabis products, including varieties with higher or lower levels of Δ9-tetrahydrocannabinol (THC) or cannabidiol (CBD), on domains related to addictive behavior deserves attention, particularly as legalization continues. Cannabis use may impact neural underpinnings of cognitive functions linked to propensities to engage in addictive behaviors. Here we consider these neurocognitive processes within the framework of the dual-process model of addictions. In this mini-review, we describe data on the relationships between two main constituents of cannabis (THC and CBD) and neural correlates of reward processing, inhibitory control and working memory.

Keywords: sustance-related disorders, addictive behaviors, cannabis, cannabidiol, cognition, reward, impulsiveness

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INTRODUCTION

Cannabis is widely used. The 2018 Monitoring the Future survey indicated that approximately one-fifth of adolescents had tried cannabis by 12th grade (1), with frequencies of past-month use having increased over several years (2). There has been increasing legalization of cannabis and cannabis-derived products (3), and a commensurate increase in novel ways to consume these products, including edibles, pills and vaping (4–6). Novel routes of consumption have accompanied products with varying amounts of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), including ones that contain only CBD, such as oils or gummies. **Table 1** illustrates several of these products, and it is likely that usage rates and formulations will continue to change as new products are developed.

Increases in legalization and multiple consumption methods have accompanied changes in perceptions, with more individuals perceiving marijuana products as safe and non-addictive (7, 8). However, individuals with heavier use of cannabis and cannabis use disorder (CUD) typically report lower qualities of life (9). Longer-term ramifications of use of different cannabis products, specifically on neural and cognitive processes associated with engagement in addictive behaviors, remain understudied. As increasing legalization looms and use of cannabis products becomes increasingly socially acceptable, understanding potential effects of cannabis use on the brain,

and how alternate methods of use or different cannabinoid products may affect the brain and propensities for addictive engagement, is particularly important.

Recent reviews of cannabis use have focused on epidemiological considerations and how use patterns have changed as legalization continues (10), and the ramifications of cannabis use on multiple domains examined using fMRI (11). Differences between THC and CBD have also been reviewed, with a focus on how acute administration may effect blood flow and neural activation (12). Here, we review data specifically relevant to the dual-process model of addiction on how cannabis may impact domains associated with reward processing and inhibitory control, as well as working memory. Each of these domains has been linked to addictive behaviors (13, 14). We review select preclinical, behavioral and brain imaging research using functional magnetic resonance imaging (fMRI) and additionally consider electroencephalography (EEG), which has not been included in past imaging-centered reviews of effects of cannabis. We also discuss differences between THC and CBD, which have very different effects.

THC AND CBD

Cannabis contains multiple cannabinoids, and the two that have received most research attention are THC (15) and CBD (16). THC is a psychoactive compound, with neurotropic effects including "highs" (17), anxiety (18), and psychosis (19, 20), the risk for which is increased with higher quantities of THC consumed (21). CBD acts as an indirect antagonist of THC's effects (16). CBD binds less tightly than THC to CB1 and CB2 receptors, and, while acute administration of THC often results in anxiety, dysphoria, and increased heart rate, effects of acute administration of CBD and placebo on these measures were indistinguishable, not generating significant changes (22). CBD is a negative allosteric modulator of the CB1 receptor (23), modifying the receptor's affinity for THC and potentially reducing THC's effects (24). Brief explanations for the mechanisms of action for THC and CBD and their binding potential are illustrated in **Table 2**, although it should be mentioned that binding affinities for these substances do not always correspond to their effects on cell action (29). CBD products, such as oils or tinctures, are typically derived from the "hemp" strain of the cannabis plant (Chemovar type III), which contains 0.3% or less THC by weight, while THC products are typically derived from high THC strains (Chemovar type I). There is little evidence of CBD alone having strong abuse liability (30–32). Despite the burgeoning use of cannabis-derived oils, tinctures and edibles in specific forms or with specific formulations focused upon THC or CBD, investigations of specific cannabinoids on domains of working memory, reward processing and inhibitory control are relatively scarce.

INHIBITORY CONTROL, REWARD PROCESSING, WORKING MEMORY AND THE DUAL PROCESS MODEL OF ADDICTION

The dual-process model of addiction suggests that sensitization of reward circuitry is coupled with poorer top-down control of reward systems, resulting in poorly controlled behaviors and drug use (33). Top-down control reflects executive functions, such as inhibitory control and working memory. Poor inhibitory control and working memory coupled with increased reward motivation may reflect imbalances in maturational trajectories of reward-related regions (34), such as the striatum, and regions involved in reward-related impulse regulation, like the prefrontal cortex (PFC), both of which are implicated in addictive disorders (14, 35). Effects on cognition may further increase risk for engagement in addictive behaviors (36), and potential effects of cannabis on these areas of brain functioning may be reflected in the "gateway drug" hypothesis wherein marijuana precedes and predisposes to other illicit drug use (37). How cannabis use may influence domains of reward processing, inhibitory control and cognitive functioning has typically focused on combustible cannabis. Alternative methods of use, including vaping and edibles, have been less well studied. Understanding effects of cannabis use, and additionally the potential effects of chronic use of THC or CBD concentrates, is particularly important given ongoing legalization efforts.

TABLE 1 | Examples of methods of cannabis administration.

	Combustible	Edibles	Vape/dab
Product/method	Smoking joints, pipes	Gummies, capsules, pills, cannabis-infused food and drink	Oils, shatter/butter
THC or CBD content	Chemovar Type I THC >0.3% and CBD <0.5%, THC dominant	Grams of THC range 1.2–5 mg (microdose) to 10 mg (recreational dose with low tolerance)	Oils up to 75% THC, 0.2% CBD (rest is non-THC content such as flavors and pigments)
	Chemovar Type II approximate 1:1 ratio THC/CBD	40–50 mg THC per day (medical grade pain relief) to 100 mg (recreational users with high tolerance)	Shatter/butter up to 80–90% THC
	Chemovar Type III <0.3% THC, CBD-Dominant	Products also include CBD only with essentially no THC (derived from Chemovar type III)	CBD oils and CBD shatter (derived from Chemovar Type III)

CANNABIS AND WORKING MEMORY

Early investigations of cognition, particularly working memory, have indicated that acute cannabis use is associated with impairments in holding, manipulating and remembering information (38–40), with impairments typically remaining after other acute effects have subsided. Memory deficits are apparent in cannabis-using college students after 24 h of abstinence (41) and with heavy use (42), and these deficits are associated with duration of use (43, 44). Imaging has revealed altered activation during working memory tasks in regions such as the anterior cingulate and the thalamus even after sustained abstinence, both in adults (45, 46) and adolescents (47). However, some data suggest that working memory impairments may precede cannabis use. In a 3-year examination of individuals with heavy cannabis use, no changes in working-memory-related brain activations (in the bilateral frontal poles and ventrolateral prefrontal, dorsolateral prefrontal, premotor, paracingulate, and inferior parietal cortices) were observed over time (48). Activation during an N-Back working memory task did not differ between individuals with and without cannabis use; however, greater activation statistically predicted escalation of cannabis use (49). While the weight of the literature points to working-memory impairments associated with cannabis use, preexisting vulnerabilities in working memory may exist and contribute to heavy use.

THC AND CBD AND WORKING MEMORY

THC has been proposed to be the primary culprit in working-memory impairment associated with cannabis use. This has been demonstrated in animal models, where exposure to THC during adolescence resulted in learning impairments (50) that persisted into adulthood (51, 52). Acute examinations of THC in humans also suggest robust effects on memory. In a study where several memory tasks were administered to adults who were given acute oral THC, THC produced increased error rates alongside faster performance (53). Similarly, acute THC administration in healthy adults impaired performance on the Wisconsin Card Sorting Task (54). However, in both studies, performance returned to normal once effects of THC had subsided. Other work has examined neural correlates of attention and working memory in individuals given intravenous THC, where it was found that the P300 amplitude, related to responses to novel stimuli, was reduced and the level of reduction correlated with subjective reports of altered perceptions (55).

In contrast, CBD may enhance cognition, particularly in cannabis-using populations (56), schizophrenia (57–59) and neurodegenerative diseases (60, 61). CBD may reduce cognitive decrements seen in people who smoke cannabis (24). An animal study demonstrated that CBD improved memory among cognitively impaired rats (62). However, no effects were seen in rats who were not impaired. In humans, effects of acute use of vaped CBD and THC on attention or simulated driving may not differ between substances (63). Further, among abstinent individuals who smoke tobacco, acute CBD administration impaired working memory and increased errors of commission during N-back task performance (64). While evidence suggests that CBD may have promise for alleviating cognitive impairment in cannabis-using or clinical samples (16, 65), more research is needed on how it may influence working memory in other populations.

TABLE 2 | Cannabis pharmacology—THC and CBD.

THC pharmacology	CBD pharmacology
Partial agonist of CB1 receptors, 5HT3 receptors in CNS -> inhibition of the release of acetylcholine and glutamate -> influencing y-aminobutyric acid, N-methyl-D-aspartate, opioid and serotonin receptors.	Lowers agonist efficacy of THC by modulating CB1 receptors, binds to distinct site on CB1 receptor
Ki values 5 (25) to 50 (26)	Ki values 4,300 (27) to 4,700 (28)

Ki values: measure of receptor affinity (high ki value = low affinity).

CANNABIS AND INHIBITORY CONTROL

Response inhibition and behavioral control, including over drug-seeking, is important in addictive disorders (66). Impairments in inhibitory control may promote risky or disadvantageous decision-making in people who use cannabis (67). Poor inhibitory control during a Go/No-Go task and disadvantageous decision-making during a gambling task have been observed in cannabis-using young adults (68), consistent with findings among general adults (69). Differences in neural correlates of inhibitory control associated with cannabis use do not appear entirely consistent. Regions associated with inhibitory control show altered activation in people who use cannabis, with lower prefrontal activation as measured by fMRI, consistent with findings in alcohol and stimulant use disorders (14). During a Go/No-Go task in cannabis-using vs. non-cannabis-using adults, the former vs. latter group showed no differences in commission errors, but showed reduced error monitoring that was associated with reduction in activation of the anterior cingulate and right insula (70). Functional imaging during a Stop-Signal Task also revealed no differences in an inhibitory network activation between cannabis-using vs. non-cannabis-using individuals, but revealed that the former group had greater connectivity between a right frontal control network and substantia nigra/subthalamic nucleus network when functional connectivity was examined (71). In a study employing a Go/No-Go task in adolescents who were abstinent for two weeks, greater BOLD responses were observed in the left frontal cortex, left cingulate cortex, and the left thalamus during correct response inhibitions in those who used cannabis, though this may reflect greater inhibitory effort required to remain abstinent (72). EEG has revealed inhibition differences associated with cannabis use, with a reduction in the No-Go-related P3 component (a component associated with inhibitory control) of the event-related potential (ERP) when compared to non-drug-using or tobacco-using groups (73). Acute administration of cannabis before a Go/No-Go task also revealed a reduction in the No-Go P3 (74). While alterations

in inhibitory control and its neural correlates appear linked to cannabis use, future work should continue examining this domain to specify precise relationships.

THC AND CBD AND INHIBITORY CONTROL

An animal model that investigated impulsivity using the 5-choice serial-reaction-time test demonstrated that THC exposure resulted in increased motor impulsivity in rats that persisted after exposure ceased (75). An investigation of acute THC in humans revealed reduced activations in left inferior frontal regions that were associated with increased inhibition errors, impaired inhibition efficiency and transient psychotic symptoms (76). Acute effects of THC were also seen on an ERP associated with inhibition, the P300, and this reduction in P300 amplitude was not reversed by CBD (77). Further, an imaging study that investigated response inhibition after acute administration of either CBD or THC to healthy subjects revealed that while there were no performance differences between conditions, THC attenuated activation in the right inferior frontal and anterior cingulate gyri, regions associated with response inhibition. In contrast, CBD administration was associated with deactivation of the left temporal cortex and insula, demonstrating that CBD effects different regions, ones less typically associated with inhibition (78). Among people using CBD for treatment-resistant epilepsy, CBD altered connectivity patterns during an attentional-control task (79). It is possible that heterogeneity in findings outlined above may relate to types of cannabis used and differing effects of THC and CBD. One study has examined this, examining functional connectivity of executive, salience, and default-mode networks during resting state (80). Individuals were given cannabis containing THC (no CBD), cannabis containing THC with CBD and placebo. Reductions in functional connectivity were seen across networks for both cannabis types, and within the salience network, cannabis with THC and no CBD reduced connectivity relative to cannabis with CBD. Further, posterior cingulate connectivity was specifically impacted by cannabis with THC and no CBD, and this effect correlated with subjective "high" sensations. This study highlights that specific chemovars of cannabis, or use of different products containing CBD, THC or both, may result in different effects on inhibitory control and cognition.

CANNABIS AND REWARD PROCESSING

Deficits in motivation and reward sensitivity may be pronounced with cannabis use, with several survey-based examinations linking self-reported lack of motivation and cannabis use (81). Blunted reward responses independent of alcohol or nicotine use have been observed with cannabis use, with greater blunting associated with more severe use (82, 83). Among cannabis-using relative to non-using subjects, reduced activation in the nucleus accumbens, caudate, left putamen, right inferior and medial frontal gyrus, superior frontal gyrus, and left cingulate was observed during monetary reward anticipation, with greater activation in the putamen observed during reward outcome (84). Another study in cannabis-using adults employing the monetary incentive delay task found that those with cannabis use showed reduced activation in the left caudate and inferior frontal gyrus during rewarding feedback, and increased activation in the left caudate and bilateral inferior frontal gyrus when successfully avoiding losing money (85). In a separate study, greater ventral striatal activation was observed during losing outcomes in men with vs. without CUD (86). Relatively increased activation to rewarding outcomes was seen in the ventral striatum during reward anticipation in an independent group of cannabis-using subjects, and this activation was positively correlated with lifetime cannabis use amounts and durations (87). Cannabis-using vs. non-using individuals showed greater activation during gain trials in orbitofrontal cortex and cingulate gyrus and less activation in loss trials in orbitofrontal cortex, suggesting greater sensitivity to reward and reduced sensitivity to loss (88). However, adolescents who used cannabis only did not differ from adolescents who used tobacco only, alcohol only, cannabis+tobacco, cannabis+tobacco+alcohol, and no drugs in nucleus accumbens activation during anticipation of monetary reward or loss (89). More research is required to understand reward processing in relation to cannabis use, particularly given that cannabis and tobacco use often co-occur.

THC AND CBD AND REWARD PROCESSING

Acute THC administration has been associated with blunted ventral striatal activation during reward processing (90). THC is not readily self-administered, with rat models demonstrating aversiveness (91), though adolescent rats who consume THC show impairments in predicting rewards when reaching adulthood (92). THC's effects on reward processing may underlie reward-related findings seen in individuals who smoke cannabis. CBD, however, has shown different relationships. CBD does not appear associated with addictive behaviors, and rather it may alleviate craving (93), reduce relapse potential (94), and decrease addiction severity for substance-use disorders (56), thereby reducing reinforcing effects of substances. Consistently, CBD administration to rats has resulted in less self-administration of cocaine (95) or methamphetamine (96). In humans, however, CBD administered via capsules did not change reinforcing subjective effects of smoked cannabis (97). CBD administered acutely before participants performed a monetary incentive delay task showed no differences in neural activations between CBD and placebo for either reward anticipation or reward receipt (98). Data on CBD and reward processing is thus somewhat inconsistent regarding whether or not it impacts THC's or other substance's effects on reward processing. Research on CBD's effects on reward processing is relatively scarce, especially with respect to longer-term effects on reward systems.

CONCLUSIONS

Simultaneous reduction in top-down control, including poorer inhibition and working memory, and blunted responsivity to non-drug rewards in people who use cannabis could set the

stage for poorly controlled drug-seeking, consistent with dual-process models of addiction. In addition, reward deficiency models suggest that blunted responses to non-drug rewards contribute to sensation-seeking and impulsivity, and, ultimately, to addictive behaviors (99). Similar processes may underlie cannabis- and other substance-use disorders (100). Altered reward responding may contribute to sensation-seeking while poorer inhibitory control may worsen tendencies to resist drug-seeking urges. Additionally, impaired working memory may contribute to disadvantageous decision-making, and thus increased tendencies to use cannabis. Chronic cannabis use, especially of strains/varieties high in THC, is associated with alterations in brain activation and behavior related to reward processing, working memory, and inhibitory control. It's effects on these neural correlates may provide a mechanistic explanation for why cannabis use, specifically of high-THC varieties, may lead to CUD and poorer quality of life (9). However, the potential impact of CBD on these domains appears subtle or non-existent, although more work on the effects of chronic CBD use is needed.

FUTURE DIRECTIONS AND ADDITIONAL CONSIDERATIONS

One aspect of cognition that may be specifically relevant to individuals with CUD and may supplement the dual-process model of addiction is emotional regulation. Negative affect is associated with craving for cannabis (101), and stress induced by lab-based social tasks has elicited craving for cannabis in people with CUD (102), particularly among people with low distress tolerance (103). Many individuals report using to alleviate distress (104), and edible CBD consumption may reduce social anxiety (105). Unfortunately, imaging studies of emotional regulation in CUD are scarce, and one group has identified decreased activation in bilateral frontal regions, including precentral and middle cingulate regions, during emotional reappraisal of negative affect in individuals with vs. without cannabis use (106, 107). Future work that investigates characteristics associated with cannabis use should also focus on regulation of emotion and how THC or CBD may influence affect.

Future research should focus on how types of cannabis administration, and use of different cannabinoids, may impact cognition, reward processing and inhibitory control. Vaping of cannabis flower or cannabis concentrates (e.g., THC) may release of higher concentrations of psychoactive ingredients (108, 109). Similarly, edibles derived from concentrates may generate slower onsets of effects (110) that may lead to greater ingestion of psychoactive ingredients that may generate long-lasting effects than combustible use (4). Surveys of adolescents have identified different experiences among those who primarily smoke, vape, or consume edibles, with edible varieties described as most potent (111). Thus, investigating impacts of edibles and vaping on neural processes linked to addictive behaviors is important. Studying vaping may be particularly relevant as it has been associated with deadly illness related to use of THC oils and vitamin E acetate (112). Additionally, more study on the effects of CBD alone and in combination with THC is warranted, especially as legalization of cannabis becomes more widespread.

AUTHOR CONTRIBUTIONS

KPM wrote the first draft of the paper and worked with the co-author on subsequent drafts. Both authors contributed to the editorial process and have approved the final submitted version of the manuscript.

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Down and High: Reflections Regarding Depression and Cannabis

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In light of the recent changes in the legal status of cannabis in Canada, the understanding of the potential impact of the use of cannabis by individuals suffering from depression is increasingly considered as being important. It is fundamental that we look into the existing literature to examine the influence of cannabis on psychiatric conditions, including mood disorders. In this article, we will explore the relationship that exists between depression and cannabis. We will examine the impact of cannabis on the onset and course of depression, and its treatment. We have undertaken a wide-ranging review of the literature in order to address these questions. The evidence from longitudinal studies suggest that there is a bidirectional relationship between cannabis use and depression, such that cannabis use increases the risk for depression and vice-versa. This risk is possibly higher in heavy users having initiated their consumption in early adolescence. Clinical evidence also suggests that cannabis use is associated with a worse prognosis in individuals with major depressive disorder. The link with suicide remains controversial. Moreover, there is insufficient data to determine the impact of cannabis use on cognition in individuals with major depression disorder. Preliminary evidence suggesting that the endogenous cannabinoid system is involved in the pathophysiology of depression. This will need to be confirmed in future positron emission tomography studies. Randomized controlled trials are needed to investigate the potential efficacy of motivational interviewing and/or cognitive behavioral therapy for the treatment of cannabis use disorder in individuals with major depressive major disorder. Finally, although there is preclinical evidence suggesting that cannabidiol has antidepressant properties, randomized controlled trials will need to properly investigate this possibility in humans.

Keywords: cannabis, depression, legalization, impact, epidemiology, mechanisms of action

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INTRODUCTION

Depression is a leading cause of disability in the world (1, 2) with a lifetime prevalence in the general population of about 15% (3). As such, any factor that modifies the course or presentation of depression has a disproportionate impact on disability and individual burden of illness.

Cannabis is a widely used substance with pleotropic effects and has been proposed both as a treatment for and as a cause of depression. Cannabis is composed of 60–500 different compounds including a class of chemicals called cannabinoids (4–6); of these, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most examined. THC is considered to be the main

psychoactive component of cannabis (4), while CBD is purported to contribute to many of its therapeutic benefits (3).

The balance of harmful and therapeutic effects of CU in depression has not yet been clarified (7).

This review aims to synthesize the literature pertaining to the relationship between depression and cannabis use (CU). Particular attention to the potential mechanisms involved in this association will be considered.

PREVALENCE OF CANNABIS USE

Cannabis is one of the most used substances worldwide (8). After alcohol and tobacco, cannabis ranks first for used substances in the United States (US) (9, 10) and Canada (11). Three to five percent of the world's population have used cannabis at least once (12, 13). Approximately 8 million Americans use cannabis every day or nearly every day (14).

CU is widespread among younger individuals with 7.6 million users in the 18–25 age group and 1.6 million in the 12–18 group in the US in 2017–2018 (15). A 2017 Canadian survey showed that the prevalence of past year cannabis use was higher in adolescents (19%) and in young adults under 25 years old (33%) than in adults over 25 (13%) (11). In the US, 60 percent of those who use cannabis for the first time are under 18 (16). In fact, in adolescents, the prevalence of CU has surpassed that of cigarette smoking (16).

The definitions of substance use disorders differ across systems of diagnostic classification (17). DSM-IV requires 3 or more of 7 criteria which include the presence of withdrawal, tolerance, use of larger amounts or over a longer time, repeated attempts to quit or control use, much time spent using, physical or psychological problems related to use and activities given up to use (17). DSM-5 requires only 2 of the 7 criteria for dependence or the DSM-IV criteria of abuse which include hazardous use, social or interpersonal problems related to use and neglected major roles in order to use (17). In DSM-IV, substance abuse included the criterion of legal problems as a consequence of use; this was eliminated in DSM-5 (17). The differing definitions relating to CU may contribute to variable results found in the literature.

The risk of developing dependence is about 9% and rises to 16% if CU is initiated in adolescence (18). Preliminary evidence suggests that the addiction potential of cannabis may depend on its THC content (19). The THC content of cannabis has increased from historic levels of 3–5% to the current levels of 25% (4, 5), potentially increasing the risk of addiction.

The prevalence of CU has increased with a prevalence in the US of 4.1% between 2001–2002 and 2012–2013 and 9.5% respectively (20). Over the same period, cannabis use disorder (CUD) prevalence in the US went up rose from 1.5 to 2.9% (21, 22).

CONTEXT AND IMPACT OF LEGALIZATION

In the US, Colorado and Washington were the first states to make recreational use and sale of cannabis legal in the United States in 2014, although medical marijuana had already been legalized in Colorado since 2000 (23). Following legislation for recreational use, past-year CU in people 18 and older increased from 15% (2008–2009) to 24% (2015–2016) (24). Intriguingly, the impact of legalization on adolescent CU is less clear with some jurisdictions showing increased and others decreased use (12). Thus, factors other than legalization may also play a role in the change of prevalence of CU after its legalization. Canada legalized recreational cannabis in October 2018 (12, 25). In the year following legalization in Canada, increases of CU were noted with over a half million first time users, the most substantial increase being in men aged 45–64 years (25). One year on, a survey conducted by Statistics Canada documented an increase in past 3 month use from 14.9 to 16.8% (26) but decrements in adolescents aged 15–17. The same survey found that reported daily use increased only in those 65 and older.

The frequent use of cannabis is associated with a plethora of negative health and social consequences (14, 22). Where this issue has been studied, an increase in related consequences has occurred concurrently with an increase in CU in the states that have legalized medical cannabis (14). These negative consequences include increases in the prevalence of serious mental illness (14) and emergency department consultations for cannabis-related mood disorders, as well as suicide and intentional self-harm (12, 27, 28). It is important to underline that potentially positive effects of CU, such as decreased anxiety, have not been systematically studied (28). As legalization becomes more widespread, it becomes pressing to evaluate the consequences of the subsequent increased consumption in vulnerable populations such as those suffering from mood disorders (7).

POTENTIAL MECHANISMS UNDERLYING THE RELATIONSHIP BETWEEN CANNABIS AND DEPRESSION

The endogenous cannabinoid (or endocannabinoids) system (ECS) (29) is involved in regulating functions such as mood, cognition, feeding behavior, pain perception, inflammation, and stress responses (8, 30). Furthermore, there is evidence that a hypoactive ECS may contribute to depression in humans (6).

The activity of the ECS is mediated by at least two cannabinoid receptors (CB1 and 2) and endogenous cannabinoids [2-arachidonoylglycerol (2AG) and anandamide] (31). THC is a partial agonist of CB1 and CB2, although its psychoactive effects derive from its activity on CB1 receptors (6). The CB1 receptor is widely expressed in regions which are involved in reward and cognitive functions (30). The CB1 receptor modulates the GABAergic, glutamatergic, serotoninergic and noradrenergic systems (5, 6, 8) and promotes myelination (32).

The ECS is further involved in the modulation of the hypothalamic pituitary axis (HPA) and brain derived neurotrophic factor (BDNF) (6, 33). The ECS also modulates inflammation: CB1 activation decreases inflammation through astrocytes, and CB2 through microglia (34). Importantly,

these systems are also involved in the pathophysiology of depression (35–37).

There role of the ECS in the pathophysiology of depression is supported by several lines of evidence. For instance, CB1/CB2 receptor gene polymorphisms are associated with the behavioral characteristics typical of depression (38, 39). In rodents, CB1 receptor deficiency provides a model for depression and genetic modifications reducing its expression are associated with depressive behaviors and vulnerability to stress or social defeat (40). *In vivo* electrophysiological studies in rats have shown that acute or chronic low-dose stimulation by a full or partial agonist of the CB1 receptor produces an activation of the serotonin (5-HT) neurons in the dorsal raphe nucleus and increases their firing rate. On the other hand, sub-chronic or long-term high-dose stimulation by a CB1 receptor agonist causes an important decrease in the firing rates of the 5-HT cells of the dorsal raphe nucleus (41). Increases in firing rates of these neurons are seen with the administration of antidepressants and are considered to be an essential mechanism of action underpinning their therapeutic effects (42).

In animal models, the effect of low-doses of CB1 receptors agonists on the firing rate of 5-HT cells of the dorsal raphe nucleus is associated with antidepressant and anxiolytic effects, in contrast with high-doses which are associated with depressant effects (43). Lower doses of cannabinoids have antidepressant and anxiolytic effects while higher doses have the opposite effect (4). The effect of THC on dopamine release follows a similar biphasic pattern with low doses enhancing dopamine synthesis and high doses decreasing it (44). The dopaminergic system has been implicated in the pathophysiology of depression and in particular anhedonia (45) and it is possible to speculate that recreational use of low dose cannabis may generate mild euphoria while high dose cannabis may lead to anhedonia. In humans, the cerebrospinal fluid of individuals with depression is characterized by a reduction of endocannabinoid precursor levels (38).

CU leads to widespread alterations in cerebral function (46). In a meta-analysis examining the residual effects of CU on cognitive function following abstinence, functional imaging in cannabis users reveals decreased activations in the anterior cingulate cortex and dorsolateral prefrontal cortex (46). These changes were correlated with cognitive deficits (46). These same regions are involved in the pathophysiology of depression and are targeted by neuromodulation treatments of depression (47).

Partial agonism at the CB1 receptor is considered to mediate, at least in part, the behavioral and abuse potential of cannabis (48, 49). In humans, activation of CB1 receptors may lead to a reduction of l-DOPA induced dyskinesia (48), adding to the evidence that this receptor modulates the dopaminergic system. Clinical use of medications that target the CB1 receptor has led to the symptomatic relief of nausea, vomiting, loss of appetite and muscular spasticity, and there is interest in their potential anxiolytic and antidepressant effects (50). In humans, antagonism of the CB1 receptor can precipitate the onset of depression and suicidal ideation (38). Indeed, in trials using the CB1 receptor antagonist rimonabant to treat excess weight, symptoms of anxiety and depression were more frequent in the experimental than the placebo group (43). Rimonabant and a similar agent, Taranabant (43), were removed from the market due to the emergence of depression and suicidal ideation (38).

The cumulative weight of the evidence is that the ECS and cannabinoids play a role in the pathophysiology of depression and have a potential role in its treatment.

RELATIONSHIP BETWEEN CANNABIS AND DEPRESSION: PREVALENCE DATA

The prevalence of depressive disorders is high in cannabis users (25%). Risk factors include female gender and earlier age of onset of use (51). The prevalence of major depressive disorder (MDD) in those with cannabis dependence (CD), CUD, and cannabis abuse (CA) is ∼6.9, 4.7, and 1.0%, respectively (52). This highlights the importance of exploring the relationship between recreational, medical and heavy cannabis use (including CUD) and depression (53). Further, a meta-analysis published in 2021 found that the odds ratio (OR) for MDD comorbidity varied with the type of CU. The odds ratio was 4.83 for MDD-CD comorbidity, 2.60 for MDD-CUD comorbidity and 2.37 for MDD-CA comorbidity (52). An older 2014 meta-analysis of longitudinal studies found an OR of 1.17 for developing depression in cannabis users compared to controls. The same meta-analysis calculated an OR of 1.62 of developing depression in heavy cannabis users compared to non-users/light users (54). Another meta-analysis of longitudinal and case-control studies found that compared to non-regular use, regular use was associated with 1.5-fold odds of developing a MDE (29). Finally, a third meta-analysis found a unidirectional risk (OR = 1.33) of developing depression in adolescent and young cannabis users (55). In contrast, a study by Turna et al. found no difference between low (<1 g/day) and moderate users (1–2 g/day) (56). This observation may indicate a non-linear relationship between the degree of cannabis exposure and the risk of developing MDD; thus, low or possibly moderate use confers little risk of developing MDD, while heavy use is likely to lead to the emergence of depression. A recent systematic review of the impact of cannabis on the onset of mood disorders concluded that CU was associated with an increased risk of later depression (57). The same correlation was also observed in studies which focused on adolescents (57). Further, in a meta-analysis of longitudinal studies published in 2019, CU in adolescence was associated with a higher likelihood of developing depression in young adulthood (OR = 1.37) (58). Some studies show that the impact of CU may be greater in women who seem to be at higher risk of subsequently developing depression (59, 60). Early and frequent CU was associated with MDD in a large twin study (61). The duration of CUD is also associated with the emergence of comorbid mood disorders, including MDD (62), adding to the evidence that the degree of exposure to cannabis is related to depression. The frequent absence of linkage between infrequent or low dose CU and the emergence of depression is compatible with preclinical data showing opposing effects on neurogenesis of baseline tonic and more intense stimulation of the ECS (33). It is thus likely that the effects of CU reflect these differential effects. Low doses have anxiolytic and antidepressant properties,

while high doses are associated with anxiety and depressive symptoms (63).

While these results may be interpreted as indicating that cannabis "causes" depression, there are also data suggesting alternative interpretations, namely that the causal relationship may involve an increased likelihood of CU in individuals with depression. The high rates of lifetime CUD in the population of individuals with MDD (39%) is much higher than in the general population (64). Indeed, depression seems to be a major risk factor for developing symptoms of CUD (65). An epidemiological study in the US described odds for lifetime CUD that were 3.9 times higher for people with mood disorders (including MDD) (65, 66). Similarly, a Canadian study found the 12-month prevalence of CD to be 7-fold higher in those with MDD, while cannabis abuse was 3.5-fold higher (66). In a meta-analysis of the prevalence of comorbid substance use in people suffering from MDD, the point prevalence of CUD was 0.117 (27). In addition, in a community-based study, a one standard deviation increase in depression in adolescence was associated with a 50% increased likelihood of CUD (67, 68).

EFFECT OF CANNABIS ON THE AGE OF ONSET OF DEPRESSION

Evidence regarding the effect of cannabis on the age of onset of depression is inconsistent. A population based longitudinal study published in 2017 reported that the onset of depression occurred at a younger age in the non-cannabis using population than in those who used cannabis (64). However, another literature review found that an earlier onset of CU was associated with a shorter time to the emergence of MDD (7). In other studies, this association was no longer significant after controlling for a variety of psychosocial factors (education, alcohol and other illicit drug use and childhood upbringing) (7, 12, 69). The frequency or dose of CU may influence the age of onset of depression. Systematic reviews conducted in 2017 and 2020 found that higher levels of CU were correlated to an earlier onset of depression (18, 57). Several other studies observed this same correlation between heavier CU and early onset of depression (7, 51, 59, 66, 70).

Overall, studies support a bidirectional relationship between depression and CU. In other words, studies support the view that CU is a risk factor for developing depression (52, 54, 57, 58, 71). Moreover, heavier CU is associated with a greater risk of developing depression (29). Inversely, the data also reveals that depression itself is a major risk factor for CU (64, 65). Individuals with depression are also at greater risk of developing CUD (65, 66). A study using a twin-model approach added further evidence of this bidirectional relationship showing an OR for the incidence of MDD in individuals with preceding CUD was 2.54 whereas the OR for the incidence of CUD in those with pre-existing depression was 2.28 (66). Although both no association (16, 18) and reverse directionality (18, 55) have been observed in some studies, this same twin-model study concluded that the model best fitting the data is that of CUD leading to MDD (66). Definitive conclusions regarding the relationship of depression and CU are premature at this stage and data suggest that other factors such as sex, genetic predisposition, personality disorder and psychosocial circumstances may underpin the relationship between CU and depression (6, 51, 59, 72–74).

INFLUENCE OF CANNABIS ON THE COURSE AND CLINICAL PRESENTATION OF DEPRESSION

In the general population, cannabis use is associated with psychomotor retardation and emotional withdrawal (18, 30), particularly at higher doses. Anxiety, cognitive impairment and addiction to cannabis have also been observed as possible adverse effects of CU (30, 75), although not in all studies (76). CU is associated with poor sleep quality, although this effect may be mediated by concomitant depressive symptoms (77).

Anhedonia is a prominent symptom of depression and engages a broad network of neuronal circuits (78). Cannabis produces a widespread reduction of brain activity, as well as more specific reductions in the ventral striatum (nucleus accumbens) and orbitofrontal cortex in response to reward (6, 79). Liu et al. described a similar alteration in the function of the nucleus accumbens in patients with MDD (80). CU as a contributor to anhedonia has been proposed as a path whereby CU may contribute to depression (5, 78). Several studies have reported apathy and anhedonia in cannabis users (81–83), while others failed to detect this phenomenon (84–86). Decreased cerebral activation in response to reward is reduced in cannabis users, and more so in those with recent heavy CU (87). Although CU may contribute to anhedonia, additional data indicate that anhedonia in adolescence may predispose to CU (88). Since apathy and anhedonia are also seen in depression, one can theorize that the effects of CU may overlap with the symptoms of depression, leading to their exacerbation or potentially confounding the diagnosis of MDD. Although anhedonia can be seen as the result of cannabis-induced inflammation (34), a recent review concludes that the ultimate effect of cannabis is anti-inflammatory (89). Decreased dopamine activity, as seen with chronic CU (44), has also been proposed to be a cause of anhedonia in depression. Since low doses of cannabis enhance dopamine synthesis, anhedonia would not be manifested among those who restrict their CU to modest concentrations (44). Exploration of the interaction of CU and anhedonia in individuals with depression may help to elucidate this interaction.

In individuals with MDD, CU and CUD are associated with having more symptoms than in individuals with MDD who do not use cannabis. These symptoms include anhedonia, changes in weight and sleep, as well as psychomotor changes (1, 64). Another longitudinal study found that CU worsened the symptoms of depression and anxiety, and was associated with poorer mental health and functioning (71).

CU seems to have prognostic implications. Evidence from a population-based longitudinal study in individuals with baseline depressive disorder and varying levels of cannabis usage showed that there was a significant association between the level of CU and the persistence of depressive symptoms at follow-up.

However, remission of MDD was not significantly different between those with CU, CUD, or no use (64). A large prospective cohort study showed an association of cannabis use with more depressive symptoms at a 3-year follow-up. Again, no correlation was found regarding the rates of remission, nor was any correlation found with functional impairment (57). CUD in the 6 month period prior to treatment is associated with an increased risk of treatment resistance in depression (3). Overall, the available data points, albeit inconsistently, in the direction of an association of CU and CUD with poorer outcomes in individuals with depression.

Results from different studies are inconsistent with regards to the suicidal risk associated with cannabis in individuals with MDD. In one study, the OR associated with suicidal ideation in people from the general population using cannabis compared to non-users was 1.50 (58). A Canadian populational study found that those who used cannabis at least once a month had a 1.55-fold OR of reporting suicidal ideation in 2012 compared to 2002 (53). In an analysis of the same data, an association between CU and suicidal ideation and attempts was apparent for women but not for men (29). Gobbi et al. noted an increased risk of suicidal attempts in cannabis users compared to non-users with an OR of 3.46 (58). A twin study involving 13,986 individuals found CU to be associated with MDD, suicidal ideation, suicidal plan and attempt (61). Several reviews conclude that CU in adolescence is a harbinger of later, variously defined, suicidal tendencies (6, 51, 61, 72). In contrast to the data pertaining to suicidal ideation, Naji et al. did not find an association between CU in individuals with mood disorders (bipolar disorder and depression) and suicide attempts (90), nor Ostergaard et al. between CUD and suicide attempts or completed suicide (91). Two reviews (18, 57) and a populational study (64) failed to document significant changes in suicidal ideation or behavior in people with MDD after adjusting for confounding factors. Finally, a study by Hesse et al. found that compared to the general population, suicide was actually less frequent in individuals with CUD who received treatments in centers for substance use disorders (HR = 0.69) (92). In all, the preponderance of evidence suggests that cannabis use is not associated with suicidal ideation, suicide attempts or completed suicide in MDD.

EFFECTS OF CESSATION OF CANNABIS USE

Cannabis withdrawal can occur amongst regular or heavy users at cessation. The reasons that motivate CU may vary (4). Using cannabis recreationally positively reinforces use. However, negative reinforcement also drives CU in order to avoid the withdrawal symptoms which emerge following the reduction or cessation of CU (4). Symptoms associated with stopping regular cannabis consumption include depressed mood, anxiety and sleep problems, among others (93). These symptoms may be mistaken for an exacerbation of depression. On the other hand, some studies show that a reduction in CU and cannabis abstinence are associated with improvements in anxiety, depression and functioning in individuals with problematic CU (14, 94). As such, these observations are consistent with the idea that mood symptoms may be secondary (not antecedent) to CU. A randomized controlled trial studying young female adults with depression found that reducing the consumption of cannabis improved mood (3).

At the neurobiological level, CB1 receptor density in the frontolimbic system has been shown to be lower in people consuming cannabis regularly. Those alterations with daily CU are reversed following a month of abstinence (8, 95). This implies that it is necessary to maintain cannabis cessation for at least a month before evaluating its impact on clinical symptoms. Eisen et al. evaluated 56 twin pair members who had either used cannabis (average of 1,085 days) or had not used cannabis (average of 5 days) (96). There were no significant differences in mental health symptoms between the two groups 20 years after their last use (96), suggesting a lack of long-lasting residual effects.

INFLUENCE OF CANNABIS ON COGNITION

The impacts of cannabis on cognition in the general population are more fully described in another article in this issue. By comparison, there is a dearth of knowledge regarding the effect of CU on cognition in depression. Cognitive complaints feature among the commonly reported side effects of CU (31). Briefly, in the general population, acute effects of cannabis on cognition include moderate deficits in working memory, verbal learning, and smaller impairments in attention and speed of processing (5). These findings are in line with findings of cannabis-associated altered cerebral function. For example, Lorenzetti et al. found abnormal activity in the frontal-parietal network of adolescent cannabis users (97). Of 13 studies, 10 found differences between cannabis users and controls. The most consistent regions affected were the inferior parietal and the anterior cingulate cortex. Although this review found changes in brain activity in chronic users of cannabis, attributions are complicated by comorbidities, a lack of information regarding the degree of use of cannabis and the varying tasks used during functional imaging. Nevertheless, the implication of the anterior cingulate cortex and the hippocampus highlights commonalities with depression.

Cannabis use is also associated with residual impairment in cognitive performance in healthy individuals (12, 18), in particular memory deficits, and verbal memory (98, 99). Schreiner and Dunn confirmed a small but significant negative effect of CU on cognitive function. However, when the analysis was limited to those studies that required at least 1 month of abstinence, no decrement in cognitive function was detected (95). The amplitude of cannabis-induced cognitive alterations may vary according to dose and age of onset. Acute and chronic CU has an impact on cerebral function and CU, particularly in adolescence, leads to changes in brain structure (41). Likewise, in the large, longitudinal studies performed thus far, deficits in attention, speed of processing and verbal memory have been observed, most particularly in the case of chronic, persistent,

cannabis use initiated during adolescence (100). Heavy use of cannabis in adolescents has been shown to produce decrements in attention, learning and processing speed which resolve within 3 months after cessation (101). Preclinical research shows that the administration of THC to adolescent mice generates changes in 5-HT6 (a serotonin receptor) by activating a signaling system, known as the mechanistic Target of Rapamycin (mTOR). This exposure is associated with cognitive deficits in adulthood (102). This same pathway has also been implicated in depression (103) and provides an intriguing physiological mechanism whereby THC consumption in adolescence may contribute to depression vulnerability.

Another factor to consider is that the effects of THC and CBD on cognition may be in opposite directions. However, this is as yet unproven (5). Furthermore, according to a systematic review on the effects of CU on cognition, brain structure and function, chronic CU was associated with changes in hippocampal volume and gray matter density, although the magnitude of the effect was relatively small (104). Similarly, a meta-analysis of task-based fMRI studies on the residual effects of cannabis showed an association between the level of cannabis use and impaired activity of the hippocampus (105). The hippocampus plays a key role in episodic memory (106), a cognitive domain that has been shown to be consistently impaired by acute and chronic cannabis use. Noteworthy, the cognitive impairment associated with cannabis in regular users may not be long lasting. Indeed, a review detected deficits 7 days after heavy use but less consistently beyond that point (104). A recent study showed recovery of cognition 2 weeks after cessation of CU (107). Nevertheless, in those who began CU before age 18, impairment could be detected as long as a year after cessation of consumption (104).

Cognitive deficits are ubiquitous in MDD (6, 98). Of moderate amplitude, these deficits include decrements in executive function, working memory, and attention (108–110). Changes in cognition may be seen as early as the first episode of depression (111) and may persist upon remission. Interestingly, structural brain changes in depression in the hippocampus and density of gray matter in some cortical regions are similar to those seen in individuals who use cannabis regularly. Changes in volume and cortical thickness in several brain regions (hippocampus, anterior and posterior cingulate gyrus, frontal and temporal lobes) may underlie the cognitive deficits of depression (112). Observations of decreased neurogenesis in the hippocampus and its reversal by antidepressants have led to the theory that changes in neuroplasticity are central to the pathogenesis of depression as well as its treatment (113, 114).

Knowledge is sparse regarding the interactions of the cognitive deficits of MDD and those linked to CU. The cognitive deficits linked to CU and MDD may be additive, especially those involving verbal learning (98). However, other data suggests that cannabis users who are not depressed have greater cognitive impairment than individuals with depression who use cannabis (115). Observations from a third study show similar deficits in verbal learning with cannabis use irrespective of the presence of depression (116). These contradictory findings are difficult to reconcile. More research is required on the impact of cannabis on cognition in individuals with MDD.

TREATMENT CONSIDERATIONS

Preclinical studies show that antidepressant treatments [desipramine, imipramine, fluoxetine, citalopram, tranylcypromine and electroconvulsive therapy (ECT)], modulate the ECS (6, 63, 117). ECT and imipramine, a tricyclic antidepressant, increase CB1 receptor density in subcortical limbic structures (hippocampus, amygdala, hypothalamus) (30, 63, 117). In addition, sleep deprivation, an intervention that is effective for the treatment of depression, also increases CB1 receptor signaling (33). Long-term treatment with antidepressants and ECT decreases basal stress-induced hypothalamic pituitary adrenal axis (HPA) activation, and increases levels of BDNF as well as neurogenesis (33). This body of evidence suggests that cannabis could have a therapeutic effect on depression. Unfortunately, there is a dearth of evidence addressing this issue.

The quality of evidence concerning the use of medical marijuana in the treatment of psychiatric disorders such as depression is low (118). To our knowledge, no randomized controlled trials have been conducted on the effect of medical marijuana on depression as a primary outcome (57, 119, 120). Preclinical data suggests that CB1 receptor ligands may modulate and potentially enhance the effects of antidepressants (121). An important observation is that CB1 receptor activation can have both depressant and anti-depressant activity (122). This may explain, at least in part, the contradictory results found in the literature of the interactions of cannabis and depression.

Clinical trials using medical marijuana and its by-products for other psychiatric and medical conditions, which included depression as a secondary outcome, have generated intriguing signals. For instance, it was found that the oral administration of nabiximols (an oromucosal spray containing a mixture of THC and CBD) (123) for numerous medical conditions had no significant effect on depression, when studied as a secondary outcome (57, 119, 120). Similar results were observed with dronabinol (an isomer of THC) (119, 124). Moreover, in a randomized, double-blind, placebo-controlled clinical trial for the treatment of neuropathic pain with the nabiximol Sativex, there were no significant modifications in measures of depression and anxiety (43). In fact, a study comparing different doses of nabiximols to placebo found out that the use of a high dose (11–14 sprays/day) exacerbated depression (119), reinforcing the signal that higher doses of cannabinoids may be pro-depressogenic. In contrast, early data from pre-clinical studies of CBD are suggestive of possible antidepressant effects (125–129). We are unaware of any randomized controlled trial investigating nabilone (synthetic orally administered THC compound) or CBD in the treatment of MDD. Finally, while CBD has been proposed to reduce the negative psychoactive effects of THC, a recent study and meta-analysis did not find support for this proposition (130, 131).

There has been little research into the treatment of CUD and comorbid MDD and the available data did not signal any efficacy for pharmacological treatment (132, 133). Several studies of psychosocial interventions have been performed in patients with severe mental illness and CUD. However, apart from a

few preliminary trials (70, 134), these studies have not focused specifically on MDD (135).

It is premature to recommend cannabis or its derivatives as a treatment for depression. A recently published review of promising preclinical evidence detailing CBD's potential as a therapeutic agent concludes with a call for further research into CBD's clinical efficacy (129). The American Psychiatric Association has concluded that *"There is no current scientific evidence that marijuana is in any way beneficial for the treatment of any psychiatric disorder. In contrast, current evidence supports, at minimum, a strong association of cannabis use with the onset of psychiatric disorders"* (22).

As discussed in this article, there is evidence linking THC with worsening of the symptoms of depression, and also a suggestion that CBD may be associated with favorable effects when used to treat depression. This information can be used to steer patients with depression away from the use of high THC content cannabinoid products, particularly during adolescence.

FUTURE DIRECTIONS

In the recent context of legalization, and the availability of cannabis characterized by higher concentrations of THC and lower concentrations of CBD, there exists an urgent need for well-designed studies on the benefits and harms of medicinal and recreational cannabis and related compounds in major depression.

In epidemiological and clinical studies, the exposure to cannabis should be more precisely defined both in terms of frequency and quantity of use in prospective studies that do not have to rely on recollection for this information. Comorbid substance use, and comorbid medical and psychiatric conditions should be documented, as they may confound findings that could be erroneously attributed to CU.

In order to clarify the role of cannabinoids as therapeutic agents for the treatment of depression, studies with this aim as a primary outcome are essential. Well-designed, appropriately powered, studies of the pharmacological treatment of MDD and comorbid CUD are essential. Trials of the efficacy of cannabis or its derivatives in MDD should have appropriate strategies for concealment and include a placebo control. The populations studied should be clearly defined and the diagnosis of MDD established through appropriate diagnostic evaluations. It is essential to examine dose-response relationships and the influence of cannabis composition (e.g., THC/CBD ratio) on treatment. Low doses of cannabis or its derivatives should be tested, as there is a clear signal that there is a different pharmacological effect of high and low dose. Future research should consider that this complex molecule also has the potential for drug-drug interactions (136–139). The dimensions of apathy, anhedonia, cognition and anxiety will be important secondary outcomes to consider.

For those who suffer from MDD and comorbid CUD, there is an urgent need to investigate, in well-designed trials, the potential efficacy of motivational interviewing and cognitive behavioral therapy. Such interventions have been shown to be efficacious for the treatment of CUD in individuals with no major psychiatric disorder. It remains to be determined if these interventions are also efficacious in individuals with MDD and CUD.

LIMITATIONS

This review was not systematic and did not restrict the definition of depression to a clinical diagnosis of MDD. Some articles used cut-off scores on scales to define depression. Further, the literature presents inconsistent results, which may be a consequence of the lack of precision regarding the concentrations of THC, CBD, and the strains consumed. Finally, some of the studies were small and thus, their results may not be generalizable.

CONCLUSIONS

CU, in particular of cannabis products higher in THC content, is likely to be associated with increased adverse psychiatric effects, including depression. Indeed, meta-analyses on the subject seem to show that cannabis use may be a risk factor for the development of depression. However, a bidirectional relationship has also been described with depression being a risk factor for cannabis consumption as well as the reverse. Gender and youth may confer increased vulnerability to the adverse effects of cannabis.

There is evidence that the endocannabinoid system is involved in the pathophysiology of depression. In the future, larger studies in the field will be needed to demonstrate this involvement, especially positron emission tomography studies examining different components of the endocannabinoid system. Components of this system are clearly potential targets for new therapeutic interventions for depression.

Preliminary evidence from clinical trials shows that low doses of cannabis and its products have different and potentially beneficial effects, in contrast to higher doses which are associated with adverse effects. While some preliminary data indicates less deleterious and possibly positive effects of CBD in depression, it is premature to recommend CBD as a treatment for depression (30). RCTs on this topic are warranted. Finally, in considering the use of cannabis and its derivatives, it is important to balance the possible alleviation of anxiety and depression against side effects such as apathy and cognitive deficits.

AUTHOR CONTRIBUTIONS

CL and ST were central to gathering data and writing the manuscript. AK and SP reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Cannabis and Cognitive Functioning: From Acute to Residual Effects, From Randomized Controlled Trials to Prospective Designs

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In recent years, several jurisdictions have revised their regulation policy toward both medical and recreational use of cannabis. These changes have elicited concerns regarding how legalization impacts academic achievement and work performance. This review evaluates the acute and long-term (residual) association between cannabis use and cognitive functioning that underlies poor academic and work performance. Relative to other reviews, this article focuses on cross-over randomized controlled trials and prospective designs given that they allow to test the impairing effects of cannabis exposure at the within-subject level. Acute cannabis cognitive effects are discussed separately for known confounding factors such as levels of delta-9-tetrahydrocannabinol (Δ^9-THC), Δ^9-THC:cannabidiol ratio, previous cannabis use and, comorbidity with psychosis-spectrum disorders. The cognitive residual effects of cannabis are detailed in relation to duration of abstinence, frequency of use, comorbidity with psychosis-spectrum disorders, types of cognitive domains assessed, and age of cannabis use initiation. Moreover, considering the fact that adequate longitudinal studies can make inferences about causality between cannabis use and impaired cognitive functioning when disentangling between-subject from within-subject variation, proofs for the three main non-mutually exclusive hypotheses about this relationship will be presented: i) the cognitive vulnerability hypothesis as part of the more general common antecedent hypothesis, ii) the concurrent cannabis impairing hypothesis, and iii) the neurotoxic hypothesis of cannabis. Current research provides evidence for mild to moderate acute cannabis effects on episodic and working memory, processing speed, and executive functions. Mild residual impairing effects were also observed in these exact same cognitive domains, suggesting that adverse effects following cannabis intoxication persist at least days or weeks following cannabis abstinence. Relative to adult-onset, adolescent-onset cannabis use seems to explain the dose-response relationship and is associated with longer lasting residual effects even in mild users (<weekly). The association between cannabis and cognition is likely explained by common antecedents, such that genetic and shared environment factors predispose individuals to both cannabis use and cognitive deficits, and to a lesser degree, neurotoxic effects.

Keywords: cannabis, delta-9-tetrahydrocannabinol, cognition, longitudinal design, memory

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INTRODUCTION

In recent years, several jurisdictions have revised their regulation policy toward both medical and recreational use of cannabis. These changes have elicited concerns regarding how state and federal legislations impact cannabis use prevalence. In addition to the Canadian legalization of recreational use in 2018, more than 30 US states have legalized medical cannabis use, and more than 10 states have legalized its recreational use. In adult populations (>26 years old), evidence points toward increases in frequency of use and in rates of cannabis use disorders (CUD) pre- to post-medical and recreational laws (1, 2). The literature evaluating adolescent cannabis users is more complex (1, 3, 4). Recreational, but not medical legalization, seems to positively affect cannabis use prevalence, and only the most severe form of cannabis misuse (i.e., CUD) is affected by legislation changes (1, 3, 5, 6).

Another concern is the marked increase in concentrations of delta-9-tetrahydrocannabinol (Δ^9-THC), the principal psychoactive agent contained in cannabis, since the 1970s and most specifically since the last decade. Concentrations of Δ^9-THC ranged between 0.5 and 4.0% in the 1970s, whereas contemporary strains from North America, Europe, and Australia attain concentrations of 15% and over (7–11).

A renewed interest in understanding the potential adverse effects of cannabis use from a public health perspective has emerged following these changes in regulatory policy and cannabis potency. One such potential adverse effect is its impact on cognitive functioning, which may translate into lower academic achievement (12–15), decreased work performance (16, 17), and a rise in the number of motor vehicle accidents (18–20). Increasingly, studies show that adolescence may be a particularly vulnerable period for the cognitive effects of cannabis use. The known psychoactive effects of cannabis are exerted through its two main components, Δ^9-THC and cannabidiol (CBD), and their action on the endogenous cannabinoid system. The endocannabinoid system is also tightly involved in neurodevelopmental processes such as neuronal specification, migration and maturation, axonal elongation, and synaptogenesis; processes that continue to occur during adolescence (21). Consequently, it has been proposed that the effects cannabis exert on cognition would be more deleterious if age of onset occurred during adolescence.

It is therefore imperative to review the literature investigating the potential effects of cannabis use on cognitive functioning to inform the public, as well as stakeholders. The first part of this article offers a narrative review of studies examining the acute effects of cannabis. An emphasis is placed on understanding the contribution of specific confounding factors such as the content in Δ^9-THC of cannabis products, the Δ^9-THC:CBD ratio, previous cannabis use, and comorbidity with psychosis-spectrum disorders. Considering that acute effects are most robustly examined with double-blind cross-over randomized controlled trials (RCT) which mitigate potential sources of experimental bias by testing effects at the within-subject level, the section on acute effects primarily discusses findings from these cross-over experiments, unless specified otherwise. In a second section, we discuss the residual effects (or long-term effects following abstinence) of regular cannabis use with a focus on both meta-analyses of cross-sectional studies and longitudinal studies. This second section will review how (i) duration of abstinence, (ii) frequency of use, (iii) psychosis-spectrum comorbidity, (iv) types of cognitive domains assessed, and (v) age of cannabis use initiation interact with the residual cognitive effects of cannabis. Considering the fact that adequate longitudinal studies can make inferences about causality between cannabis use and impaired cognitive functioning when disentangling between-subject from within-subject variation, proofs for the three main non-mutually exclusive hypotheses about this relationship will be presented: (i) the cognitive vulnerability hypothesis as part of the more general common antecedent hypothesis, (ii) the concurrent cannabis impairing hypothesis, and (iii) the neurotoxic hypothesis of cannabis.

ACUTE EFFECTS

Acute effects refer to those relative to exposure–that is, cannabis-induced intoxication. The vast majority of studies on acute effects report impaired cognitive performance following cannabis/Δ^9-THC exposure. A recent meta-analysis including more than 52 studies and 1,580 healthy individuals shows that verbal learning and memory (e.g., encoding, consolidation, retrieval), and working memory are the cognitive domain most impaired by acute cannabis-induced intoxication (22). Indeed, exposure to Δ^9-THC or cannabis extract exerts moderate cognitive deficits (effect sizes: $g = 0.69$; $g = 0.51$; $g = 0.51$, respectively), in these three domains (22). These results echo prior well-documented evidence of acute impairments in these domains, notably in humans (23) as well as in rodents and non-human primates (24). Administration of cannabis also seems to elicit mild to moderate adverse effects on processing speed ($g = 0.38$) and executive functioning ($g = 0.37$) (22). Lastly, the latter meta-analysis explored the effects of acute cannabis exposure on attention and inhibitory (i.e., response inhibition and decision making) performance and reported only mild detrimental effects ($g = 0.24$; $g = 0.28$, respectively) (22). Regarding the speed of processing domain, we found that the harmful effects of cannabis/Δ^9-THC were smaller in the oral administration studies relative to studies using other routes of administration, including smoked administration (effects are reported in **Table 1**).

One sub-domain of cognitive functioning that has recently received much attention is social cognition, which refers to a set of processes involving social interactions. These processes include mainly emotion recognition and the interpretation of others' emotional states (e.g., theory of mind). Among the few studies that investigated the acute effects of cannabis use on performance during social cognition tasks, some have reported impairments in emotional recognition of ambiguous faces (25) or threatening emotions such as fear and anger (26, 27), while this was not the case for other studies (28, 29). It is probable, but not certain, that exposure to Δ^9-THC induces deficits in emotional recognition. Additional studies are needed to assess the quality of the evidence. As such, research linking cannabis

TABLE 1 | Acute effects of cannabis use on cognitive functions.

Cognitive domain	N studies	Effect size (g) 95% CI
Attention	30	**−0.24 (−0.11, −0.36)**
Verbal learning	14	**−0.69 (−0.49, −0.89)**
Verbal memory	12	**−0.51 (−0.37, −0.65)**
Working memory	23	**−0.51 (−0.37, −0.66)**
Executive function	13	**−0.37 (−0.25, −0.49)**
Processing speed	38	**−0.38 (−0.28, −0.49)**
Impulsivity	14	**−0.28 (−0.17, −0.39)**

CI, Confidence Interval.
Effects presented in bold are significant.
This Table has been adapted from Zhornitsky et al. (22). Effect sizes are negative, which means that decreases in cognitive performances were observed in users relative to non-users. An effect size of ∼−0.2 is considered as small; an effect size of ∼−0.5 is considered as moderate; an effect size of −0.8 is considered as large.

use to impairments in theory of mind is insufficient and does not allow for the interpretation of potential effects on this sub-domain of socio-cognitive functioning.

Δ^9-THC Content

Cross-over designs have demonstrated that the effects of cannabis in infrequent users on several cognitive functions occur in a dose-response fashion (refer to **Supplementary Table 1** for a summary of studies). For instance, it was demonstrated that for smoking, intravenous and oral administration of Δ^9-THC, the higher dosage (or higher serum concentration) induced significantly more detrimental effects on verbal learning and memory, reaction times, and response inhibition relative to lower doses (30–35). Hart et al. (36) also found a dose-response relationship when investigating reaction times on various cognitive tasks, but not on performance accuracy when task time limit was not a factor. In addition to the absence of a time limit, this negative finding on performance accuracy from Hart et al. (36) could be explained by the fact that participants were daily users. Indeed, daily cannabis users often exhibit tolerance to the acute effects of cannabis on cognition (see section Previous cannabis use) and this may hinder efforts to demonstrate a dose-response relationship of cannabis on cognition.

Two studies have specifically investigated the effect of increasing concentration of Δ^9-THC on decision making tasks (33, 37). The first demonstrated that the proportion of trials showing impairment increased as a function of serum concentration of Δ^9-THC (33). The second found that only the higher dose yielded impairments relative to placebo (37). The failure to observe an effect at both doses in the second study may be due to the participants being daily users with tolerance to the impairing effects of cannabis and to the use of a small dose lower than reported to have an effect in occasional users.

Specifically for attention and working memory domains, the literature reports mixed findings: while most studies observed that the severity of impairments are a function of Δ^9-THC content or performance is solely affected by the higher dose (30–32, 34, 35, 38, 39), some found that these domains were unaffected by Δ^9-THC (32, 34, 36). Reconciliation of these contradictory findings is challenging considering the heterogeneity in the tasks used. A detailed analysis of 15 published studies assessing the dose effects of Δ^9-THC on digit-span performance, demonstrated that negative results may be due to short task length (and low number of trials, e.g., 3-min Digit Span task), which imparts lower sensitivity to detect an effect compared to longer task durations (39). Altogether, there is converging evidence that the cannabis impairing effects on verbal learning and memory, response inhibition, and psychomotor speed occur in a dose-response fashion. The linear relationship between exposure to higher Δ^9-THC content and worse performance on decision making, attention, and working memory were less robust, and are therefore probable at best.

Δ^9-THC:CBD Ratio

While Δ^9-THC is responsible for the widely known psychoactive effects of cannabis (e.g., euphoria, psychological well-being, sensory experiences and appetite) (40), the effects of CBD are less well-understood. CBD is believed to be responsible for the anxiolytic and anti-inflammatory effects associated with cannabis use (41). When administered alone, without other cannabinoids, CBD may also have antipsychotic effects (41). What complicates research and generalizability of findings is that concentrations of Δ^9-THC and CBD vary as a function of cannabis strains. For example, low doses of CBD can potentiate intoxicating Δ^9-THC effects, while higher doses of CBD may reduce the intoxicating properties of Δ^9-THC (42). As such, because of their different and sometimes even antagonistic properties (40), it is highly probable that Δ^9-THC and CBD also exert distinct effects on cognitive functioning. To disentangle the ramification of these chemical compounds, an increasing number of experimental studies have specifically investigated the effect of different Δ^9-THC:CBD ratios on cognition [(43), refer to **Supplementary Table 2** for a summary of studies].

When investigating memory function (the cognitive domain most consistently impaired by cannabis), Schoedel et al. (44) observed that working memory performance (i.e., reaction times) was impaired by a high dose of synthetic Δ^9-THC (dronabinol) compared to a placebo. However, performance following three different dosages of nabiximol (a compound with a Δ^9-THC:CBD ratio of 1) was not different from placebo. On the contrary, in another within-subject cross-over design, administration of both Δ^9-THC alone and Δ^9-THC in combination with CBD induced deficits on episodic and working memory tasks. Only in the condition of exclusive CBD administration did subjects perform as well as during the placebo condition (45). The discrepancy in findings between these two studies could be explained by different Δ^9-THC:CBD ratios, such that only at specific ratios does CBD attenuates the impairing effects of Δ^9-THC. Between-subject designs provide further evidence of CBD attenuating the acute memory effects of Δ^9-THC (46–48). For example, an experimental study exploring between-subjects contrasts found that healthy participants treated with placebo prior to receiving Δ^9-THC presented poorer delayed but not immediate recall relative to baseline, while the group pre-treated with CBD showed no impairment (48). However, pre-treatment with

CBD did not attenuate the deficits observed in other cognitive domains, such as working memory, psychomotor functioning and executive functions. Using a naturalistic design, studies have also reported that while individuals who used cannabis strains with lower CBD content had marked impairment on various memory tasks, those smoking cannabis high in CBD concentrations showed no performance deficits relative to the placebo condition, independent of Δ^9-THC levels and baseline performance (46, 47).

Among other cognitive domains, Hindocha et al. (25) demonstrated that Δ^9-THC exposure led to impaired emotional recognition when compared to both placebo and combined Δ^9-THC and CBD conditions. For psychomotor function and driving performances, mixed evidence was found regarding the attenuating effect of CBD on Δ^9-THC (45, 49, 50). Lastly, in an effort-related decision making task, CBD did not mitigate the impairing effect of Δ^9-THC relative to placebo (51).

Altogether, CBD seems to dampen the deleterious cognitive effects of acute Δ^9-THC exposure, for memory at the very least. While encouraging, these findings do not provide information on the potential long-term protective effects of higher CBD concentrations on chronic cannabis use. Unfortunately, this question remains difficult to address, even following legalization of cannabis use. Investigators would need to gather information on Δ^9-THC and CBD concentrations in cannabis strains, in large cohorts of participants, followed longitudinally.

Previous Cannabis Use

Another confound observed in the literature relating to the acute effects of cannabis is the users' status (e.g., non-/occasional users or regular/heavy users) (refer to **Supplementary Table 3** for a summary of studies). Tolerance to the undesirable physiological effects of cannabis use among regular users was evidenced by RCT. Indeed, following Δ^9-THC exposure, frequent users presented blunted perceptual alterations, psychotomimetic effects, anxiety, and increases in cortisol relative to occasional cannabis users, findings that could not be explained by group differences in plasma Δ^9-THC (52). Five studies using a between-subject approach (difference between groups) of a cross-over placebo-controlled design have further investigated the presence of tolerance effects for the impairing effects of cannabis on cognition. Individuals with a cannabis use disorder (CUD), relative to non-users (i.e., <once/month), showed smaller Δ^9-THC-induced impairments in immediate and delayed verbal memory tasks, while performing worse during the placebo condition (52). Similarly, administration of Δ^9-THC (following pre-treatment with haloperidol) produced significant performance deficits on verbal learning and spatial working memory (not on verbal memory) in non-users specifically (53). However, Colizzi et al. (54) demonstrated that occasional and non-users did not perform differently on verbal memory during the drug condition. Of note, in this latter study, the authors failed to observe general Δ^9-THC induced memory deficits across the whole sample. This negative finding could be explained by a lower sample size ($n = 24$ vs. 28 and 52) and/or the use of an intermediate oral dosage of Δ^9-THC (10 mg; a dosage typically lower than those used in studies quantifying impairments by Δ^9-THC content, refer to doses in **Supplementary Table 1**).

Working memory performance was also shown to be associated with tolerance effects: non-users made more errors during the Δ^9-THC condition relative to placebo when compared to occasional users (53). Similarly, reduced accuracy and increased reaction times on attention tasks were observed only among occasional users relative to placebo, and not among regular/heavy users (52, 55, 56). Studies investigating how previous cannabis use modulates performance on response inhibition tasks showed inconsistent evidence (54–56). In summary, it appears that the most frequent users of cannabis develop a targeted tolerance to the most robust Δ^9-THC effects on cognition (i.e., memory, working memory, and attention).

Comorbidity With Psychosis-Spectrum Disorders

Considering that acute Δ^9-THC exposure can induce transient positive psychotic symptoms among healthy individuals (30), and that cannabis-related cognitive deficits resemble the constellation of cognitive impairments observed in psychosis (57), this section focused exclusively on the modulating effect of a psychosis diagnosis or psychosis vulnerability in the relationship between cannabis and cognition. Results from robust between-subject comparison (patients vs. healthy controls) of cross-over placebo-controlled designs (within-subject design) do suggest an enhanced sensitivity to the cognitive impairing effect of Δ^9-THC in psychosis (refer to **Supplementary Table 4** for a summary of studies). For instance, D'Souza et al. (58) demonstrated that schizophrenia patients, relative to non-psychiatric individuals, showed greater verbal learning and verbal memory deficits following Δ^9-THC administration relative to placebo. Another study revealed that adults with a genetic vulnerability to the psychosis-inducing properties of cannabis (Val/Val carriers on the catechol-O-methyltransferase (COMT) gene) were significantly more impaired on verbal and visual memory (not learning) following Δ^9-THC exposure, relative to those with a low genetic vulnerability (Met/Met and Val/Met carriers) (59). However, these studies failed to observe other drug condition (Δ^9-THC vs. placebo) by group (diagnosis or genetic vulnerability) interactions for attention performance and psychomotor speed (60, 61). Finally, in at least one study, negative results on the attention task seem to be driven by missing data and thus a low sample size (60). Convincing evidence from within-subject design revealed that a psychosis comorbidity may exacerbate the cognitive-impairing effects of cannabis, at the very least for memory.

RESIDUAL EFFECTS

Cross-Sectional Studies

Residual effects refer to an array of measurable negative effects that persist after the state of intoxication. These residual effects have been assessed between ∼12 h following cannabis exposure to more prolonged periods of abstinence (e.g., over 1 year). At least five meta-analyses including over 69 cross-sectional studies have collected data from more than 8,000 cannabis users and non-users who had undergone cognitive assessment

(60–64). Worsened performances were consistently reported for learning and memory domains, with effect sizes ranging from small to moderate (60–64). Converging evidence from the meta-analyses also showed small deficits (Cohen's d ∼0.2–0.3) in attention, executive functioning (i.e., inhibition and cognitive flexibility), and processing speed (refer to **Table 2**) (60–62). Interestingly, most of these domains (i.e., learning and memory, processing speed, and executive functions) were also more negatively affected in acute phases of intoxication, which suggests that adverse effects following cannabis intoxication persist days following cannabis abstinence. However, these cognitive deficits are categorized as mild. In comparison, residual effects of other substances, namely alcohol, cocaine and methamphetamine, are generally categorized as moderate (refer to **Table 2**) (65–67).

The aforementioned meta-analyses also investigated the potential moderating effect of covariates such as age of cannabis use onset, age of participants, duration of use, duration of abstinence, and frequency of use. There is converging evidence that neither age of cannabis initiation, age of participants (adolescents vs. adults), nor duration of use were significant moderators (60–64). The other two covariates are discussed in the following sections. Finally, in section Comorbidity with psychosis-spectrum disorders we discussed results from other meta-analyses which have focused on how psychosis spectrum comorbidity impacts the residual cognitive effects of cannabis use.

Duration of Abstinence

When meta-analyses focused on more chronic residual effects relative to effects from short abstinence periods, users (generally adults) no longer showed cognitive deficits, or showed significantly milder deficits. This finding was demonstrated by Scott et al. (62) for abstinence periods that persisted for more than 3 days, by Schoeler et al. (64) following 10 days of abstinence, and by Schreiner et al. (60) after ∼1 month of cannabis use abstinence. This suggests that these residual effects have a short-term duration, but more importantly, that they are reversible. In the case of other substances like alcohol, cocaine and methamphetamine, residual effects that persisted after a month of abstinence (e.g., attention, learning, memory, and executive functioning) were instead categorized as moderate to large effect sizes. Before prematurely concluding that cannabis use is safer than other substance use, it should be noted that the majority of studies focusing on alcohol, cocaine and methamphetamine only included individuals who correspond to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for substance abuse, which complicates comparisons between various substances.

Deficits Increase as a Function of Use

When the effects of the frequency of cannabis use or a diagnostic of CUD are assessed on the amplitude of associated cognitive deficits, research showed a dose-response effect. Schoeler et al. (64) ascertained that mild use (e.g., <10 joints per month) was not associated with decreases in cognitive functioning; regular use (multiple times per week) was associated with deficits that were characterized as mild; and finally, daily use was associated with deficits that ranged from mild to moderate. Moreover, the cognitive deficits from daily use resembled alcohol-induced impairments in terms of importance, more specifically with regards to episodic memory. Similarly, individuals who are seeking treatment for substance abuse show global cognitive deficits of moderate amplitude, whereas those who do not seek treatment for substance abuse show only mild deficits (62). These moderate effect sizes for heavy cannabis users (criteria for abuse) resemble the severity of cognitive impairments reported in studies investigating the residual effects of other substances. Of note, the comparison between the residual cognitive effects of cannabis relative to other substances is challenging considering that the meta-analyses investigating alcohol, cocaine and methamphetamine included individuals meeting criteria for abuse and/or dependence (65–67), while the vast majority of studies on cannabis included a wide range of users (from light to heavy users) not meeting those criteria. With regards to the duration of cognitive deficits in regular and daily users, findings are difficult to interpret, given that they are controversial. That is, many authors report that cognitive deficits in intelligence quotient (IQ), attention and episodic memory (e.g., learning) that are associated with chronic (daily) cannabis use persist even 3 to 4 weeks following abstinence (68–70). However, other studies have also shown that these residual effects are reversed with >1 month of abstinence, and this was also the case for chronic users (71–74).

Altogether, residual effects of cannabis use can be observed on a myriad of cognitive abilities, such as learning and memory, executive functions, and processing speed. These deficits are generally less severe than those observed for alcohol, cocaine and methamphetamine and also seem to be reversed more quickly. However, effects of cannabis on memory (also possibly executive functioning and processing speed) are similar to those of alcohol and cocaine when frequency and severity of use are considered.

In the absence of experimental designs, studies evaluating the residual effects of cannabis are observational and usually utilize cross-sectional between-subject designs, in which users are compared to non-users matched on potential confounding variables. This type of research design does not allow for inferences on causality—that is, if the observed cognitive deficits were present or not before cannabis use and if they are not explained by other confounders. Consequently, the following section focused on longitudinal population-based and genetically-informed (co-twin designs) studies that better address these issues.

Comorbidity With Psychosis-Spectrum Disorders

Meta-analyses of cross-sectional studies do not provide support for hypothesis that individuals with psychosis are more sensitive to the residual effects of cannabis, in contrast to observations from acute challenge studies. To the contrary, two meta-analyses concluded that cannabis-using psychosis patients exhibited superior (small-to-moderate effects) cognitive functioning for attention, executive functions, working memory, delayed memory, verbal fluency, and visuo-spatial abilities relative to non-using patients (75, 76). A further meta-analysis of first-episode psychosis patients did not observe significant

TABLE 2 | Residual effects of cannabis use on cognitive functions in comparison to other substances.

Cognitive domain	Substances			
	Cannabis effect size (*d*)	Alcohol effect size (*d*) (95% CI)	Cocaine effect size (*d*) (95% CI)	Methamphetamine effect size (*d*) (95% CI)
Intelligence quotient	–	**−0.33 (−0.53, −0.13)**	–	–
Attention	**−0.36**	**−0.70 (−1.08, −0.32)**	**−0.59 (−0.87, −0.32)**	**−0.50 (−0.80, −0.20)**
Learning	**−0.35**	**−0.45 (−0.59, −0.32)**	**−0.55 (−0.74, −0.36)**	**−0.48 (−0.60, −0.37)**
Memory	**−0.25**	**−0.38 (−0.62, −0.15)**	**−0.56 (−0.77, −0.34)**	**−0.40 (−0.51, −0.28)**
Working memory	–	**−0.53 (−0.70, −0.36)**	**−0.52 (−0.74, −0.30)**	**−0.54 (−0.68, −0.40)**
Executive function	**−0.21**	**−0.53 (−0.63, −0.44)**	**−0.32 (−0.48, −0.16)**	**−0.45 (−0.55, −0.36)**
Processing speed	**−0.34**	**−0.47 (−0.58, −0.36)**	**−0.45 (−0.60, −0.29)**	**−0.37 (−0.49, −0.25)**
Visuospatial abilites (motor component)	–	**−0.49 (−0.62, −0.36)**	**−0.33 (−0.58, −0.08)**	−0.27 (−0.56, 0.01)
Verbal fluency	**−0.23**	**−0.40 (−0.54, −0.25)**	**−0.22 (−0.38, −0.06)**	**−0.43 (−0.65, −0.20)**

CI, Confidence Interval.

Effects presented in bold are significant.

Data presented in this table represent effect sizes (Cohen's d) calculated from meta-analyses. Cannabis effect sizes represent the mean of effect sizes reported in the five meta-analyses investigating the residual cognitive effects (60–64); thus, the confidence interval is not reported. Alcohol, cocaine, and methamphetamine effect sizes come from the following meta-analyses: (65–67), respectively. Effect sizes are negative, which means that decreases in cognitive performances were observed in users relative to non-users. An effect size of ∼−0.2 is considered as small; an effect size of ∼−0.5 is considered as moderate; an effect size of −0.8 is considered as large. Among studies that investigated residual effects of cannabis use, cognitive assessments were done after a period that varied from many hours to 31 days (4 ½ weeks). Similarly, the average abstinence period in studies focusing on alcohol was between 0 and 31 days. For studies focusing on cocaine, abstinence periods varied from a few days to 12 weeks. At last, the average abstinence periods for studies focusing on methamphetamine was 3.3 months.

differences in neurocognitive performance between patients with and without cannabis use (77). It is important to interpret these results with caution. For example, studies that utilize a diagnosis of CUD as an inclusion criterion often include individuals with a current diagnosis alongside those with a history of CUD who are now in remission (75), therefore introducing noise to the data. Moreover, results that support higher cognitive function in cannabis-using patients do not extend to those with heavy use (daily) or CUD. In their large multi-country study, Ferraro et al. (78) confirmed that the higher IQ observed in cannabis-using patients relative to non-using patients was attributable to patients with occasional but not daily use. A recent exploratory analysis reported that among psychosis patients with CUD, greater cumulative cannabis exposure was associated with poorer performance across several cognitive domains (attention, working memory, delayed memory, decision making, and response inhibition) (79). The direct comparison of cognitive performance between cannabis users with and without co-morbid psychotic disorders provides further support for the hypothesis that individuals with psychosis are more sensitive to the cognition-impairing effects of heavy cannabis use. Following a 1-month abstinence period, significant improvements in verbal memory were observed for psychosis patients with CUD relative to non-psychiatric individuals with CUD while controlling for performance prior to abstinence (70). It was proposed that this greater recovery of memory function following abstinence reflects a greater vulnerability to its impairing effects in psychosis. Altogether, the available evidence suggests that individuals with psychotic disorders who are occasional (but not heavy) users of cannabis may represent a phenotypically distinct patient group with more intact (premorbid) cognitive functioning. Importantly, more severe patterns of cannabis use (e.g., CUD or daily use) eventually negatively interfere with cognitive performance; a finding that is in agreement with the literature on acute effects.

Longitudinal Observational Studies

Results from prospective designs may agree with three non-mutually exclusive hypotheses linking cannabis use and cognitive functioning. The *cognitive vulnerability* hypothesis postulates that cognitive deficits are already present before the onset of cannabis use for individuals who present higher risk of becoming regular users. This vulnerability hypothesis is often formulated within the more general common antecedent hypothesis. The latter proposes that common factors may predispose individuals to both cannabis use and mild cognitive decline in users, without cannabis use being the cause of these cognitive deficits, and without any specificity about the timing of such deficits. In contrast, the *concurrent* hypothesis posits that cannabis use is associated with cognitive deficits when controlling for premorbid cognitive performance, but only in short-term. It is proposed that abstinence or decreases in cannabis use should help alleviate these deficits. Lastly, the *neurotoxicity* hypothesis stipulates that past cannabis use induces a cognitive decline that persists even after individuals refrain from or decrease their cannabis use, when adjusting for cognitive functioning prior to cannabis use (see **Figure 1** for a graphical representation of the three hypotheses within the context of mixed effects linear modeling).

Cognitive Vulnerability and Common Antecedent Hypotheses

The premorbid cognitive vulnerability hypothesis (e.g., before the onset of cannabis use) has been confirmed by recent studies. Findings show that future cannabis users already show lower

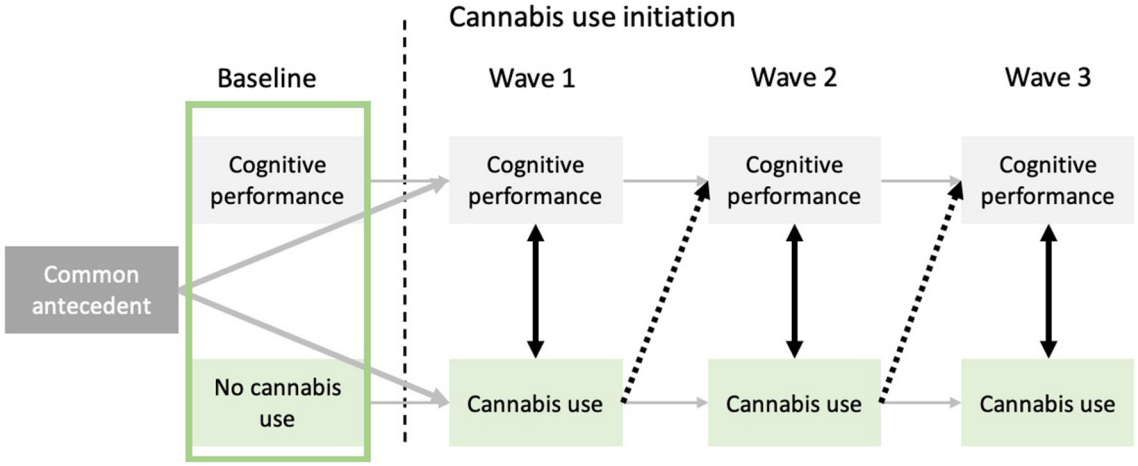

FIGURE 1 | Representation of the cognitive vulnerability, concurrent, and neurotoxicity hypotheses relative to the association between cannabis use and cognitive functioning. The cognitive vulnerability hypothesis (represented by the green square) posits that before onset of cannabis use, future cannabis users already exhibit cognitive deficits. The common antecedent hypothesis, which offers a more general framework than the cognitive vulnerability hypothesis, posits that unknown common factors could be responsible for cannabis use onset and mild cognitive deteriorations, without cannabis use being the causal factor of the aforementioned cognitive deficits. Black dotted arrows allow to investigate the neurotoxic hypothesis by testing if previous cannabis use ($t-1$) predicts subsequent cognitive functioning (t), while controlling for frequency of cannabis use at time t. Lastly, black bidirectional arrows between cognitive abilities and cannabis use at every time-point represent the concurrent hypothesis. Indeed, cognitive performance at time t is associated with cannabis use at time t, without necessarily persisting effects through time.

performance at IQ tasks (non-verbal and verbal), memory, and executive functions (e.g., inhibitory control) when compared to individuals who remain non-users (80–84). As such, specific cognitive deficits seem to predispose individuals to earlier onset and more regular cannabis use. However, other studies did not provide evidence that cognitive impairment was apparent prior to cannabis use initiation (68, 85–88). As evidenced by rigorous co-twin designs, this cognitive vulnerability disappears when investigating individuals nested in a family, such that monozygotic and dizygotic twins discordant for cannabis use or cannabis dependence do not show differences in cognitive abilities prior to cannabis initiation (83, 84). These later twin studies do not support the purely cognitive vulnerability hypothesis, but do support the idea that common antecedents such as family factors (i.e., genetic and shared environment factors) explain this cognitive vulnerability observed at the population level. Clinical and behavioral factors have been put forth as common factors that predispose individuals to both cannabis use and cognitive deficits (89). For example, externalizing disorders as well as behavioral disinhibition have been positively associated with substance use and negatively associated with IQ (90, 91), suggesting that youths exhibiting externalizing symptoms and delinquency are less likely to be motivated to perform well at school and thus disengage from learning, and are more likely to use substances as a consequence of these problems.

Concurrent Hypothesis

When accounting for premorbid cognitive performance, cannabis use was associated with cognitive decline, at least in the short-term (during the same assessment intervals), in executive functioning, general IQ, memory, processing speed, and visuospatial abilities in several studies (68, 71, 81, 85, 88, 92, 93). Declines in cognitive functioning were observed years after the onset of cannabis use and were obvious even when taking into account other substance use (68, 71, 81, 85, 93), academic achievement (68, 85, 92), externalizing problems or other mental health comorbidity (68, 71), and socioeconomic status (71, 81, 85, 88, 94). Without eliminating the possibility that these factors could have played a mitigating role, controlling for these covariates increases our confidence in the idea that cannabis could have deleterious effects on cognitive functioning. Only a few studies did not report concurrent impairing effects of cannabis use (82, 86). Of note, among the studies that investigated the concurrent hypothesis from a within-subject perspective, two out of three revealed that if an individual shows increases in cannabis use frequency at a given assessment, they will also show lower executive functions performance during that same assessment period (80–82). The results were partially replicated within co-twin designs. Among several tests measuring non-verbal and verbal IQ, as well as executive functioning (i.e., working memory, response inhibition, and cognitive flexibility), poorer performance in twins who used cannabis more frequently than their co-twin was limited to two tasks (one measuring working memory, the other, non-verbal IQ) (83, 84, 95). Altogether, these findings are in line with impairments in cognitive domains that were underlined by meta-analyses of cross-sectional studies investigating residual effects of cannabis use, as well as studies focusing on the acute effects of Δ^9-THC intoxication.

Neurotoxic Hypothesis

Longitudinal studies provide mixed evidence for the neurotoxic hypothesis. On the one hand, former regular users showed better

cognitive development than current regular users (92) and even performed as well as non-users (71), suggesting that cannabis impairing effects tend to resolve following abstinence. Similarly, Jacobus et al. (93) demonstrated that cannabis users performed more poorly than non-users across various cognitive domains, yet this performance difference disappeared at the last follow-up when users had reduced their overall consumption. On the other hand, cannabis use frequency was shown to predict subsequent cognitive decline in executing functioning and verbal intelligence regardless of whether cannabis use continued (87, 88). Specifically, Castellanos-Ryan et al. (80) and Meier et al. (68) provided evidence that a significant reduction of cannabis use (from daily to light user) or abstinence in the 12 months prior to cognitive testing were still significantly associated with a decline in executive functioning and general IQ. Furthermore, in their population cohort, Morin et al. (81) observed that over and above the concurrent impairing effect of cannabis use at the individual level, if one increases their cannabis use frequency in a given year, one will also show lower performance on response inhibition a year later. This latter study provides robust evidence of a long-term (at least 12 months) or neurotoxic effect of cannabis use considering that individuals who changed their patterns of cannabis use through the follow-ups were compared to themselves. Despite these proofs of neurotoxic effects from cannabis use with extensive covariate control, we cannot rule out the possibility that part of the variance between cannabis and subsequent poorer cognitive performance comes from indirect causal effects, for example, through social milieu (96, 97).

Factors Modulating the Residual Cognitive Effects of Cannabis

Quantities Used

In line with cross-sectional studies, it is when we distinguish occasional, regular and heavy users that cognitive deficits in memory or processing speed become more apparent (71). Indeed, memory deficits associated with weekly use of cannabis are in the range of moderate effect sizes (98), which bears resemblance to the effects of alcohol abuse. Similarly, other findings show that for each 5-year period of cannabis use, performance on memory tasks progressively decrease (99). Beyond long-term memory, research has shown that frequency and dependence of cannabis use are positively related to worse executive function and IQ deficits (68, 80, 81, 84, 85, 87). A paucity of studies did not report dose-response effects on associated cognitive deficits (82, 83, 86, 100, 101) however, some of these studies assessed cognitive domains that are not considered to be affected by cannabis use (e.g., lexical knowledge) (83, 101).

Cognitive Domains

It is important to underline that not all longitudinal studies have assessed residual effects of cannabis use on cognitive functioning more broadly. For example, a few studies have focused solely on the association between cannabis use and verbal fluency (88) or orientation [Mini Mental State Examination: (101)], and have therefore not reported any associations between cannabis use and cognitive deficits. When considered alone, these studies may falsely lead us to believe that cannabis use does not alter cognitive performance, regardless of the studied cognitive domain. However, converging findings from all studies help better explain the relation between cannabis use and cognitive deficits. Indeed, among 10 prospective studies that assessed memory, eight reported specific deficits in this cognitive domain (71, 74, 80–82, 92, 93, 98–100). Likewise, 7 of 10 studies investigating associations between cannabis use and executive function (i.e., response inhibition) showed declines in performance linked to cannabis use (68, 80–82, 84, 87, 93, 95, 99, 100). Findings of effect on processing speed, however, are less robust with three of seven studies reporting declines in performance linked to cannabis use (68, 71, 82, 92, 93, 98, 99). Finally, long-term effects of cannabis use on non-verbal IQ are mildly probable, as 6 of 10 studies have failed to show significant associations here (68, 71, 81–86, 93, 95).

Age of Cannabis Initiation

An increasing number of studies have endeavored to test the hypothesis that adolescence consists in a vulnerable period to the impairing effects of cannabis use. Generally, results can be summarized as follows (i) for an equivalent consumption, cognitive deficits seem to be more important in those who initiated cannabis use younger (e.g., during adolescence) (68), (ii) deficits noted in adolescents are similar to those observed in adults, but appear following less intensive use of cannabis (80, 81, 87); (iii) a combination of both. For example, an interesting study showed potentially additive negative effects on global performance on IQ tasks between the number of years of cannabis use and age of onset that is earlier than 18 years old (68). Moreover, the dose-response relationship highlighted by Meier et al. (68) on IQ performance was explained by adolescent-onset cannabis use, not adult-onset use. Studies conducted on three independent samples of Canadian and US adolescents have shown that increases in cannabis use during high school predicted cognitive declines in performance on memory and executive functions tasks a few years after assessment (80, 81, 87). In addition to this, it should be noted that these cognitive effects were noted in young individuals who were for the most part not heavy users (<weekly use). Moreover, age of onset of cannabis use that was prior to 15 years old compared to age of onset that occurred after 14 years old was related to impaired development of inhibition capacities, independently of the frequency of cannabis use (80). Critically, these deficits seemed more permanent than the ones reported by adults (71, 98). That is, increases in cannabis use during adolescence were associated with declines in executive functioning and IQ scores at age 20, and even until age 38, and this was also the case for individuals who had considerably reduced their consumption 12 months prior to cognitive assessments (68, 80). Taken together, these findings suggest that adolescence represents a critical period for vulnerability to deleterious effects of cannabis use on cognitive functioning.

DISCUSSION

The current comprehensive review highlights that the acute administration of cannabis/THC produces moderate

impairments in episodic and working memory, as well as small to moderate deficits in processing speed and executive functions. Impairments in attention and impulsivity have also been documented but are smaller. In the case of speed of processing, there is evidence showing that the impairments are less severe in oral administration studies relative to studies using other routes of administration (e.g., smoked, inhaled, injected). Although some studies have shown that higher Δ^9-THC concentrations are associated with more prominent cognitive impairments, further studies are required to establish what doses are problematic. Likewise, there is preliminary evidence showing the cannabidiol may attenuate Δ^9-THC-induced cognitive impairments, but results are inconclusive thus far. While several studies on the acute effects of cannabis/Δ^9-THC have paid attention to traditional cognitive domains such as attention, episodic memory, executive functions, speed of processing, and working memory, there is a relative lack of research on the effects of cannabis/Δ^9-THC on social cognition (e.g., theory of mind and emotion recognition).

Cross-sectional studies on the residual cognitive effects have generally shown that cannabis is associated with cognitive deficits that are relatively small and seem to abate after a relatively short period of abstinence. Such studies seem to indicate that cannabis produces smaller cognitive deficits than those produced by alcohol, cocaine or methamphetamine, which typically produce moderate deficits in several cognitive domains. It is crucial to point out, however, that the meta-analyses on alcohol, cocaine and methamphetamines have been performed using studies involving individuals with a substance use disorder, whereas the great majority of studies on cannabis have been performed in occasional, regular or frequent users. Future studies in the field will need to pay attention to individuals meeting the criteria for a cannabis use disorder.

Due to the methodological limitations of cross-sectional studies, a growing number of high-quality longitudinal studies have been performed in recent years. In these studies, residual impairments were observed mostly in the same cognitive domains (e.g., verbal learning and memory, speed of processing) that have been shown to be impaired in the acute administration studies. Research results suggest that the cognitive effects following cannabis intoxication persist at least days or weeks following cannabis abstinence in regular users. Relative to adult-onset, adolescent-onset cannabis use seems to explain the dose-response relationship that has been observed and is associated with longer lasting residual effects even in not so heavy users (<weekly). The association between cannabis and cognition is likely explained by common antecedents, such as genetics and shared environment factors. To a lesser degree, cannabis may also produce neurotoxic effects. Further large-scale longitudinal studies on the cognitive effects of cannabis are required, paying careful attention to premorbid cognitive performance, dose-response, cannabis constituents, and potential common antecedents.

As for the cognitive effects of cannabis in individuals with a comorbid psychiatric disorder, such as schizophrenia, research results are unfortunately difficult to interpret as the vast majority of studies in the field have adopted cross-sectional designs. Clearly, longitudinal studies in these populations are warranted. Finally, it is worth mentioning that the literature on "synthetic cannabinoids" is scarce. Considering that "synthetic cannabinoids" are full agonists at CB_1 receptors (in comparison, Δ^9-THC is a partial agonist), they may theoretically produce cognitive impairments that are more prominent and longer lasting than those of cannabis (102). With a growing number of states and countries liberalizing their policies on cannabis, the study of the cognitive effects of cannabis has important implications, since cannabis smoking may be associated with lower academic achievement, decreased work performance, and increased rates of motor vehicle accidents. Careful attention will need to be paid to policies and program that could minimize these undesirable outcomes. Such measures include disseminating public health campaigns on the hazards of cannabis use, implementing evidence-based preventive interventions in schools, prohibiting the marketing of cannabis products in ways that are attractive to youth, taxing cannabis products based on their Δ^9-THC content, and regulating maximal Δ^9-THC concentrations.

AUTHOR CONTRIBUTIONS

JB and SP reviewed the literature. JB wrote the manuscript. SP provided critical comments.

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SUPPLEMENTARY MATERIAL

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Assessing Changes in Symptoms of Depression and Anxiety During Four Weeks of Cannabis Abstinence Among Adolescents

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Background: Cannabis use is prevalent among adolescents, and many report using in attempts to alleviate negative mood and anxiety. Abstinence from substances such as alcohol and tobacco has been reported to improve symptoms of anxiety and depression. Few studies have examined the effect of cannabis abstinence on symptoms of anxiety and depression.

Objective: To test the effect of 4 weeks of continuous cannabis abstinence on depressive and anxious symptoms.

Methods: Healthy, non-treatment seeking adolescents who used cannabis at least weekly ($n = 179$) were randomized to either 4 weeks of cannabis abstinence achieved through a contingency management paradigm (CB-Abst) or cannabis use monitoring without an abstinence requirement (CB-Mon). Abstinence was assessed by self-report verified with quantitative assay of urine for cannabinoids. Anxiety and depressive symptoms were assessed weekly with the Mood and Anxiety Symptom Questionnaire (MASQ).

Results: Symptoms of depression and anxiety decreased throughout the study for all participants (MASQ-AA: stnd beta $= -0.08$, $p = 0.01$, MASQ-GDA: stnd beta $= -0.11$, $p = 0.003$, MASQ-GDD: stnd beta $= -0.08$, $p = 0.02$) and did not differ significantly between randomization groups (p's > 0.46). Exploratory analyses revealed a trend that abstinence may be associated with greater improvement in symptoms of anxiety and depression among those using cannabis to cope with negative affect and those with potentially hazardous levels of cannabis use.

Conclusions: Among adolescents who use cannabis at least weekly, 4 weeks of cannabis abstinence was not associated with a significant change in anxiety or depressive symptoms compared to continued use. For recreational cannabis users who may be concerned about reducing their use for fear of increased symptoms of anxiety and depression, findings suggest that significant symptom worsening may not occur within the first 4 weeks of abstinence. Further studies are needed in clinical populations where

anxiety and depression symptoms are measured more frequently and for a longer period of abstinence. Future studies are also needed to determine whether there are subgroups of adolescents who are uniquely impacted by sustained cannabis abstinence.

Keywords: cannabis, cannabis abstinence, depression, anxiety, contingency management, youth, adolescents

INTRODUCTION

More high school students use cannabis daily than any other substance (1) and perception of cannabis-related harm among adolescents, a key indicator of uptake of use, is at its lowest level in nearly four decades (1, 2) while cannabis potency has significantly increased (3). Youth cannabis exposure is growing with expanding commercial recreational cannabis markets across the United States, that impose few potency limits and derive the majority of profit from products such as candies that appeal to youth (4, 5).

Many people who use cannabis endorse using cannabis in an attempt to cope with stress, anxiety, and depression (6–8), and this is true for youth who are recent or frequent users (7, 9). Using cannabis to cope with negative emotions, however, has been associated with more persistent use, cannabis-related problems, cannabis dependence, and psychiatric dysfunction (9–12). Thus, though many cite alleviation of mood symptoms as a primary motive for cannabis use, there is reason to believe cannabis use may *in fact* exacerbate these symptoms. Cross-sectional studies report associations between cannabis use and higher odds of depression (ORs: 1.2–1.7) (13–16), and longitudinal studies show elevated rates of subsequent depression and anxiety in young cannabis users, even after adjustment for baseline covariates. There is an urgent need to understand the effect of cannabis use and its discontinuation on symptoms of depression and anxiety, particularly in adolescents.

Randomized controlled trials of cannabis abstinence can help clarify the effect of cannabis on depression and anxiety symptoms. By randomizing cannabis users to a period of abstinence, we can examine the potential unique effect of cannabis abstinence on depression and anxiety symptoms regardless of an individual's baseline symptoms or motivations for substance use. Abstaining from other recreational drugs (alcohol, tobacco) is associated with clinically significant improvement in depression, anxiety, and perceived stress (17, 18). It is important to understand the impact of cannabis abstinence on these symptoms. Due to the similar symptomatology (e.g., amotivation, anhedonia) (19, 20), mechanisms (e.g., dysregulation of CB1 receptors) (21), and neurocircuitry (e.g., abnormalities in the reward structures and limbic system) (22–27) shared by cannabis use and mood disorders, it is anticipated that symptoms of anxiety and depression would fluctuate during cannabis abstinence as seen with other substances. The magnitude, direction, and duration of psychiatric symptom fluctuation is essential information for clinicians to inform the extent to which they should monitor depression and anxiety during an abstinence attempt or advise on mood and/or anxiety benefits associated with abstinence.

In this study, we randomized adolescent cannabis users to 4 weeks of either frequent monitoring with incentives provided for completion of assessments without requirement for abstinence (monitoring) or monetary incentives contingent upon continuous, biochemically verified cannabis abstinence (contingency management). Contingency management (CM) using financial incentives has been shown to reliably induce verified abstinence from many types of drugs, including cannabis (28–39). The goal of this study was to understand the effect of cannabis abstinence on depression and anxiety symptoms in youth who use cannabis at least weekly. Based on previous literature, we hypothesized that youth who discontinued frequent cannabis use would have a greater reduction in symptoms of depression and anxiety over 4 weeks of abstinence compared to youth who continued frequent cannabis use.

METHODS

Participants

Participants for the present study are part of an ongoing clinical trial examining the effects of cannabis abstinence on cognition (NCT03276221). Participants were recruited from the community as well as middle and high schools in the greater Boston area. Participants were non-treatment seeking, medically healthy, at least weekly cannabis users who were willing to abstain from cannabis use for 4 weeks. Additional eligibility criteria included English fluency and no history of severe developmental delays.

Procedures

Prior to beginning study procedures, written informed consent was obtained for all participants ages 18 years and older, and written parental consent and participant assent were obtained for participants under the age of 18 years. All study procedures were approved by the Partners Healthcare Human Subjects Committee. A detailed description of study procedures has been documented elsewhere (40–43). Briefly, at the baseline visit participants were randomized to 4 weeks of cannabis abstinence using an escalating financial incentive structure (contingency management; CB-Abst) or 4 weeks of monitoring with no abstinence requirement (CB-Mon). Randomization was stratified by sex (male or female), age (13–16 or 17 and older), and frequency of cannabis use (1 day per week or >1 day per week). CB-Abst and CB-Mon completed in person visits to verify abstinence at baseline and at an average of 2 days (visit 2), 3 days (visit 3), 1 week (visit 4), 2 weeks (visit 5), 3 weeks (visit 6) and 4 weeks (visit 7) after baseline. For these analyses, we evaluated data collected at baseline, and weeks one through four (visit 1 and 4–7).

Assessments

Anxiety and depression symptoms were assessed weekly using the Mood and Anxiety Symptom Questionnaire (MASQ) Short Form (44, 45) which has four subscales; general distress anxious symptoms (GDA), anxious arousal (AA), general distress depressive symptoms (GDD), and anhedonic depression (AD). Higher scores indicate greater severity of symptoms. Motives for cannabis use were assessed at baseline using the Marijuana Motives Measure (MMM) (46). Of the four subscales of the MMM, we focused on the coping motives subscale for the current study, which consists of five questions assessing the extent to which participants used cannabis to cope with negative emotions and experiences (e.g., "To forget my worries," "Because it helps me when I feel depressed or nervous"). Frequency of cannabis use over the past 90 days was assessed at baseline using a modified Timeline Follow-Back interview (47). The Cannabis Use Disorders Identification Test-Revised (CUDIT-R) was used to assess the severity of cannabis use at baseline (48). To examine differences in subjective experiences of withdrawal between groups, cannabis withdrawal symptoms were assessed at every visit in both the CB-Abst and CB-Mon groups using the intensity subscale of the Cannabis Withdrawal Scale [CWS-I; (49)].

Urine samples were collected at every visit from all participants and cannabis was assessed qualitatively, via immunoassay rapid dip drug test (RDDT; Medimpex United Inc.), and quantitatively, via liquid chromatography-tandem mass spectrometry (Dominion Diagnostics, North Kingstown, Rhode Island, USA). Self-reported cannabis abstinence was biochemically verified in the CB-Abst group by progressively decreasing concentrations of creatinine adjusted 11-nor-9-carboxy-Δ9-tetrahydrocannabinol [CN-THCCOOH, (50)].

Analytic Approach

Participants randomized to CB-Abst who did not meet abstinence criteria during the first week of the 4-week abstinence period were given the opportunity to recommit to abstinence and if subsequently successful were included in this study. Those that recommitted to abstinence but did not meet abstinence criteria after the first week of the 4-week abstinence period were excluded from the present study. Participants in the CB-Abst group who met abstinence criteria during the first week but not for the entire 4-week period were censored at the point of resumption of use. We compared the CB-Abst and CB-Mon groups on baseline characteristics using *t*-tests and chi-square tests as appropriate. To assess change in withdrawal, we computed change scores in CWS-I from baseline for each weekly time point. We tested the difference in CWS-I between groups using *t*-tests. For the primary analyses, examining change in MASQ scores by group, time was analyzed as a continuous measure representing days from baseline (date of randomization). Linear mixed effects models were used to test the effects of randomization group, time, and their interaction on the MASQ subscales in the full sample. We also explored effects in two subsets: one in those participants who endorsed frequently using cannabis to cope with negative emotions (MMM coping subscale score ≥ 3; $n = 40$) and one in participants with probable cannabis use disorder (CUDIT score $\geq$ 12; $n = 116$). Age, sex, Hispanic ethnicity, baseline CN-THCCOOH and baseline MASQ score were included as fixed effects covariates. Participant was included as a random effect on both the intercept and the time since baseline slope. All models were estimated with the lme4 package in R (version 4.0.2). Significance values were computed using the lmerTest package (51).

TABLE 1 | Participant characteristics by CB-Abst and CB-Mon groups.

Measure	CB-Abst	CB-Mon
N	101	78
Age	19.7 (2.0)	19.2 (2.3)
Sex - female	45 (44.6%)	35 (44.8%)
Race - nonwhite	33 (32.7%)	37 (47.4%)
Ethnicity – Hispanic*	9 (8.9%)	17 (21.8%)
Age of first cannabis use	15.4 (1.9)	15.4 (2.0)
Days per week of cannabis use	4.6 (2.0)	4.5 (2.2)
Baseline CN-THCCOOH*	150.2 (187.6)	294.6 (536.5)
Baseline CUDIT-R	14.0 (5.6)	13.6 (5.1)
Baseline CWS - I	33.6 (24.6)	30.3 (17.4)
Baseline MASQ – GDA*	19.7 (6.6)	17.4 (6.1)
Baseline MASQ - AA	24.8 (6.7)	24.3 (7.0)
Baseline MASQ – GDD*	23.1 (9.2)	19.9 (8.0)
Baseline MASQ - AD	58.7 (13.1)	56.3 (11.4)
Baseline MMM-Coping*	2.3 (1.0)	2.05 (0.8)

*For continuous measures numbers represent the mean (SD); for categorical measures numbers represent n (%). CUDIT, Cannabis Use Disorder Identification Test; CWS-I, Cannabis Withdrawal Scale - Intensity subscale; MASQ, Mood and Anxiety Symptoms Questionnaire; GDA, general distress anxious symptoms; AA, anxious arousal; GDD, general distress depression symptoms; AD, anhedonic depression; MMM, Marijuana Motives Measure. *$p < 0.05$.*

RESULTS

Participant Characteristics

See **Table 1** for descriptive statistics. There were no differences between the CB-Abst and CB-Mon groups except on number of Hispanic participants, baseline CN-THCCOOH, baseline MASQ-GDA, baseline MASQ-GDD, and baseline MMM-Coping scores. While the sample was ascertained from the community, 64.8% of participants reported CUDIT scores $\geq$12 at baseline, indicating a potential cannabis use disorder.

Abstinence Rates in CB-Abst Group

Of the participants randomized to the CB-Abst group ($n = 112$), 76.8% ($n = 86$) were abstinent for the full 4 weeks. Four participants resumed use within the first week of abstinence but per study protocol were allowed to recommit to abstinence and were successfully abstinent for the remainder of the study, totaling 90 participants with ∼4 weeks of abstinence (80%). Data from an additional 11 participants were censored from these analyses due to resumption of cannabis use between weeks one through four; three of whom used between weeks one and two, five of whom used between weeks two and three, and three of whom used between weeks three and four. Participants in the CB-Abst group who resumed cannabis use, withdrew consent or

were lost to follow up ($n = 22$) were more frequent cannabis users (5.5 days per week vs. 4.5 days per week, $p = 0.03$) and had significantly higher CUDIT scores (17.2 vs. 13.7, $p = 0.01$) than participants who remained in the study and remained abstinent ($n = 93$). Participants in the CB-Abst group who remained abstinent did not significantly differ on baseline MASQ scores from participants in the CB-Abst group who did not remain abstinent or were lost to follow up (p's > 0.18). None of the CB-Mon participants were voluntarily abstinent for the full 4 weeks. Comparing cannabis use at the baseline visit to the week four visit in the CB-Mon group, we found no significant change in the number of days they used (M = 0.02, sd = 2.3, $p = 0.95$) or the number of grams used per week (M = −0.54, sd = 5.6, $p = 0.45$) but a significant increase in the number of times/sessions per week they used (M = 1.99, sd = 6.6, $p = 0.02$). As demonstrated previously in this sample (42), urine metabolites decreased in the CB-Abst group and did not change in the CB-Mon group (see **Figure 1**).

Change in Withdrawal Over Time

CB-Abst had a greater change in CWS-I scores from baseline than CB-Mon 1 week after randomization (diff in means = 5.96, $p < 0.001$). There was no difference between groups in CWS-I change from baseline at 2, 3, and 4 weeks post randomization (p's > 0.09).

Change in Mood Symptoms During Abstinence

There was no significant main effect of age, sex, ethnicity, or baseline CN-THCCOOH levels in any of the models (p's > 0.27). There was a significant main effect of baseline symptoms for each MASQ subscale (GDA, AA, GDD, AD) (stnd beta = 0.65–0.72, all p's < 0.001), suggesting that baseline mood and anxiety symptoms predicted average mood and anxiety symptoms across all study visits. There was no main effect of randomization group on any of the MASQ subscales (p's > 0.46) during the study period, suggesting that overall anxiety and depression symptoms did not differ between CB-Abst and CB-Mon. There was a significant effect of days since baseline on MASQ-GDA (stnd beta = −0.11, $p = 0.003$), MASQ-AA (stnd beta = −0.08, $p = 0.01$), and MASQ-GDD (stnd beta = −0.08, $p = 0.02$), such that symptoms decreased over time on average across randomization groups. There was no interaction between randomization group and days since baseline on any of the MASQ subscales (p's > 0.12), suggesting changes in mood and anxiety symptoms did not significantly differ as a function of cannabis abstinence (see **Figure 2**).

Mood Changes Among Those Who Use Cannabis to Cope With Mood

With the exception of baseline symptoms (stnd beta = 0.44–0.79, p's < 0.001), no other covariates or randomization group were associated with MASQ scores in a subgroup of participants who endorsed using cannabis to cope with negative emotions on half or more of the times they used ($n = 40$; p's > 0.15). There was a significant main effect of days since baseline on MASQ-GDA (stnd beta = −0.17, $p = 0.02$), MASQ-GDD (stnd beta = −0.16, $p = 0.03$), and MASQ-AD (stnd beta = −0.24, $p = 0.006$), such that scores on these scales decreased over time on average across randomization groups. Within this subgroup, there was a trend toward an interaction effect of randomization group and days since baseline on MASQ-AD ($p = 0.056$), with greater declines in scores over time in the CB-Abst group compared to the CB-Mon group. There were no significant interaction effects on any of the other MASQ subscales (p's > 0.22).

Mood Changes Among Those With Problem Cannabis Use

In a subgroup of participants who reported baseline CUDIT scores ≥12 ($n = 116$), there was a significant main effect of baseline MASQ symptoms for each subscale (stnd beta = 0.64–0.74, p's < 0.001) and a significant main effect of days since baseline on MASQ-GDA (stnd beta = −0.17, $p = 0.0004$), MASQ-AA (stnd beta = −0.08, $p = 0.039$), and MASQ-GDD (stnd beta = −0.099, $p = 0.033$). None of the other covariates or randomization group were significantly associated with any MASQ subscale (p's > 0.21). Within this subgroup, there was a significant interaction effect of randomization group and days since baseline on MASQ-GDA ($p = 0.043$) and a trend toward an interaction effect of randomization group and days since baseline on MASQ-GDD ($p = 0.097$). For both subscales, there was a greater decrease over time in the CB-Abst group compared to the CB-Mon group.

DISCUSSION

In this study, we examined whether mood and anxiety symptoms changed during the 4 weeks following cannabis cessation among a non-clinical sample of adolescents with regular cannabis use. Given the growing number of youth that report using cannabis to cope with symptoms of anxiety and depression, it is important to understand whether mood improves or worsens with abstinence.

While we demonstrate a slight decrease in symptoms of anxiety and depression throughout the study period, this effect did not significantly differ between the abstinence and monitoring groups. This stability of mood is maintained despite increased cannabis withdrawal symptoms during the first week of abstinence. Cannabis withdrawal can include both physiological and psychological symptoms, with the most common symptoms being irritability/anger, nervousness or anxiety, decreased appetite or weight loss, restlessness, and sleep difficulties (52–54) and less common but still reported symptoms including depressed mood, stomach pain, shakiness, chills and sweating. With regard to the psychological symptoms, these onset within the first few days of abstinence and peak around 1 week from last use (52, 55). Additionally, adolescents show a lower prevalence and magnitude of withdrawal symptoms compared to adults (56). By assessing anxiety and depression symptoms for the first time at 1 week of abstinence, our study may have missed the peak of these symptoms caused by withdrawal. However, we see significantly greater withdrawal scores at 1 week after randomization in the abstinence group compared to the monitoring group but no increase in symptoms of anxiety and depression. This indicates that even if individuals experience

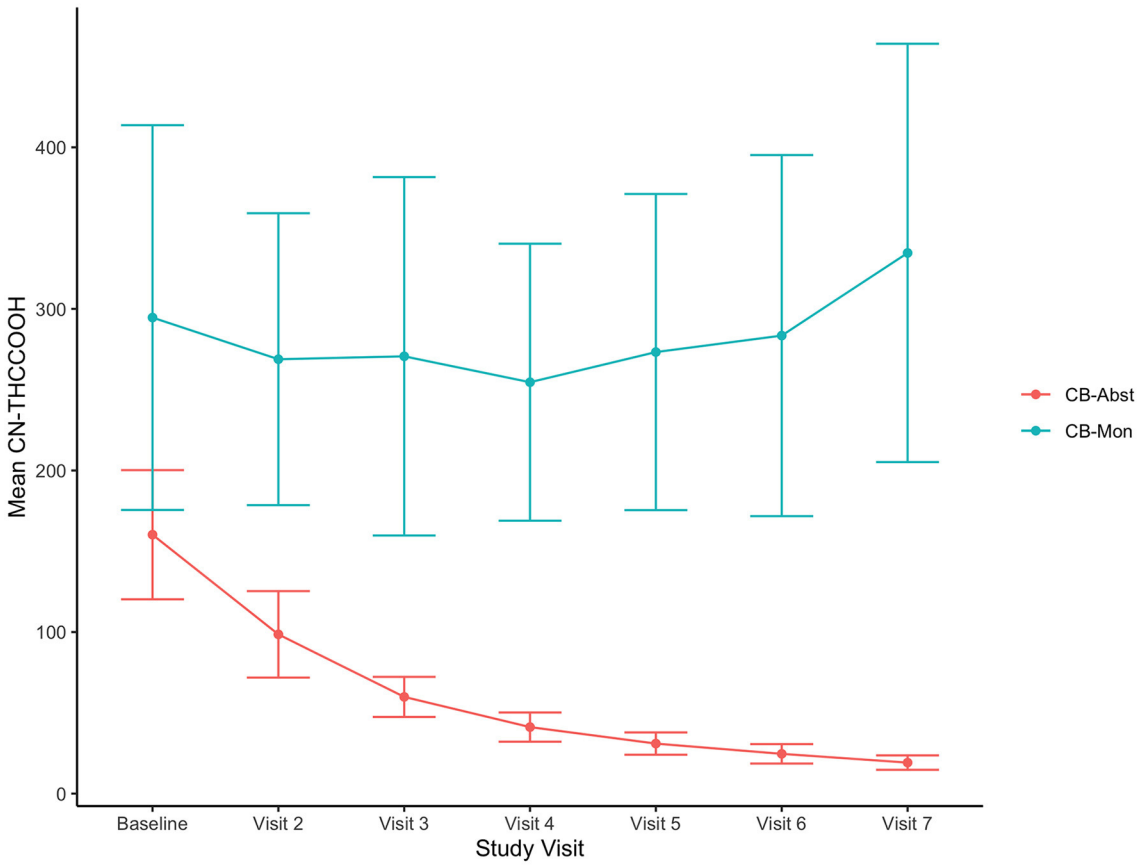

FIGURE 1 | Decreasing CN-THCCOOH concentrations in CB-Abst. Figure shows average urine creatine adjusted 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (CN-THCCOOH) concentration (ng/mL) and confidence intervals at each study visit for CB-Abst and CB-Mon groups.

increased depression and anxiety due to cannabis withdrawal it is likely to dissipate by the end of the first week of abstinence.

Our findings are interesting in light of the common perception among some youth cannabis users that cannabis helps treat anxiety and depression symptoms (7, 9). Mood disorders are a common reason that individuals seek medical marijuana (8). Individuals similarly use other substances, such as tobacco and alcohol, to cope with anxiety and depression. However, despite the alleviation of symptoms as a primary motive for use, cessation of use frequently benefits individuals. A definitive meta-analysis (18) reported that tobacco abstinence was associated with improved depression, anxiety, and stress, as well as positive mood and improved quality of life, with effect sizes equal to or larger than those of antidepressant medications. Other studies have shown that alcohol cessation is also associated with improved depressive symptoms (17). Again, this occurs despite self-report of people who claim that these substances improve mood and alleviate anxiety (17, 18). A previous study has shown a reduction in depression symptoms during cannabis abstinence in adults with comorbid cannabis use disorder and major depressive disorder (57). While the present study did not show improved mood symptoms after cannabis abstinence, the absence of worsening symptoms further demonstrates a conflict between people's motivations for substance use and their self-reported outcomes from cessation of use.

Our findings are in contrast to findings from Jacobus et al. (58) which demonstrate a significant reduction in depression scores but not anxiety in a group of non-treatment seeking adolescents undergoing a CM protocol, compared to a non-using control group. The current study differs from Jacobus et al. in several important ways. First, the sample size of the current study is significantly larger ($N = 179$ vs. 56). Second, the present study includes a control group of non-abstinent cannabis users who are following the same protocol (except the abstinence requirement) as the abstinent group. In the current study, we observe a decline in symptoms with abstinence, with an effect size similar to what was observed by Jacobus et al. (58); however, this change was also observed in a monitoring control group with no change in cannabis use. The decrease in symptoms over time in both the current study and the study by Jacobus et al. suggests that the effect may be better attributed to beneficial effects of participating in the study on mood symptoms and/or regression to the mean. Indeed, in Jacobus et al., there were baseline differences in mean depression scores, and it is possible that since the control group started with such low depression scores there is a floor effect such

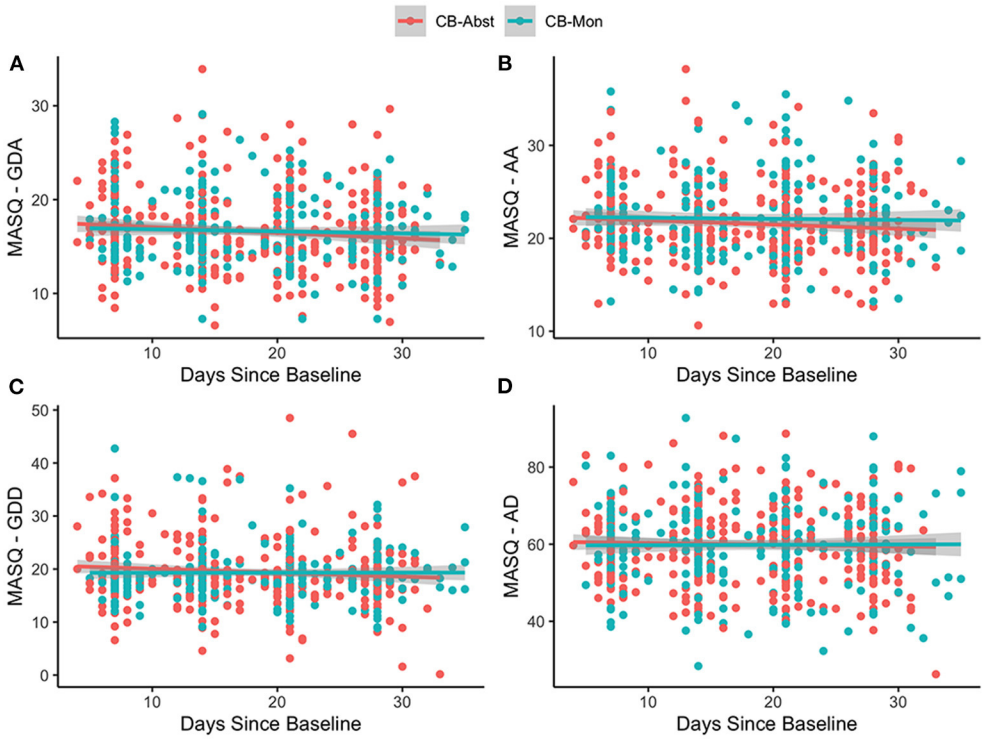

FIGURE 2 | MASQ scores by group over time. Figures show the individual observations of each MASQ subscale which have been adjusted for age, sex and baseline MASQ subscale as well as predictive slopes across time by randomization group; CB-Abst in coral and CB-Mon in teal. **Supplementary Figure 1** displays the mean group differences with confidence intervals between CB-Abst and CB-Mon by visit. **(A)** age: stnd beta = −0.03, $p = 0.58$, sex: stnd beta = 0.01, $p = 0.96$, ethnicity: stnd beta = 0.08, $p = 0.57$, baseline CN-THCCOOH: stnd beta = −0.01, $p = 0.81$, baseline MASQ-GDA: stnd beta = 0.65, $p < 0.001$, time: stnd beta = −0.11, $p = 0.003$, group: stnd beta = −0.02, $p = 0.86$, time by group interaction: stnd beta = 0.08, $p = 0.18$. **(B)** age: stnd beta = −0.04, $p = 0.41$, sex: stnd beta = 0.002, $p = 0.98$, ethnicity: stnd beta = 0.07, $p = 0.64$, baseline CN-THCCOOH: stnd beta = −0.006, $p = 0.91$, baseline MASQ-AA: stnd beta = 0.72, $p < 0.001$, time: stnd beta = −0.08, $p = 0.01$, group: stnd beta = 0.07, $p = 0.51$, time by group interaction: stnd beta = 0.07, $p = 0.20$. **(C)** age: stnd beta = −0.01, $p = 0.84$, sex: stnd beta = 0.11, $p = 0.27$, ethnicity: stnd beta = 0.04, $p = 0.75$, baseline CN-THCCOOH: stnd beta = 0.01, $p = 0.84$, baseline MASQ-GDD: stnd beta = 0.66, $p < 0.001$, time: stnd beta = −0.08, $p = 0.02$, group: stnd beta = −0.07, $p = 0.46$, time by group interaction: stnd beta = 0.08, $p = 0.12$. **(D)** age: stnd beta = −0.05, $p = 0.36$, sex: stnd beta = −0.03 $p = 0.73$, ethnicity: stnd beta = 0.13, $p = 0.32$, baseline CN-THCCOOH: stnd beta = 0.01, $p = 0.84$, baseline MASQ-AD: stnd beta = 0.69, $p < 0.001$, time: stnd beta = −0.03, $p = 0.34$, group: stnd beta = −0.04, $p = 0.72$, time by group interaction: stnd beta = 0.03, $p = 0.53$.

that the control group had no room to similarly decrease in their depression scores as a function of participating in the study.

While the present study is strengthened by the experimental design, randomization to abstinence, and larger sample size over previous work, the findings of this study should be viewed in the context of several limitations. First, the participants were youth engaging in recreational cannabis use and were willing and able to cease use for 4 weeks. Additionally, participants who were unable to maintain abstinence or withdrew from the study were more frequent and more severe cannabis users. Therefore, these findings may not generalize to individuals who are unable or unwilling to remain abstinent from cannabis or who are using cannabis for medical/medicinal use rather than recreational use. We were also unable to test the relative concentrations of THC or CBD in the products participants were using. It is possible that differing concentrations could have an effect on mood symptoms during abstinence. Another limitation is that mood symptoms were only assessed at weekly time points after abstinence. Since the cannabis withdrawal syndrome can begin as early as 1–2 days post-cessation and peaks around 1 week (53), we may have only caught the tail end of the period where mood symptoms are at their worst in response to withdrawal. Relatedly, we do not know the effects of longer periods of abstinence on anxiety and depression symptoms. It may take 30 days or more for cannabinoids to leave the system (41) and therefore residual cannabinoids may still be impacting the central nervous system in our current study. Finally, symptoms of anxiety and depression were assessed through self-report. It is possible that any potential level of change in these symptoms may have been too subtle for the individual to notice or that they exhibited a response bias as they were not blinded to treatment. Therefore, future studies should include clinician ratings of anxiety and depression symptoms.

In conclusion, we show that despite the common motive among adolescents of using cannabis to address mood symptoms, cannabis abstinence may not have a detrimental effect on symptoms of depression and anxiety, and may even be beneficial among adolescents who specifically report using cannabis to

cope or have severe levels of use. Findings may be relevant to messaging to youth reluctant to abstain due to concerns of mood worsening. In contrast to some previous studies we do not show an significant improvement of symptoms as a function of abstinence (58, 59). This likely due to our inclusion of a matched control group of cannabis users which served to model normative fluctuations in mood within this population which further emphasizes the importance of including such control groups in experimental designs of adolescent cannabis use. Future studies will be needed to further explore the extent to which these findings translate to key subgroups, such as those with psychiatric diagnoses (cannabis use disorder, major depressive disorder, etc), and examine the effect of longer abstinence periods on these effects.

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 Institutional Review Board at Massachusetts General Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RS, AE, and JG contributed to the conceptualization and design of the original study. RS, JG, BT-C, and MC designed the current research question and data analyses. EL and NR were responsible for data collection. MC, BT-C, EL, and NR organized and cleaned the data. MC performed the statistical analysis and wrote the first draft of the manuscript. RS, JG, BT-C, and AE wrote sections of the manuscript. RS 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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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.689957/full#supplementary-material

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SYSTEMATIC REVIEW
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The Impact of THC and CBD in Schizophrenia: A Systematic Review

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Background: People with schizophrenia are more likely to develop cannabis use disorder (CUD) and experience worse outcomes with use. Yet as cannabis is legalized for medical and recreational use, there is interest in its therapeutic potential.

Objectives: To conduct a systematic review summarizing the design and results of controlled trials using defined doses of THC and CBD in schizophrenia.

Method: A keyword search of eight online literature databases identified 11 eligible reports.

Results: One placebo controlled trial (13 stable patients without CUD) found that intravenous THC increased psychosis and worsened learning/recall. Two reports of a functional magnetic resonance (fMRI) study of smoked or oral THC in 12 abstinent patients with schizophrenia and CUD found no change in symptoms and cognition, and an amelioration of impaired resting state brain function in areas implicated in reward function and the default mode network. One 4 week trial in acutely psychotic inpatients without CUD (mean age 30 y) found 800 mg CBD to be similarly efficacious to amisupride in improving psychosis and cognition. Two 6 week studies of CBD augmentation of antipsychotics in stable outpatients reported mixed results: CBD 600 mg was not more effective than placebo; CBD 1,000 mg reduced symptoms in a sample that did not exclude cannabis use and CUD. A brain fMRI and proton magnetic resonance spectroscopy study of single dose CBD in a sample that did not exclude CUD and cannabis use found that CBD improved symptoms and brain function during a learning/recall task and was associated with increased hippocampal glutamate.

Discussion: There is substantial heterogeneity across studies in dose, method of drug delivery, length of treatment, patient age, whether patients with cannabis use/CUD were included or excluded, and whether patients were using antipsychotic medication.

Conclusion: There is insufficient evidence for an effect of THC or CBD on symptoms, cognition, and neuroimaging measures of brain function in schizophrenia. At this

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time, research does not support recommending medical cannabis (THC or CBD) for treating patients with schizophrenia. Further research should examine THC and CBD in schizophrenia with and without comorbid CUD and consider the role of CBD in mitigating symptom exacerbation from THC.

Keywords: cannabis, marijuana, Schizophrenia, psychosis, CBD, THC, legalization, fMRI

INTRODUCTION

Schizophrenia is a chronic neurodevelopmental disorder experienced by 0.5 to 1.0% of the population worldwide (1, 2). This condition typically begins in late adolescence or early adulthood and includes positive symptoms, such as hallucinations, and negative symptoms, such as avolition. Cognitive impairments, such as with attention and working memory, are core features of schizophrenia, and an impaired ability to anticipate reward has also been documented (3). Significant anxiety is common, though not a core symptom of schizophrenia (4, 5). Co-occurring substance use disorders are more common in people with schizophrenia than the general population, and cannabis is the most common illicit drug used by people with this condition (6–9). Up to 43% of people with schizophrenia develop a cannabis use disorder (CUD) (10–13) compared to 6.3% in the general population (14).

Interestingly, epidemiological studies have demonstrated that heavy cannabis use in early adolescence is associated with an increased risk for the development of new psychotic symptoms and schizophrenia-spectrum disorders (15–19). A dose-response relationship has been observed, with a higher incidence of schizophrenia found in heavy cannabis users compared to light or non-users (17). Additionally, among people who have an established schizophrenia spectrum disorder, observational studies have shown that recreational use of cannabis and cannabis use disorder are associated with worse symptoms and course of illness (20–23). As we will further delineate below, examining the effects of both THC and CBD, alone and together, may help the field better understand the mechanism of action of the effects of cannabis, the pathophysiology of schizophrenia, and whether there is any therapeutic role for these cannabis components in people with schizophrenia both with and without cannabis use disorders.

Cannabis is a genus of plants with several species containing over 100 types of cannabinoids. Species are bred to promote varying levels of cannabinoids, especially (–)-*trans*-Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which have differing effects. THC is responsible for the intoxicating "high" of cannabis and is likely a component of cannabis that is responsible for the development of CUD in about 10% of users [for review, see (24)]. In contrast, CBD does not appear to cause intoxication, nor is it reinforcing (25, 26).

Controlled laboratory studies in healthy participants have demonstrated that THC administration results in acute psychotic symptoms and transient dose-related cognitive impairments, including in working memory and the executive control of attention, in up to 50% of healthy individuals (27), and for review, see (28). Some studies show a dose effect for psychosis [e.g., (27)]. Pre-treatment with CBD has been shown to mitigate such THC-induced symptoms and impairments (29–32), but not the positive and reinforcing effects (26). Notably, the THC content in typical street cannabis has risen from ∼4% in 1995 to ∼12% in 2014 (33), and the proportion of CBD to THC has diminished to almost zero in many strains, although high CBD strains are also available (34). THC and CBD are used to create a variety of high potency products for sale especially in locales where medicinal and recreational cannabis is legal. Thus, easily available high-THC recreational cannabis has strong potential to cause negative effects.

Although use of recreational cannabis (assumed to be high in THC and low in CBD) has been associated with worse outcomes in schizophrenia, several case reports suggested that CBD itself might be beneficial in the treatment of psychosis (35, 36). A more recent cross-sectional report indicated that use of cannabis with high CBD content was associated with significantly lower psychotic symptoms in patients with schizophrenia (32). Research using animal models examining CBD's anti-psychotic-like properties determined that CBD leads to behavioral responses similar to responses to an atypical antipsychotic drug (35), contributing to interest in testing CBD for its ability to improve symptoms in patients with schizophrenia.

As Canada and parts of the U.S. have legalized cannabis for recreational (16 states as of 2021) or medical (12 states as of 2021) purposes (37), the production and sales of cannabis have skyrocketed and the public increasingly perceives cannabis as helpful rather than harmful. Recent surveys showed that almost half of Americans indicated they believed that cannabis may provide relief from anxiety and depression (38). Thus, in locales where cannabis is legal for recreational or medical use, many people seek cannabis to address mental health issues. For example, in one U.S. report, over a third of people who used medical cannabis reported using it to reduce anxiety (39), and several Canadian studies reported that cannabis was widely used to treat anxiety, depression, and sleep (40, 41), symptoms common across an array of mental health conditions, including psychotic disorders (42).

Thus, as stakeholders are increasingly interested in the possible therapeutic effects of cannabis, they need reliable information about the effects of THC and CBD, particularly among vulnerable populations such as people with schizophrenia. Several prior reviews have addressed the effects of THC or CBD in people with schizophrenia (43–50). We sought to provide an updated review, as well as detailed and critical review of the literature including studies of both CBD and THC considered together, as well as a critical review of the research

methods, quality of the research, and directness of evidence for each study (51), focusing on randomized controlled trials (RCTs), as they provide the highest level of evidence. This review therefore provides a review of the evidence of the potential benefits and harms of THC and/or CBD in schizophrenia to date. We conducted a systematic review of published prospective, controlled studies testing the impact of THC and/or CBD on symptoms, cognition, and neuroimaging measures of brain function in people with schizophrenia-spectrum disorders.

METHODOLOGY

Information Source and Search

Literature searches using PubMed/MEDLINE, PsycINFO, PsycARTICLES, CINAHL, EMBASE, Scopus, Cochrane, and Academic One File were conducted for English-language papers published between January 1st, 1970, and June 15, 2021. Search terms included: "cannabidiol AND schizo*"; "cannabidiol AND psycho*"; "CBD AND schizo*"; "CBD AND psycho*"; "tetrahydrocannabinol AND schizo*"; "tetrahydrocannabinol AND psycho*"; "THC AND schizo*"; "THC AND psycho*." In addition, we examined recent peer-reviewed scientific reviews of the literature on cannabinoids and psychosis, as well as reference sections of papers garnered from the online literature search, for any other relevant articles.

Inclusion and Exclusion Criteria

All studies reporting prospective RCTs testing specific doses of whole-plant cannabis, CBD, THC, or both compounds compared with placebo or control condition with standardized assessments of symptoms of psychosis, cognition, and/or neuroimaging in humans with schizophrenia spectrum disorders were considered. Any commercially available or synthetic THC or CBD formulation was accepted, as well as any route of administration for any period of time. Age, sex, and race/ethnicity were not included in the selection criteria. We excluded cross-sectional studies, observational studies without a control condition, studies examining cannabis that did not use a specified dose of THC and/or CBD, CBD used for psychiatric illnesses other than schizophrenia, papers not written in English; studies not reporting original research, and studies with participants less three.

Assessment of Study Quality

Once studies were selected, we conducted an assessment of study quality using a checklist for the "grading of recommendation, assessment, development, and evaluation (GRADE" approach (51). The GRADE is a widely used, transparent classification system for rating research quality and developing evidence summaries that provides a systematic approach for making clinical practice recommendations (52–54). We used two categories: study quality/risk of bias and directness/indirectness of evidence.

RESULTS

Study Selection

The initial search yielded 6,003 reports. After removing duplicates, studies were screened base on titles, resulting in the inclusion of 722 citations. Abstracts were then screened, which resulted in exclusion of 512 citations. The remaining papers (235) were reviewed for eligibility by two authors (C.N.S. and S.A.). Any disagreements were mediated by a third reviewer (MB). A total of 226 papers did not fit the inclusion criteria, resulting in 11 full-text articles that met inclusion criteria. The selection steps are shown in **Figure 1**.

Study Characteristics

Table 1 provides the characteristics of the nine prospective, placebo-controlled studies of cannabis, CBD and/or THC. These studies were published between 2005 and 2021 and employed a variety of methods, which are described in the table and below.

Characteristics of CBD Studies

Four RCTs (reported in six papers) met inclusion/exclusion criteria. Three were longitudinal treatment studies that were 4 to 6 weeks in duration (59, 61, 62), and one was a single dose laboratory study reported in two papers that used functional magnetic resonance imaging (fMRI) (63) and proton magnetic resonance spectroscopy (^{1}H-MRS) (64). We also included one single session, non-randomized, balanced trial assessing cognition (58) and a placebo-controlled cross-over treatment case series of three patients (35). Four of these RCTs assessed CBD vs. placebo for antipsychotic augmentation (58, 61–64), while another compared CBD to amisulpride in acutely ill patients off antipsychotics for at least 3 days, which was reported in two papers (59, 60).

A total of 152 stable outpatients and 45 acutely psychotic inpatients with schizophrenia schizophreniform, or brief psychotic disorder were examined. Sample sizes ranged from 15 (63) to 28 (58) in the single dose laboratory studies, and 36 to 88 in the longitudinal clinical trials (59, 61, 62). The CBD studies had heterogeneous study samples and study designs, which are reviewed below.

Regarding demographics, several studies had young adult samples with mean age under 30 (35, 59, 60, 63, 64) and two trials reported mean patient age in the 40s. The majority of participants (58–89%) were male. While the majority of participants identified as White/Caucasian in two studies (61, 62), the other four papers did not provide the race/ethnicity of their samples.

Two studies enrolled outpatients on medication who had chronic illness (58, 61, 62), one enrolled patients on medication who were within 5 years of illness onset (63, 64). Two studies involved chronic patients who were acutely psychotic inpatients at the time of participation (35, 59, 60), and these patients initiated the trial off antipsychotic medication. One study appears to have included a mixed sample of outpatients on or off antipsychotic medications (58).

Three studies excluded participants with cannabis, alcohol, and other substance use or substance use disorders (58–61), but only one used urine drug screens as verification in this process

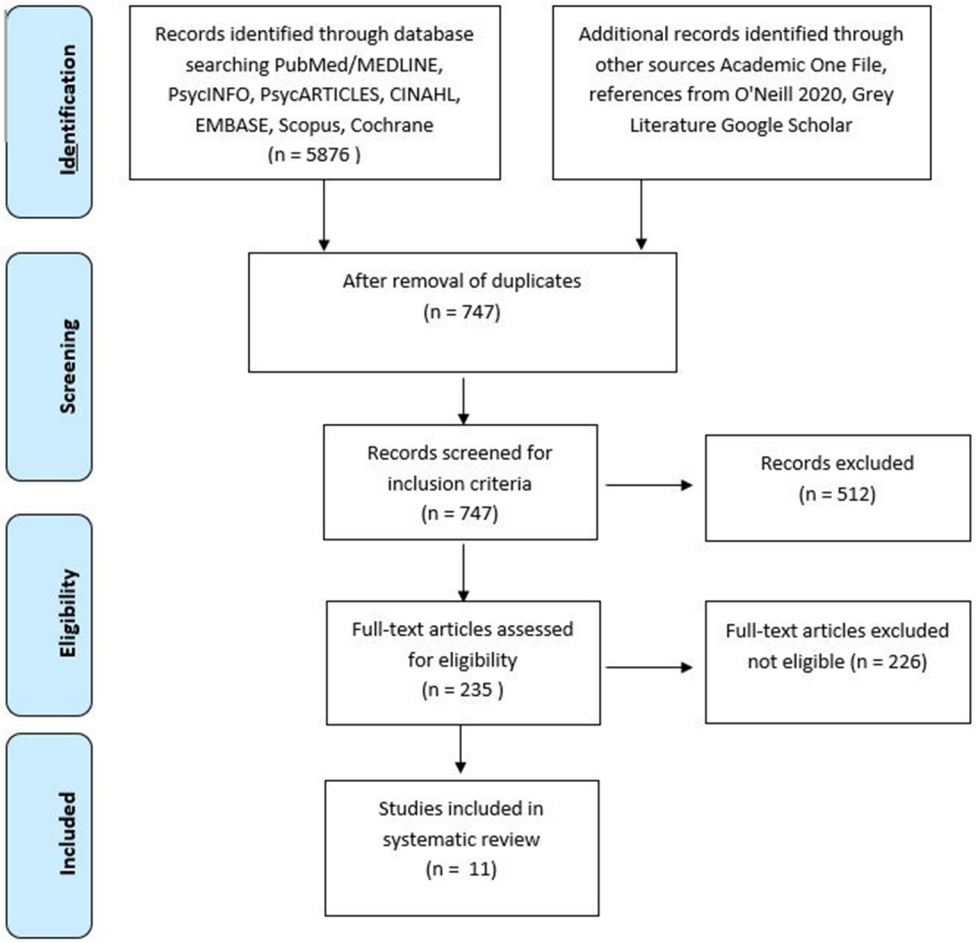

FIGURE 1 | Flow diagram.

(59). Two studies allowed cannabis use during the trial (62–64). One of these two studies excluded patients meeting criteria for current diagnosis of alcohol or substance dependence or positive drug screen, but allowed current CUD and cannabis use before and during the trial (63, 64). One study did not exclude those with an alcohol or substance use disorder history, and use of all substances was permitted during the trial (62). The case series provided no information pertaining to the inclusion/exclusion of those with a history of alcohol or substance use disorder (35). Nicotine use was generally not excluded, but only one study reported on smoking status (61).

The dose and duration of CBD treatment varied widely across studies. CBD dose ranged from 300 mg to 1,280 mg/day. Three RCTs and the case series provided daily doses over 4 to 6 weeks (35, 59–62). Two administered a single dose (58, 63, 64).

Outcome measures included symptoms, side effects, cognition, ^{1}H-MRS, and brain activation as measured using fMRI. Clinical symptoms were most commonly assessed using the Brief Psychiatric Rating Scale [BPRS (65)] and Positive and Negative Symptom Scale [PANSS (66)]. CBD effects on clinical symptoms was reported by five studies (35, 59, 61–63). Side effects were assessed in these same five studies. Motor side effects were commonly assessed using measures such as the Barnes Akathisia Scale [BAS (67)], Simpson Angus Scale [SAS (68)], and the Abnormal Involuntary Movements Scale [AIMS (69)]. Cognition was assessed in five studies (58, 60–63) with a variety of measures, and three included laboratory tests (59, 60, 62, 63). One study evaluated the effects of CBD on a fMRI activation during a verbal learning and memory task (63) and ^{1}H-MRS to measure left hippocampal glutamate levels (64). A variety of other measures were occasionally used, such as weight (59, 62) and skin conductance (58).

Characteristics of THC Studies

Only three publications report on the effects of THC among patients with schizophrenia (55–57); two examining different data analyses from the same trial (56, 57). These studies included a total of 25 stable, medicated outpatients with chronic schizophrenia, mean age of patients 32.2 (57) and 44.5 (55). The proportion of men ranged from 58.3% (56, 57) to 76.9%

TABLE 1 | Methods and results of studies of CBD and THC in the treatment of Schizophrenia.

References	Participants	Design	Substance use criteria	Primary outcome measures	Findings	Symptom scores
Studies of THC						
D'Souza et al. (55)	13 medicated outpatients with SCZ or SCZAF (DSM-IV), mean age 44.46 ± 10.4, 76.9% male. 22 HC, mean age = 29 ± 11.6, 63.6% male	RCT double blind, repeated-measures (at least 1 week apart), within-subject cross-over design of single dose intravenous Δ-9-THC 2.5 mg, 5 mg, or PLB	Excluded Lifetime CUD or recent substance abuse (3 m) or dependence (1 yr), other than nicotine. Abstain from all substances, verified via self-report and urine drug screen	Symptoms: PANSS, CADSS, VAS (high, calm and relaxed, tired, panic) Cognitive: HVLT, Gordon CPT, verbal (letter) fluency test Side effects: BAS, SAS, AIMS	THC worsened: verbal learning and recall; positive symptoms; more prominently for patient group; negative symptoms; clinician- and self-related perceptual alterations THC resulted in a trend toward increased VAS ratings of "panic" and "tired" and rigidity, worse AIMS score and akathisia, and increased plasma prolactin and cortisol	PANSS Total, screening: 34.1 ± 9.4 Post THC scores not provided
Fischer et al. (56)	12 medicated outpatients with SCZ and CUD (DSM-IV-TR), mean age [smoked cannabis 36.2 ± 9.6; THC capsule 32.17 ± 8.32, male), 583% male 12 HC, mean age 33.5 ± 7.8, 75% male	RCT double blind, parallel group study of smoked 3.6% THC cannabis cigarette immediately prior to scan ($n = 6$), or 15 mg THC capsule 3 h prior to scan ($n = 6$) Two scan sessions (T1, no drug; T2, drug) at least 1 week apart	Required to have a CUD and recent cannabis use. Excluded other substance use disorders. Abstain from all substances, except nicotine and caffeine >7 days prior to scan verified via TLFB, urine screens, plasma THC	Symptoms: PANSS, VAS (high, liking and craving), CWS, MCQ Imaging: fMRI resting state functional connectivity of BRC	Reduced connectivity at BL in patients between nucleus accumbens and prefrontal cortical BRC regions (i.e., anterior prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex). Both oral and smoked THC incr connectivity between these regions, which correlated with incr in plasma THC levels	No change after THC (PANSS scores not reported)
Whitfield-Gabrieli et al. (57)	Same as Fischer et al. (56)	Same as Fischer et al. (56)	Same as Fischer et al. (56)	Symptoms: PANSS, VAS (high, liking and craving), CWS, MCQ Cognition: LNS Imaging: fMRI resting state functional connectivity of DMN	At BL, patients had DMN hyperconnectivity that correlated with positive symptoms, and reduced anticorrelation between DMN and ECN. THC reduced DMN hyperconnectivity and increased DMN-ECN anticorrelation. The magnitude of anticorrelation in controls, and in patients after THC, correlated with working memory)	PANSS Positive Score BL—T1 (13.82 ± 3.19) or Pre-drug—T2 (12.91 ± 3.21) No change after THC (PANSS scores not provided separately from smoked cannabis and oral THC and not reported for T2 after THC)
Studies of CBD						
Zuardi et al. (35)	3 unmedicated inpatients with treatment-resistant SCZ (DSM-IV), age 21–22 years, all male	Case Series of 6 week CBD titration up to 1,280 mg/day, PLB lead in and washout, then switch to olanzapine	None reported	Symptoms: BPRS, PANSS-N Functional: CGI Side effects: BAS, SAS, UKU Side effect Rating Scale	CBD 1,280 mg/day associated with: Pt 1—trend toward improved BPRS (general, positive, and negative symptoms); Pt 2—no benefit; Pt 3—"very minimal improvement" of positive and negative symptoms In two patients, symptoms worsened after CBD discontinued. No side effects reported	*BPRS Total*: Patient 1: PLB 19, CBD 10 Patient 2; PLB 30, CBD 28 Patients 3: PLB 29, CBD 26 PANSS-N scores not reported

(Continued)

TABLE 1 | Continued

References	Participants	Design	Substance use Criteria	Primary outcome measures	Findings	Symptom scores
Hallak et al. (58)	28 outpatients with SCZ (DSM-IV), all BPRS scale scores <2, at least 18 years of age, 64.3% male	Single dose non-randomized, double blind, parallel group study of CBD augmentation 300 mg ($n = 9$) or 600 mg ($n = 9$) or PLB ($n = 9$)	History of substance abuse or adverse reaction to marijuana were excluded	Symptoms: BPRS, PANSS Cognition: SCWT Other: electrodermal responsiveness	PLB and 300 mg CBD: less SCWT interference errors during 2nd session, but only a trend for 600 mg CBD group, indicating worse selective attention No group differences in electrodermal responsiveness or symptoms, but no analysis of within-group symptom change reported	*BPRS Total*: PLB: BL 8.6 ± 4.1, drug 7.9 ± 5.76 CBD 300 mg: BL 11.3 ± 7, drug 10.9 ± 6; CBD 600 mg: BL 8.9 ± 5.1, drug 8.2 ± 5.9 *PANSS Total*: PLB: BL 21.9 ± 6.9, drug 21.9 ± 7.2; CBD 300 mg: BL 23.6 ± 9.4, drug 23.4 ± 9.6 CBD 600 mg: BL 20.2 ± 7.7, drug 19.1 ± 7.0
Leweke et al. (59)	42 acutely ill unmedicated inpatients with SCZ (DSM-IV), BPRS Total ≥ 36 and BPRS THOT ≥ 12, 18–50 years of age [CBD mean 29.7 ± 8.3 yr, amisulpride mean 30.6 ± 9.4 yr, 82.1% male	4 week RCT, double blind, parallel group study of CBD augmentation 800 mg ($n = 20$) or amisulpride 800 mg ($n = 19$), 1 week titration and 3 weeks treatment (modified intent-to-treat)	History of SUD or positive urine drug screen (including cannabinoids) were excluded	Symptoms: BPRS, PANSS Functional: CGI Side effects: SAS, EPS	BPRS and PANSS (total, positive, negative, general scores) improved over time in both groups. CBD group had less: extrapyramidal symptoms, weight gain, and prolactin elevation Serum anandamide levels were higher in CBD than amisulpride group, with extent of increase associated with PANSS Total score improvement	PANSS Total Scores CBD score at BL 91.2 (14.0) Changed-−18.8 (10.7) on day 14, −30.5 (16.4) on day 28 Amisulpride score at BL 95.9 (17.1) Changed-−18.8 (19.9) on day 14 −30.1 (24.7) day 28
Leweke et al. (60)	Same participants as above 42 acutely ill unmedicated inpatients with SCZ (DSM-IV), BPRS Total ≥ 36 and BPRS THOT ≥ 12, 18–50 years of age [CBD mean 29.7 ± 8.3 yr, amisulpride mean 30.6 ± 9.4 yr, 82.1% Male	Same as above 4 week RCT, double blind, parallel group study of CBD augmentation 800 mg ($n = 20$) or amisulpride 800 mg ($n = 19$), 1 week titration and 3 weeks treatment (modified intent-to-treat)	Same as above History of SUD or positive urine drug screen (including cannabinoids)	Symptoms: BPRS, PANSS Functional: CGI Cognition: Visual Backward Masking Task, CPT, LNS, SOPT, DRT, AVLT, RCFT, Digit Symbol, TMT, Verbal Fluency Task	From pre- to post-treatment, both groups improved in visual memory, processing speed CBD improved sustained attention and visuomotor coordination Amisulpride improved working memory performance Changes in neurocognitive performance were not systematically associated with symptom improvements nor change in serum anandamide	Differences in cognitive improvement not statistically significant after correction for multiple tests Visual memory (CBD: 0.49, $p = 0.015$ vs. AMI: 0.63, $p = 0.018$); processing speed (CBD: 0.41, $p = 0.004$ vs. AMI: 0.57, $p = 0.023$). Sustained attention (CBD: 0.47, $p = 0.013$ vs. AMI: 0.52, $p = 0.085$); visuomotor coordination (CBD: 0.32, $p = 0.010$ vs. AMI: 0.63, $p = 0.088$). SOPT–AMI: 0.53, $p = 0.043$ vs. CBD: 0.03, $p = 0.932$ and LNS–AMI: 0.67, $p = 0.017$ vs. CBD: 0.08 $p = 0.755$)

(Continued)

TABLE 1 | Continued

References	Participants	Design	Substance use criteria	Primary outcome measures	Findings	Symptom scores
Boggs et al. (61)	36 medicated outpatients with SCZ (DSM-IV-TR), 18–65 years of age [CBD mean 48.4 ± 9.3; PLB mean 46.4 ± 9.5], 66.7% to 72.2% male	6 week RCT, double blind, parallel group study of CBD augmentation 300 mg twice daily ($n = 20$) or PLB ($n = 19$)	Diagnosis of substance abuse within 3 months or dependence within 6 months of participation (other than nicotine) were excluded	Symptoms: PANSS Cognition: MCCB Side effects: BAS, SAS, AIMS, UKU Side Effect Rating Scale	No difference in reduction in PANSS scores (Total, General, Positive, Negative) over time. PLB but not CBD group had small improvement on MCCB (Composite score, Reasoning and Problem Solving domain scores). CBD group had greater sedation compared to PLB	*PANSS screening visit scores*: *Total*: CBD 76.6 ± 17, PLB 82.7 ± 8.8 *Positive*: CBD 18.8 ± 4.7, PLB 20.6 ± 3.8 *Negative*: 20.7 ± 4.6, PLB 20.9 ± 4.7 *General*: 37.1 ± 10.3, PLB 41.2 ± 5.6
McGuire et al. (62)	88 medicated outpatients with SCZ or related psychotic disorder (DSM-IV), PANSS score < 60 at screening excluded, 18–65 years of age (mean 40.8 ± 11.69), 58% male	6 week RCT, double blind, parallel group study of CBD augmentation 500 mg BID ($n = 43$) or PLB ($n = 45$)	Alcohol or substance use history allowed; use of alcohol, cannabis or other substances not prohibited during study; positive baseline urine THC test in 1 CBD and 2 PLB group patients	Symptoms: PANSS, SANS Functional: GAF, CGI-I, CGI-S Cognition: BACS Side effects: SAS	CBD group had greater reduction of positive symptoms and more likely to be rated by treating clinician as having improved and have less severe illness than PCB. CBD showed trend for greater improvement in overall level of functioning, cognition (BACS composite score and executive function domain), and motor speed. No group difference for adverse events or side effects	*PANSS Total*: CBD: BL 79.3 ± 12.5, end of Tx 68.1 ± 14.8 PLB: BL 80.6 ± 14.9, end of Tx 71.9 ± 15.5 *PANSS Positive*: CBD: BL 18.0 ± 3.9, end of Tx 14.8 ± 4.0; PLB: BL 17.5 ± 3.3, end of Tx 15.7 ± 3.7
O'Neill et al. (63)	15 outpatients (14 medicated) with SZ, SCZAF, or Brief Psychotic Disorder (DSM-IV) within 5 years of diagnosis, mean age 27.73 ± 4.61 years, 66.7% male 19 HC, mean age 23.89 ± 4.15 years, 57.9% male	RCT double blind, repeated-measures (1 week apart), within-subject cross-over design of single dose 600 mg oral CBD or PLB	Allowed: current cannabis abuse, dependence, or use Excluded: Current alcohol or substance dependence; or intoxicated or positive urine drug screen on the day of scanning. No alcohol for 24 h or caffeine for 12 h before sessions. No drugs except cannabis for 2 weeks prior to scan	Symptoms: PANNS, STAI-S Imaging: fMRI verbal paired associate learning task completed 3 h after CBD or PLB (13 patients completed both scans)	CBD associated with trend toward reduced median PANSS Total. Compared to HC, patients on PLB had abnormal activation within prefrontal region during verbal encoding, and abnormal prefrontal and mediotemporal activation as well as greater hippocampal-striatal functional connectivity during recall. CBD resulted in partial normalization of activation in these regions, as well as reducing hippocampal-striatal hyperconnectivity	PANSS Total: PLB: T1 48.8 ± 18.9, T3 44.6 ± 18.07 CBD: T1 51 ± 20, T3 41.53 ± 11 *PANSS Positive*: PLB: T1 12.53 ± 5.62, T3 11.67 ± 4.99 CBD: T1 12.93 ± 5.72, T3 10.73 ± 3.41 *PANSS Negative*: PLB: T1 12.4 ± 6.4, T3 11.53 ± 6.06 CBD: T1 12.47 ± 6.56, T3 10.2 ± 3.05 Note: T1 is 60 min pre-drug and T3 270 min post-drug administration

(Continued)

TABLE 1 | Continued

References	Participants	Design	Substance use criteria	Primary outcome measures	Findings	Symptom scores
O'Neill et al. (64)	Same participants as above 15 outpatients (14 medicated, 1 non-compliant) with SZ, SCZAF, or Brief Psychotic Disorder (DSM-IV) within 5 years of diagnosis, Mean age 27.73 (4.61, 66.7% male)	Same as above Double-blind, randomized, placebo-controlled, repeated-measures (1 week apart) within-subject cross-over design 600 mg oral CBD or PLB	Same as above Allowed: current cannabis abuse, dependence or use	Symptoms: PANSS Imaging: ^{1}H-MRS spectra were acquired 180 min after CBD or PLB administration (13 patients completed both scans)	CBD associated with greater improvement in PANSS Total and greater hippocampal glutamate levels compared to PLB ($p = 0.035$). An adjusted multivariable model showed an inverse predictive relationships between hippocampal glutamate and post intervention PANSS ($p = 0.047$), but no relationship to CBD group	PANSS symptom scores Same as above

AIMS, Abnormal Involuntary Movements Scale; AMI, amisulpride; AVLT, Auditory-Verbal Learning Test; BACS, Brief Assessment of Cognition in Schizophrenia; BAS, Barnes Akathisia Scale; BPRS, Brief Psychiatric Rating Scale; BPRS THOT, BPRSD Thought Disorder factor; BRC, Brain Reward Circuit; CADSS, Clinician-Administered Dissociative States Scale; CIWS, Cannabis Withdrawal Scale; CBD, cannabidiol; CGI, Clinical Global Impressions Scale; CGI-I, Clinical Global Impression-Improvement scale; CGI-S, Clinical Global Impression-Severity scale; CPT, Continuous Performance Test; CUD, cannabis use disorder; DMN, Default Mode Network; ECN, Executive Control Network; EPS, Extrapyramidal Symptom Scale; fMRI, Functional magnetic resonance imaging; GAF, Global Assessment of Functioning; HC, Healthy comparison subjects; LNS, Letter-Number Sequencing test from the Wechsler Adult Intelligence Scale-Third edition; MCCB, MATRICS Consensus Cognitive Battery; MCQ, Marijuana Craving Questionnaire; PANSS, Positive and Negative Syndrome Scale; PLB, placebo; RCT, Randomized Control Trial; RCFT, Rey-Osterrieth Complex Figure Test; SANS, Scale for the Assessment of Negative Symptoms; SAS, Simpson Angus Scale; SCZ, Schizophrenia; SCZAF, schizoaffective disorder; SCWT, Stroop Color Word Test; SOPT, Self-Ordered Pointing Task; STAI-S, State Trait Anxiety Inventory state subscale; SUD, substance use disorder; THC, Tetrahydrocannabinol; TLFB, Timeline Follow-Back; TMT, Trail Making Test.

(55). Race composition varied, with the proportion identifying as Caucasian ranged from 46% (55) to 100% (56, 57).

One study excluded all substance use disorders except nicotine and caffeine (55), while the other (56, 57) explicitly included CUD. Participants in the D'Souza study (55) were required to abstain from caffeinated beverages, alcohol, and illicit substances from 2 weeks prior to start of testing until study completion, verified via self-report and urine drug screen. In contrast, the Fisher and Whitfield-Gabrieli studies required that patients met criteria for cannabis abuse and/or dependence, and had used the substance within the past month. Patients then abstained from all substances, with contingent reinforcers, except nicotine and caffeine for at least 7 days prior to test sessions, which was verified using the Timeline Follow Back method (70), urine drug screens, and changes in quantitative urine THC to ensure abstinence.

THC dose and route of administration varied in these studies. One used a single dose of 2.5 mg and 5 mg of THC administered intravenously at different sessions (55). Patients in the studies by Fisher et al. and Whitfield-Gabrieli et al. either smoked a single dose of 3.6% THC cigarettes or ingested 15 mg oral THC on one occasion.

All three studies assessed the effects of THC on symptoms using the PANSS, as well as changes in feeling "high" and other symptoms such as "panic" using a Visual Analog Scale (VAS). Fisher et al. and Whitfield-Gabrieli et al. also included formal measures of cannabis withdrawal and craving. The studies included measures of cognition, and two reports used fMRI to assess brain activation during a resting state (56, 57, 63). All of the studies collected blood samples to assess plasma THC, while one also collected cortisol and prolactin (55).

Study Summaries

Effects of THC in Schizophrenia

One double blind RCT assessed the effects of intravenous THC 2.5 and 5 mg vs. placebo in 13 stable, abstinent outpatients with schizophrenia or schizoaffective disorder without any substance use disorder who were stable on antipsychotic medication. Results were compared to 22 healthy participants who had completed a similar protocol (27). Participants received study drug over three sessions, separated by at least 1 week. Abstinence from caffeinated beverages, alcohol, and illicit drugs from 2 weeks was required before testing began until study completion, verified via self-report and urine screens for illicit drugs. Symptoms and cognitive testing was completed 10 and 30 min after infusion, respectively. THC resulted in worsening of positive symptoms (80% of patients had PANNS subscale score worsened by at least 3 points with the 2.5 mg dose). Verbal learning and recall also worsened, and these changes were more prominent for the patient group compared to the healthy participants. Effects on positive symptoms were not different by dose, whereas there was a dose effect on learning and recall. THC also worsened negative symptoms, clinician- and self-related perceptual alterations and movement symptoms (AIMS and akathisia scores). THC increased plasma prolactin and cortisol greater than placebo. The requirement for abstinence from

smoking during the testing day could have resulted in nicotine withdrawal-associated exacerbation of symptoms.

Two reports were published from a trial evaluating the effect of oral THC 15 mg or smoked THC from a 3.6% NIDA joint on symptoms, cognition and brain circuitry using fMRI (56, 57). Twelve stable, treated, abstinent outpatients with schizophrenia and CUD were assessed, in contrast to the D'Souza trial, in which CUD was excluded. Alcohol dependence and other illicit substance use disorders were excluded. Patients were abstinent from substances, with the exception of nicotine and caffeine, for at least 7 days prior to MRI scan days, verified via self-report, urine drug screen and quantitative testing thrice weekly. Tobacco smokers smoked a cigarette 90 min prior to scanning. Patients completed two fMRI scan sessions at least 1 week apart. The first (baseline) session was completed without pharmacological manipulation. During the second (drug) session, patients were randomized to either a smoke 3.6% THC cannabis cigarette using an MRI-compatible, hookah-like device immediately prior to scanning ($n = 6$), or ingest a 15 mg THC capsule 3 h prior to scanning ($n = 6$). A group of 12 healthy controls also completed two scanning sessions.

Results from this study were published in two reports. In the first report (56), at baseline, patients showed reduced resting state functional connectivity between the bilateral nucleus accumbens (NAc) seed region and prefrontal cortical regions involved in reward processing (i.e., anterior prefrontal cortex, orbitofrontal cortex, and ventral anterior cingulate cortex), as well as dorsolateral prefrontal and premotor cortices, insula, and parahippocampal gyrus. Only one region, within visual cortex, showed greater connectivity with the NAc in patients than controls. Both smoked and oral THC increased connectivity between the accumbens and prefrontal regions, with greater connectivity associated with higher plasma THC level in the combined patient sample (i.e., smoked cannabis and oral THC). THC was not associated with changes in symptoms or cognition, but scores were not included in the paper. Cannabis craving and withdrawal also did not change with THC vs. placebo in these abstinent participants, but scores were also not reported. Furthermore, no relationship was observed between connectivity and patient ratings of high, liking and craving. The authors interpreted these findings to be consistent with the hypothesis that reward circuitry is disrupted in schizophrenia and CUD, and that by ameliorating this disruption, low dose THC may have the potential to reduce cannabis use in this population.

In further analyses, Whitfield-Gabrieli et al. (57) examined connectivity of the default mode network (DMN) in the 12 patients described above. At baseline, relative to the healthy group, patients showed DMN hyperconnectivity that correlated with greater PANSS positive symptom severity as well as reduced anticorrelation between the DMN and the executive control network (ECN). THC resulted in reduction of this hyperconnectivity and increased DMN-ECN anticorrelation. Furthermore, stronger anticorrelation between DMN and ECN was associated with better performance on a verbal working memory task in the healthy but not the patient group at baseline, and this association emerged in the patient group after THC administration. The authors interpreted their findings to indicate a possible dose effect, with a lower dose of THC providing benefit, improving circuit function, and higher doses of THC potentially disrupting circuits related to psychosis.

THC Study Strengths and Weaknesses

Only two controlled trials reported in three papers are available. Both studies have many strengths including use of placebo controls, careful measurement of previous exposure to THC, and a healthy control comparison group as shown in **Table 1**. Additionally, the D'Souza et al. study (55) utilized two doses of THC, providing a test of dose effect. Only the Whitfield-Gabrieli et al. (57) study reported serum THC levels, confirming moderate increases that corresponded to the study dosing strategy. Both studies had small sample sizes that likely limited their power to detect small effects. The two publications of the fMRI study did not clearly describe the randomization process, a potential for bias, nor report on symptom or cognitive measure scores, thus evidence was indirect, nor did the study report any specific side effects (**Tables 1**, **2**).

Effects of CBD in Schizophrenia

In an early placebo-CBD-olanzapine crossover case series, Zuardi et al. (35) evaluated the effects of CBD on symptoms and side effects in three male inpatients with treatment-refractory schizophrenia. Patients first received placebo for 5 days, then CBD on days 6 to 35, titrated from 40 to 1,280 mg/day. On day 36, CBD was replaced by placebo for the next 5 days, and then to olanzapine for 15 days. Symptoms were systematically assessed during each treatment period. In one patient, CBD was associated with a trend toward symptom improvement (BPRS general, positive, and negative symptoms) at the 1,280 mg/day dose, and symptoms worsened following discontinuation. A second patient showed no benefit from CBD, though negative symptoms worsened following discontinuation. The third patient showed "very minimal improvement" of symptoms. Cognition was not assessed. All three patients tolerated CBD well and no side effects were reported.

Hallak et al. (58) examined the effects of CBD 300 or 600 mg vs. placebo on selective attention and electrodermal response in 28 outpatients with schizophrenia using a repeated session, non-randomized design. Participants were assessed with the Stroop Color Word Test to assess selective attention, as well as psychophysiological assessment of skin conductance, given prior research indicating that poorer selective attention is associated with low electrodermal responsiveness in patients with schizophrenia (71). Subjects were assessed in two sessions 1 month apart, with study drug in the second session, in which participants were sorted into three groups matched for age, sex, years of education, and symptom profile. Each group received a single dose of placebo or either 300 or 600 mg CBD and, after 1 h, completed the Stroop and skin conductance assessments. In contrast to hypothesized effects, the 600 mg CBD group made more errors on the Stroop Color Word Test interference condition than the other two groups, reflecting worse selective attention. Furthermore, while the placebo and 300 mg CBD

TABLE 2 | Study quality and assessment of potential for bias.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Complete outcome data / no attrition bias	No selective reporting	Absence of other sources of bias	Directness of evidence
D'Souza et al. (55)	Unclear	Unclear	Yes	Yes	Yes > 80%	Yes	Yes	High
Fisher et al. (56)	Unclear	Unclear	Unclear[c]	Unclear[c]	Yes > 80%	Yes	No[d]	Medium[f]
Whitfield-Gabrieli et al. (57)	Unclear	Unclear	Yes	Yes	Yes > 80%	Yes	No[d]	Medium[f]
Zuardi et al. (35)	No	No	No	No	Yes > 80%	Yes	No[a]	High
Hallak et al. (58)	No[e]	Unclear	Yes	Yes	Yes > 80%	Yes	Yes	High
Leweke et al. (59)	Yes	Yes	Yes	Yes	Yes > 80%	Yes	Yes	High
Leweke et al. (60)	Yes	Yes	Yes	Yes	Yes > 80%	Yes	Yes	High
Boggs et al. (61)	Unclear	Unclear	Yes	Yes	Yes > 80%	Yes	No[a]	High
McGuire et al. (62)	Yes	Yes	Yes	Yes	Yes > 80%	Yes	No[a,b]	High
O'Neill et al. (63)	Yes	Yes	Yes	Yes	Yes > 80%	Yes	No[a,b]	High
O'Neill et al. (64)	Yes	Yes	Yes	Yes	Yes > 80%	Yes	No[a,b]	High

[a] *Other source of bias: trial funded or partially funded by pharmaceutical company.*
[b] *Other source of bias: subjects with cannabis and other substance use were not excluded.*
[c] *Publication from same parent study (56) indicated there was double blinding.*
[d] *Principal Investigator received industry funding for other research, but not for this study.*
[e] *Pseudo-random assignment.*
[f] *Symptom and cognition scores not reported; fMRI indicators could be considered surrogate outcome.*

groups improved performance on the second relative to the first session, the 600 mg CBD group did not. Psychiatric symptoms were not reported. This study was limited by very small size and the testing may have been conducted prior to full absorption of the CBD.

Leweke et al. (59, 60) performed a 4 week, double-blind, parallel-group non-inferiority RCT of CBD vs. amisulpride 800 mg in four divided doses among 42 acutely psychotic inpatients with schizophrenia and without substance use disorder. After at least 3 days off antipsychotics, patients received either CBD or amisulpride, titrated over 1 week, and maintained at 800 mg for an additional 3 weeks. Symptoms (positive, negative, and total), reported in the 2012 report, improved in both groups, including a 30-point reduction in PANSS total symptom scores and about a nine-point reduction in positive symptoms by the 4 week endpoint. There was no group difference in symptom improvement, suggesting that CBD had an antipsychotic effect similar to amisulpride, although the non-inferiority test did not achieve significance (59). Results from a battery of cognitive tests administered pre- and post-treatment, reported in the 2021 report, demonstrated that both groups showed improvement of visual memory and processing speed. The CBD group only improved in sustained attention and visuomotor coordination, while the amisulpride group improved in working memory. These cognitive findings, however, were not statistically significant after correction for multiple comparisons (60). CBD was well-tolerated and associated with fewer extrapyramidal symptoms, less weight gain, and lower prolactin increase than amisulpride (60). Furthermore, serum anandamide levels increased more among those treated with CBD than amisulpride, and the extent of increase was associated improvement in PANSS total score in the CBD group but not the amisulpride group. This finding was interpreted as suggesting a link between the antipsychotic effect of CBD and inhibition of anandamide degradation (72). Anandamide levels and PANSS scores were not correlated with cognitive performance. The authors interpreted this finding as suggesting a different mechanism for the effect of CBD on cognition. Treatment groups were small and the study was underpowered due to enrollment challenges.

Two 6 week, placebo-controlled trials assessed the efficacy of CBD augmentation of antipsychotics. In the first, Boggs and colleagues (61) conducted a 6 week, double blind, parallel group RCT of CBD 300 mg BID vs. placebo among 36 outpatients with chronic schizophrenia and no past 3 month substance use disorder on a stable dose of antipsychotic medication. Mean age was 48. Psychotic symptoms decreased over time, but improvement was not different between treatment conditions (PANSS positive symptom scores improved 2–3 points). In contrast to the direction of the hypothesized effect, the placebo group showed small improvements in MCCB Composite score, as well as Reasoning and Problem Solving domain scores. Sedation was greater (20% vs. 5%), and gastrointestinal symptoms were less frequent (33.3% vs 55.5%) in the CBD group.

In the second 6 week augmentation trial, McGuire and colleagues (62) conducted a 6 week, double-blind, parallel-group RCT of a higher dose of CBD (500 mg BID) vs. placebo among a larger group, 88 patients with schizophrenia spectrum disorders, mean age 41 years, who were stable with at least a partial response to antipsychotic treatment. In addition to using a higher dose of CBD, this trial differed from the previous trial in that substance use disorder was not exclusionary and use of alcohol, cannabis, or other illicit substances was not prohibited during the trial, but DSM-5 substance use disorder diagnosis was not reported. At

baseline, only 2.3% of the CBD group and 4.4% of the placebo group had a THC-positive urine screen, suggesting that most participants were not regular cannabis users prior to the study. Serum CBD levels were positive in all participants in the CBD group at study end suggesting adequate adherence. Following the 6 week treatment phase, compared to placebo, the CBD group showed greater improvement in positive symptoms (3.2 vs. 1.7 point reduction) and was more likely to be rated as improved by their treating clinician. Total PANSS score change was not significantly different between groups (7.9 vs. 8.9 points). Trends were also observed for cognition (composite score and executive function domain), as well as small but significant amelioration of motor speed. Although information on substance use during the course of the study was generally not provided, the authors reported that one patient in the CBD group was cannabis dependent at baseline and did not change their pattern of use during the study, and another in the CBD group was alcohol dependent at baseline, but not by the end of treatment. CBD was well-tolerated, but, in contrast to the Boggs study above, CBD participants did not report somnolence (0% vs. 6.7%), and were more likely to have gastrointestinal side effects than the placebo group (18.6% vs. 6.7%). Because participants using THC were not excluded and measures of THC use were not systematically assessed over time, an interaction between use of cannabis or other substances during the study and the effect of CBD on symptoms could not be ruled out.

O'Neill et al. (63, 64) evaluated the effect of a single dose of augmentation with CBD 600 mg vs. placebo on symptoms, fMRI assessments of mediotemporal and prefrontal cortex (primarily the middle frontal and inferior frontal gyri) activation, as well as mediotemporal–striatal functional connectivity during verbal recall, and ^{1}H-MRS assessment of hippocampal glutamate level (which was corrected for the cerebral spinal fluid content of the hippocampal region of interest). They studied 13 medicated outpatients with schizophrenia (within 5 years of illness onset; mean age 28), in a double blind, repeated-measures, within-subject cross-over design. Patients with CUD were allowed whereas alcohol and other substance dependence were excluded, as were those who were intoxicated or had a positive urine drug screen for other drugs on the day of scanning. Over half (57.1%) of patients were using cannabis. Nineteen healthy comparison (HC) participants also completed two sessions, but without drug administration for the fMRI study. All participants completed a block-design verbal paired associate learning task (engaging learning and memory) in the scanner 3 h after drug administration.

CBD was associated with a trend toward reduced median PANSS total score, but not with changes in state anxiety or verbal paired associate learning task performance. As compared to the healthy group, patients had abnormal activation within the prefrontal region during encoding, while during recall they had abnormal prefrontal and mediotemporal activation as well as greater hippocampal-striatal functional connectivity. CBD partially normalized activations in these regions, as well as reduced hippocampal-striatal functional hyperconnectivity. The researchers interpreted their findings to indicate that the changes in these regions underlie the antipsychotic effects of CBD.

Furthermore, in a follow-up report, O'Neill et al. (64) observed a significant increase in left hippocampal glutamate levels in the CBD group compared to placebo. No group differences were observed for other metabolite levels including glutamate–glutamine, myoinositol, N-acetyl aspartate, and glycerophosphocholine. A multivariable model adjusted for baseline PANSS score demonstrated a significant inverse predictive relationship between glutamate levels, but not CBD condition, and total PANSS scores. The authors interpreted these findings to be supportive of the possibility that CBD may produce an antipsychotic effect via modulation of hippocampal glutamate levels.

The study sample was small but the authors provided a power calculation indicating adequate power for the fMRI study. The design included adequate time for CBD absorption, enabling detection of drug effect. However, because half of participants were using recreational cannabis, the authors could not determine whether the CBD-associated improvements were due to ameliorating THC-induced impairments vs. impairments fundamental to schizophrenia.

CBD Study Strengths and Weaknesses

All five studies had considerable strengths with prospective random assignment, a control or comparison condition, and systematic assessment of symptoms and/or cognition. The 4 and 6 week trials also carefully measured impact on movement disorders and adverse effects. In the single dose trials, one study may not have included adequate time for absorption of oral CBD. The different sample characteristics (age, presence of CUD, or recent use of cannabis), different CBD dose, treatment duration, outcome measures and timing of assessments could contribute to the heterogeneity of findings. A notable point of study design heterogeneity is the inclusion or exclusion of CUD and/or cannabis use during the trial; both studies with positive findings did not omit participants with CUD. The small sample sizes of these studies limited the power to detect small to medium effects. The Boggs study did not clearly describe the randomization process and pharmaceutical company funding for some of these studies could contribute some potential for bias in the findings (**Table 2**).

DISCUSSION

THC, Psychotic Symptoms, Cognition, and Adverse Effects

Controlled laboratory research to date has used heterogonous methodology and reported different findings. The D'Souza study, which was carefully designed to assess symptoms, documented increased positive, negative, and general symptoms of psychosis, as well as impaired cognition when intravenous THC was given to patients with schizophrenia. While there was a clear dose effect for learning and recall, there was not a clear dose effect for positive symptoms (55). These results are consistent with findings in healthy subjects, where 15 trials have demonstrated that THC can induce psychosis in many people (28).

In contrast, the other study, which included patients with schizophrenia having co-occurring CUD, did not report

symptom changes with administration of a modest dose of oral and smoked THC; THC significantly increased serum THC and resulted in a trend toward tachycardia, as expected. This study demonstrated that THC reduced the resting state functional hyperconnectivity in regions of the DMN and improved the DMN-ECN anticorrelation in brain circuits associated with schizophrenia symptomatology (57), an effect that is opposite of what might be expected if THC worsened psychosis.

Hyperconnectivity of the DMN has been reported in medicated (73) and medication naïve patients with schizophrenia (74) who do not have CUD. The decreased DMN-ECN anticorrelation found has also been documented in medication naïve (74–76) and chronic patients taking medication (73, 77, 78). Thus, the authors asserted that these abnormalities may be core features of schizophrenia. They interpreted their findings to indicate that THC may have a dose effect, with low dose providing benefit to brain circuits involved in psychosis, and higher doses causing disruption. The other report from this study showed a normalization of resting state activity in circuits involved with reward (56), and proposed that low dose THC could also have the therapeutic potential to reduce cannabis use in patients with co-occurring schizophrenia and CUD.

Regarding the effect of THC on cognition in schizophrenia, intravenous THC worsened learning and recall in patients with schizophrenia without substance use disorder, with a dose effect in which 5 mg had a greater effect than 2.5 mg (55). Although the Whitfield-Gabrielli study in abstinent patients with CUD reported that THC improved anticorrelation between the DMN and ECN, and the magnitude of the anticorrelation between the DMN and ECN correlated with working memory performance, cognition scores in relation to THC vs. placebo were not reported. The THC effect in the D'Souza study is consistent with findings that THC acutely worsens cognition in the general population (55) as well as a meta-analysis indicating better neuropsychological functioning in patients with schizophrenia having a lifetime history of cannabis use, but not those with current or recent use, relative to patients without co-occurring cannabis use (79).

In addition to the different dose effect suggested by Whitfield-Gabrielli et al. (57), other potential explanations for the different symptom and cognition findings regarding THC and psychotic symptoms in these studies of chronic schizophrenia include the possibility that patients with schizophrenia and co-occurring CUD may be less susceptible to the psychotomimetic effects of THC than those who do not have a CUD, either due to different underlying biological risk, a notion that others have proposed (80), or due to developing neural adaptations resulting in tolerance to this effect after long term cannabis use. Regarding heterogeneous biological risk for psychosis, inter-individual susceptibility to THC-induced psychotic symptoms has been observed in people without psychotic disorders (27, 81). Assuming such heterogeneity also exists in people with schizophrenia, it is possible that those with lower susceptibility to symptom exacerbation may be more likely to develop a CUD, as they would not suffer immediate negative consequences with using THC. The problematic course of illness associated with CUD in schizophrenia may be due to the more general impairing impact of substance use disorders in schizophrenia, including medication non-adherence (82–84). Alternatively, people with schizophrenia and CUD may have developed tolerance to the psychotogenic effects of THC, as has been demonstrated in people without psychotic disorders (81, 85).

CBD, Psychotic Symptoms, Cognition, and Side Effects

Controlled prospective research on the impact of CBD to date is mixed. The small study comparing 800 mg CBD to amisulpride among 42 symptomatic, unmedicated inpatients (mean age 30 years) who tested negative for THC and substance use disorder demonstrated a 30 point reduction in PANSS total scores over 4 weeks and about a 9 point reduction in positive symptoms of psychosis in both groups (59). Although this study did not have a placebo control group, the findings strongly suggested that CBD has an antipsychotic effect. A recent paper also reported on assessments of cognition from this same study, indicating similar levels of improvement with CBD and amisulpride, but without statistical significance after correction for multiple comparisons (60). The four small placebo controlled studies of CBD augmentation in schizophrenia provide mixed, limited support for the ability of CBD added to an antipsychotic to further reduce symptoms of psychosis and improve cognitive impairments. In contrast to the research on THC, this research did demonstrate that CBD did not worsen psychosis or cognition compared to placebo.

These inconsistent results regarding potential beneficial effects of CBD could be due to differing doses of CBD, differing patient age, and presence of recent/current recreational THC and other substance exposures in these studies. Among the two 6 week augmentation trials, the study that demonstrated a positive effect on symptoms and cognition (62) used a higher dose of CBD (1,000 mg vs. 600 mg) and enrolled subjects with a lower mean participant age (41 vs. 48 years). Thus, it is possible that a higher dose is necessary, or that younger patients may respond better to CBD. The findings of the effect of CBD using fMRI in the studies reviewed here (63), which also recruited young subjects, are similar to recent fMRI studies in young, antipsychotic-naïve adults at clinical high risk for psychosis. These trials found partial normalization of circuitry involved in verbal learning and memory (86) and motivational salience (87) following a single dose of CBD. The novel ^{1}H-MRS findings suggest a possible mechanism for the impact of CBD on symptoms in schizophrenia (64). Together, these findings suggest that the effects of CBD on brain functioning in schizophrenia cannot be readily accounted for by illness-related factors such as medication history and chronicity.

A point of significant interest is that studies finding a positive effect for CBD augmentation (62–64) did not omit participants with CUD or current cannabis use and did not carefully measure cannabis use throughout the study period. Previous research has demonstrated that CBD in robust doses can mitigate THC-induced psychotic symptoms in healthy individuals (29, 30). Thus, it is possible that CBD was influencing THC-induced

impairments rather than impairments due to schizophrenia in these two studies with positive results. It is also possible that people with schizophrenia who use cannabis or have a CUD may respond differently to CBD that those who do not have CUD, but no studies have carefully examined the effect of CBD in patients with schizophrenia and CUD. Additionally, we found no published laboratory studies testing the combination of CBD with THC in schizophrenia, nor among those with co-occurring CUD. Patients with co-occurring disorders are of particular interest given the preliminary findings that low dose THC normalized resting state functional connectivity in areas related to reward processing and executive control without increasing symptoms or worsening cognition (56, 57).

This review is limited by the small number of controlled studies available on the topic, yet the consideration of studies of both CBD and THC together with careful review of study methodology and findings provides an important current appraisal of the evidence on the effect of cannabis in schizophrenia. Importantly, prior reviews have not taken into careful consideration whether patients were using alcohol or substances of abuse (including cannabis) at the time of participation and/or had a prior history of alcohol or substance use disorder. Alcohol/substance use history may be especially salient to consider as it may affect the outcomes of THC or CBD trials in schizophrenia. This possibility is raised by research indicating differential effects of acute cannabinoid administration on cognition (88, 89) and ratings of intoxication (90, 91) in frequent and infrequent cannabis users without schizophrenia, as well as higher initial maximal plasma THC level in frequent users (90, 92).

Overall, there is insufficient evidence regarding the ability of THC or CBD to impact symptoms and cognition in patients with schizophrenia, such that neither cannabinoid should be recommended for treating this group until further research enables a clearer picture of their impact on this disease and among people who have schizophrenia and CUD. In the era of legalization, public health officials could consider whether there is enough THC-related evidence (from one high quality laboratory study that is consistent with epidemiologic research and effects in people without psychotic disorders) to provide public warnings that THC can worsen symptoms among some people with schizophrenia. Studying the effect of THC and CBD in schizophrenia is challenging, but additional research is warranted to examine the impact of these cannabinoids among individuals with schizophrenia who do and do not have co-occurring CUD.

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/s.

AUTHOR CONTRIBUTIONS

CS and MB determined study design and contributed to developing the original protocol. SA and CS contributed to the original screening of papers, data extraction, and writing the first draft of the manuscript. RR contributed to the study design. MB and RR conducted analysis, interpretation of literature review, and critical revision of the manuscript. MB, RR, and SA contributed to editing the final draft. All authors approved the final version.

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REVIEW
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Cannabis and Driving

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As more states in the U.S legalize recreational and medicinal cannabis, rates of driving under the influence of this drug are increasing significantly. Aspects of this emerging public health issue potentially pit science against public policy. The authors believe that the legal cart is currently significantly ahead of the scientific horse. Issues such as detection procedures for cannabis-impaired drivers, and use of blood THC levels to gauge impairment, should rely heavily on current scientific knowledge. However, there are many, often unacknowledged research gaps in these and related areas, that need to be addressed in order provide a more coherent basis for public policies. This review focuses especially on those areas. In this article we review in a focused manner, current information linking cannabis to motor vehicle accidents and examine patterns of cannabis-impairment of driving related behaviors, their time courses, relationship to cannabis dose and THC blood levels, and compare cannabis and alcohol-impaired driving patterns directly. This review also delves into questions of alcohol-cannabis combinations and addresses the basis for of *per-se* limits in cannabis driving convictions. Finally, we distinguish between areas where research has provided clear answers to the above questions, areas that remain unclear, and make recommendations to fill gaps in current knowledge.

Keywords: cannabis use, driving impairment, motor vehicle driving, public health, roadside testing, THC, cannabinoids

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INTRODUCTION

As increasing numbers of states in the USA legalize cannabis for medicinal and recreational purposes, the number of users is growing (1). Alongside this, the number of individuals operating motor vehicles under the influence of cannabis is necessarily also increasing. Since acute cannabis intoxication impairs some of the cognitive and psychomotor skills necessary for safe driver performance and decrements driving ability, the obvious concerns are the likely public health consequences for traffic safety of having more cannabis-intoxicated drivers on the road, and how to detect such drivers reliably. In turn this raises legal issues involving criminalization of

cannabis-impaired driving. This raises the question of what strategies and procedures most reliably and validly detect cannabis-impaired drivers, in the extent of the knowledge base for making such decisions.

These topics are more complex to address than commonly assumed, and raise additional questions – not all of which have straightforward answers. Although these issues are examined in the following report, its intent is less be a comprehensive literature review, but rather more a systematic, critical exploration of the major questions in the field, their associated assumptions, and the extent to which current research has addressed (or not addressed) them. In those cases where these answers or adequate evidence to address important questions are still lacking, we point out the gaps in knowledge and suggest how they might be addressed. The major topics addressed are as follows:

- What is the epidemiologic evidence that cannabis is linked to motor vehicle crashes?
- How does the pharmacokinetic profile of THC differ from that of alcohol?
- What are epidemiologic trends in cannabis-related motor vehicle crashes?
- To what extent does cannabis impair driving-related behaviors and cognitive processes, which behaviors and abilities are most affected, and to what extent, following an acute cannabis dose?
- How do we assess cannabis-intoxicated drivers at the roadside?
- How valid is it use simulated driving research methods to make conclusions about the effect of cannabis on real-world driving ability? Does cannabis impair both virtual and actual on-road driving ability?
- How do the intoxication profiles of alcohol and THC differ in regard to driving impairment?
- Is cannabis' impairment related temporally to cannabis dose or to blood levels of THC or its metabolites?
- What is the time course of cannabis-related driving impairment?
- Can we detect cannabis-impaired drivers at the roadside reliably, and what is the validity of "*per se*" THC blood level limits in detecting cannabis-impaired drivers?
- Are alcohol/cannabis combinations more impairing (synergistic) than either substance used alone?

Background: Cannabis Remains a Public Health Concern With Regard to Motor Vehicle Crashes

Motor vehicle accidents (MVAs) are among the top 10 leading causes of morbidity and mortality worldwide (2). In 2012, within the United States (US) there were about 33,561 fatal MVAs, in addition to 1,634,000 reported MVAs that caused injury (3). Fatal crashes were 32,166 by 2015 and 36,800 in 2018. Traffic crashes are amongst the leading cause of death in 5–34 year-olds (4), and are arguably preventable. While overall fatal crashes have remained stable or decreased over time, those due to drugged driving are trending up over time, from estimates in the US of 1,716 in 1993, to 6,612 in 2015 (5). Alcohol and cannabis are very important contributors to both impaired driving and MVA's (6). Aside from alcohol, cannabis is the primary drug detected in the US drugged driving cases and fatal motor vehicle crashes. But as we explore later, this statistic may be misleading due to the very marked persistence of THC in the body after consumption that is not necessarily reflective of impairment.

In the Fatality Analysis Reporting System (FARS) of the NHTSA, there were 8,617 reported crashes in 2012 involving drivers with a BAC $\geq$ 0.04, which resulted in 9,428 fatalities (3): in 2013 the NHTSA estimated that alcohol-impaired-driving fatalities accounted for 31% of motor vehicle crash (MVA) fatalities (7). In the National Survey on Drug Use and Health, cannabis was the most commonly used illicit drug in 2013 (8). Daily or almost daily use of cannabis increased from 5.1 to 8.1 million persons between 2005 to 2007, and 2013 (8). In 2013, 9.9 million persons and 40% of current illicit drug users admitted to driving under the influence of substances at least once in the past year (6). According to the FARS, in 2012, 2,083 reported MVAs occurred while driving under the influence of cannabis (DUIC) resulting in 2,208 fatalities (3). Many of these reliable figures came from research done nearly a decade ago. Now, with the increasing legalization and decriminalization of recreational cannabis and the legalization of medical cannabis in many states in the US the numerator in terms of more drivers being exposed to cannabis has increased. In addition there are long-term trends in cannabis available for public consumption, both a greater percentage of THC and increasing THC-to-CBD ratios (9). It is prudent to expect that as greater numbers of motor vehicle drivers are exposed to increasingly higher concentrations of THC, the likely trend is that more cannabis-related motor vehicle crashes will occur.

Next to alcohol, cannabis is the second most frequently found substance in the bodies of drivers involved in fatal MVAs. In Colorado, the proportion of drivers in fatal MVAs who were cannabis-positive increased from 5.9% in the first 6 (prior to the commercialization of cannabis) to 10% by the end of 2011 (post-commercialization) (10). Similarly, in Washington State, the average yearly percentage of DUIC cases positive for Delta-9-tetrahydrocannabinol (THC) and its principal metabolite THC-COOH increased from 19.1 and 27.9%, respectively, in 2009–2012 to 24.9 and 40.0%, respectively after the legalization of cannabis (11). Furthermore, while the prevalence of alcohol and other drugs in the same population of suspected impaired drivers submitted for testing did not change during this same 5 year period; cannabis was the only drug to increase in frequency (11). Interestingly, the proportion of cannabis-positive drivers involved in fatal MVAs has not changed in non-medical cannabis states (10). While this does not necessarily establish causality, it suggests that an increase in the use and acceptance of cannabis may be associated with DUIC. In Canada, DUIC within 1 h of cannabis use increased from 1.9% in 1996–7 to 4% in 2004 (12). In 2012, ∼35% of all fatal MVAs involved either alcohol or cannabis, and when used together (BAC $\geq$ 0.04 and positive for cannabis) they accounted for 948 reported crashes and 1,025 fatalities (12). An important caveat to these data relates to the persistence of THC in the body long after the phase of acute intoxication has passed, an issue discussed below in the pharmacokinetics section.

While the effects of alcohol on driving are well-known and have been widely studied (13), the effects of cannabis or its constituent cannabinoids on driving are less clear (14), and even less is known about the effects of the combination of alcohol and cannabinoids on driving. While there are penalties to driving with a blood alcohol content (BAC) higher than 0.08%, there are not corresponding clear-cut limits to blood THC levels. Also, using simple formulas that take into account use the number of drinks consumed within a specified time frame, individuals can estimate their current BAC and therefore, make assumptions about whether it is legal for them to operate a motor vehicle. Reliable, corresponding information for cannabis is not available.

Before examining some of these and other surrounding issues in more detail, it is important to review briefly basic information that underpins many of the issues that we will discuss. This review takes place in the following two sections.

What Is Driving?

Before looking in detail at cannabis' effects on driving, let's first ask a more basic question: "what is driving?" One way to consider this issue is to conceptualize driving as a pyramid of component behaviors and abilities, many of which are employed in other behavioral and cognitive contexts. A bottom-up view, beginning at the base of the conceptual pyramid, comprises specific constituent cognitive domains necessary for driving, starting with the least complex, such as simple visual perception and more habitual motor skills such as steering, that exists more at an operational level, and are located conceptually at the pyramid's base. As one ascends the pyramid, one travels through increasingly more complex domains such as visual reaction time, to higher-level tasks such as visual-motor integration, divided visual attention and visual working memory. Mid-level driving abilities such as car-following involve tactical skills. The most complex tasks such as overtaking, involving higher-level strategic skills are located toward the top of the pyramid, with driving itself as an emergent property, at the apex (15).

Pharmacokinetics of THC Compared to Those of Ethanol

Many of the questions regarding the onset and duration of cannabis' impairing effects, the meaningfulness of detecting THC and its metabolites in biological samples relative to impaired driving and correlations between such levels and degree of impairment derive directly from knowledge of the pharmacokinetics of THC. Thus, a discussion of the facts regarding this topic is essential as a prelude to the following sections. And because so much conceptual confusion has arisen from attempts to equate the pharmacokinetics of THC with those of ethanol, a brief section contrasting the two is fruitful.

Ethanol in the form of beverage alcohol is extremely water-soluble. Because of this, alcohol can be easily diluted in aqueous solutions, so that spirits such as grain alcohol or high-proof vodka can be transmuted into the form of cocktails. Once imbibed, alcohol distributes to all physiological compartments quickly and evenly in predictable ways, since the human body is mostly composed of water. And thus biological samples from blood or breath (which contains high amounts of water) reflect both the amount of alcohol imbibed, and the amount present in the brain, which in turn reflects current levels of intoxication and impairment. Breath and blood alcohol concentrations can be straightforwardly measured (using a rather simple device, the "breathalyzer" in the case of breath) and breath alcohol concentrations (BrAC/BAC) can therefore be readily and quickly assessed at the roadside, indexing impairment. Because of ethanol's straightforward distribution in the body and fairly rapid, non-complex metabolism, BAC levels are proportional to ingested dose and decline predictably over several hours thereafter. The only complicating factor is gastric emptying, which can delay alcohol absorption when slowed, such as after eating fatty foods.

Almost none of these above facts apply to the pharmacokinetics of THC, the main intoxicating ingredient in cannabis (16, 17). As a separate issue, herbal cannabis itself is complex in several respects, containing not only THC but cannabidiol which can modulate THC's intoxicating effects, as well as various terpenes that may enhance THC intoxication or alter its passage across the blood brain barrier (18). The pulmonary route is extremely effective as a means of efficiently conveying THC or CBD to the bloodstream and hence to the brain. However, cannabis is administered in very different formulations and by various routes: orally as "edibles," by smoking in cigarettes with or without tobacco, via tinctures oro-mucosally and from vaporizers that either evaporate cannabinoids from plant material, or use concentrated extracts of THC with or without other chemicals mixed with a vehicle, often in "vaping" devices such as pens. Each of these routes of administration and formulations is associated with different characteristic absorption patterns as regards rates and efficiency. And in common with alcohol, individual rates of metabolism vary with the extent (quantity, frequency) of use (16, 19).

Smoking and "vaping," common routes of cannabis administration, are quick and efficient methods of delivering THC from the lungs to the brain. Slightly lower, but generally similar peak THC concentrations are achieved after smoking as compared to intravenous administration. Plasma THC levels are detectable almost immediately after the first cigarette or vape puff, with subjective and objective drug effects appearing shortly thereafter. Plasma THC concentrations increase rapidly, peaking at ∼3–10 min after the final inhalation (16, 19). They then fall rapidly as the drug is absorbed and within about 20–30 min reach a low, relatively stable plateau that persists over several hours. THC-induced impairment on many measures declines slowly for ∼5–6 h following acute dose in a manner that is generally unrelated to this post-peak THC blood level.

Oral absorption is slower and less efficient than with smoking, with a significantly more delayed onset of drug effect, and with intoxication that is then more sustained (20), with lower peak THC concentrations than those that follow smoking. Reasons for these differences include more variable absorption from the gut, gastric breakdown of THC, and significant first-pass metabolism in the liver to both psychoactive 11-OH-THC (that is more potent as an intoxicant than THC) and to inactive metabolites (21). The delay (∼120 min) to reach peak concentration is significantly longer than with smoking. Inhaled THC is often

referred to as having an average bioavailability of around 30% (17, 22), although it had a systemic bioavailability of ∼50% in a recent, carefully controlled study using protocol-based inhalation of vapor, compared to estimates from other studies of ∼6% for oral dosing (23). It should be noted that these estimates are only approximate, since there is also substantial variability e.g. in how different individuals smoke cannabis cigarettes, e.g. in terms of amount and depth of inhalation.

Rather than being hydrophilic like alcohol, THC is extremely lipophilic. It distributes quickly into organs with higher blood supplies including the brain, heart and liver, moving later into body areas with less perfusion. Because of its fat solubility, it leaches into, and persists in body regions with high fat content, including the brain and adipose tissues. With chronic use, significant accumulation in these latter tissues can occur with gradual release, even if cannabis is not smoked for a period of time. This release and redistribution can lead to its subsequent metabolism and detection in bio-samples including urine days to weeks following last cannabis use. THC is metabolized primarily in the liver and excreted in the urine and feces.

Because its absorption, distribution and metabolism differ so markedly from that of alcohol, the relationship between plasma THC and intoxication is also both different and more complex than that of ethanol levels and intoxication. The concentration of THC in brain and in plasma are dissociated in time, so that by the time intoxication is beginning to ramp up, the plasma peak of THC is already long past. Plasma levels do not clearly reflect dose once the plasma peak has subsided. Intoxication too, is less dose-related than with alcohol, and peak THC blood levels are not clearly related to subsequent maximal levels of behavioral impairment. In contrast, as we noted above, with alcohol peak blood and breath alcohol levels correspond closely in time and are proportional to peak levels of intoxication and drug-related impairment.

Because breath is moist and does not contain lipids, there is almost no available THC present; the number of molecules of the compound is in the picogram range and an extremely sensitive technology is necessary to detect it. All of these factors pose multiple problems for law enforcement personnel attempting to link the presence and amount of THC in blood to recency of use and to the degree of impairment in motor vehicle drivers who may be operating under the influence of cannabis. This difficulty is further amplified when considering the significant lag between intercepting such drivers and obtaining blood specimens in which to measure THC concentration.

What Is the Epidemiologic Evidence That Cannabis Is Linked to Motor Vehicle Crashes?

An important part of the evidence that cannabis impairs motor vehicle driving and consequently leads to more motor vehicle crashes and deaths relies on epidemiologic reports. While the annual number of fatal vehicle crashes in the US is trending down in recent years (in part due to more consistent enforcement of regulations and higher penalties for drunk driving), the number of motor vehicle crashes involving positive THC tests has increased (24). As summarized by McCartney et al. (25), these data derive from two main sources. The first is the numbers of motor vehicle crash drivers who are found post-crash to have THC or other cannabis metabolites in their blood. The second source derives from epidemiologic trends in motor vehicle crashes in those states that have legalized or decriminalized cannabis consumption, compared to those that have not.

Rogeberg and Elvik's (25) meta-analyses (25–27) looked at data derived from ∼240,000 individuals across multiple published studies, investigating the association between acute cannabis consumption and an individual either being responsible for or being involved in a motor vehicle crash. The overall odds ratio showed a low- to-moderate magnitude, but significant risk, with the OR for such involvement being 1.36. For comparison, that number is much less than that for alcohol, where the OR is ∼20 at a BAC of 0.10, as estimated by the same authors. Other estimates e.g., Biecheler et al. (28), provide ORs of 2.3 for cannabis alone, 9.4 for alcohol alone, and 14.1 for cannabis and alcohol in combination.

Annual patterns of excess traffic fatalities due to cannabis were examined by Kamer (29) who quantified changes in traffic for mortality rates from 2008 in Alaska, Oregon, Washington and Colorado compared to control states that had not legalized cannabis. These authors documented increased fatality rates in Alaska and Oregon and initial increases followed by decreases in Washington and Colorado. Their overall conclusion was that approximately double excess deaths in the USA occurred per billion vehicle miles traveled due to cannabis intoxication. Both the Kamer study and a separate investigation by Aydelotte (30) agreed that an approximate doubling of excess motor vehicle related deaths occurs attributable to cannabis. If accurate, this statistic translates into cannabis being involved in ∼18.6% of overall US motor vehicle deaths, equivalent to an additional 6,800 individuals involved traffic fatalities (based on the official estimate of ∼36,800 in 2018).

There are methodologic caveats applicable to both of the above-mentioned approaches. What's unknown, yet germane is when these drivers had consumed cannabis relative to the indexed MVA. This question is important because as noted above, THC and several of its metabolites can persist in blood and body tissues for days-to-weeks following acute use. Thus, detection of THC or one of its metabolites does not necessarily equate to current intoxication. Also not always recorded is what percentage of the presumed cannabis-impaired drivers also had alcohol or other driving-impairing substances in their blood, even if these were below the legal cutoffs for intoxication. As we explore later, few experiments that have examined the synergistic effects of acute cannabis exposure concomitant with legally permissible levels of blood alcohol. If the two substances are synergistic in their ability to impaired driving, then quantifying both is clearly important.

There are also some methodologic problems in tracking temporal patterns of motor vehicle crashes or traffic fatalities following cannabis legalization in a particular state, compared to states that did not legalize. One is that the date of the enabling legislation does not align well with availability of

TABLE 1 | Cannabis impairment effects on driving-related cognitive tasks.

Useful Field of View (31–37)
Motor Pursuit/Tracking (32, 38–50)
Time Estimation or Self-Paced timing (51–58)
Distance Estimation [57*, 61*]
Set shifting/Task switching (59)
Working Memory/Executive functioning (37, 49, 60–62)
Serial Addition/Subtraction (63)
Hand/Body Steadiness/Coordination (38, 39, 45–48, 64–66)
Choice Reaction Time (33, 40, 45, 46, 63, 65, 67–69)
Short-term Memory (61, 70–77)
State dependent learning (78)
Vigilance, signal detection (33, 47, 79)
Visual Search [36*, 62*, 73*]
Information processing speed [34∼, 67∼, 77, 84, 85]
Maze Accuracy (80)
Danger perception/Risk taking [5, 36*, 50, 61*, 87–90]
Stress/distraction Susceptibility (47, 81)
Attentional Allocation (EEG) (82, 83)

**Indicates that results were cannabis dose dependent.*
∼Indicates that data were collected during actual vehicle driving.

TABLE 2 | Impairment of driving behaviors by cannabis.

Driving measure	Cannabis effect
Fewer Fine Manipulative Steering Movements/Steering Instability	No effect (34, 50, 85, 86)
Increased Steering Wheel Reversals/Variability	No effect (34, 74, 87)
Increased Speed Variance/Excessive Speed or Slowness	No effect (34, 49, 61, 86, 88–90)
Decreased Cornering Stability, Speed Variability on Curves	(41, 89)
Increased Braking Distance/Stop Time	(41, 49, 61, 86)
Increased Lateral Position Errors, Variability, or Lane Deviation	(74, 88, 89, 91–94)
Increased Collisions, Decreased Time to Collision, or Slowness Avoiding Other Vehicles or obstacles	No effect (49, 88–91, 93)
Errors in Speedometer Tracking	(86)
Altered Passing Behavior	(58, 88, 95)
Increased Start Time (in response to light signal)	(57, 61)

"No effect" indicates that the behavior was measured but no cannabis-related impairment was detected.

cannabis in the legalizing state. From the time point that the legislation is passed, to customers being able to buy cannabis from dispensaries may vary from months to years, a factor which needs to be taken into account. In addition, would-be purchasers may be able to cross state lines from a non-legal to a legal state in order to make purchases, interfering with a researcher's ability to make accurate relative cross-state comparisons.

Does Cannabis Impair Driving–Related Behaviors and Cognitive Processes?

The weight of evidence from many epidemiologic studies, studies of chronic cannabis smoking, and laboratory studies of the consequences of acute dosing, strongly support that cannabis use deleteriously affects driving-related cognitive test performance on a variety of tasks conceptually linked to motor vehicle driving. Relevant data on acute dose effects are summarized in **Table 1** through 3 below. Meta-analytic studies summarize acute cannabis-provoked impairment affecting multiple domains relevant to vehicle operation (84) **Table 1** details these acute cannabis effects on driving-related cognitive tasks. **Table 2** lists studies that have examined actual driving behaviors, mainly in simulated or on-road driving, whereas **Table 3** summarizes this information relative to the three major driving skill levels detailed in the "what is driving?" section above.

Three major inter-related questions derive from consideration of these data. 1. What is the evidence linking the listed domains in **Table 1** to actual impaired on-road driving, as opposed to theoretical impairment? 2. How useful are available neurocognitive tests for detecting recent cannabis use? 3. How do we best use this informational foundation to guide research that seeks to identify field sobriety tests which can (a) accurately detect drug-induced cognitive impairments and/or (b) predict risky driving? These questions are addressed in subsequent sections. Notably, cannabis-induced changes on a computer-based critical tracking task significantly correlated to altered tactical vehicle tracking behavior during on-road driving (98).

Driving-Relevant Cognitive Tasks That Were Sensitive to Cannabis-Related Impairment in Previous Studies

Key to Table 1

The above studies were conducted using a wide variety of dosing routes, doses of administered cannabis and volunteer subject types as regards prior experience with cannabis. Experimental designs varied widely, and impairment within each category was measured using a wide selection of metrics. This variability makes both comparisons across studies and drawing of generalized conclusions difficult. However, the first three metrics (useful field of view, motor pursuit tracking and time estimation), showed robust impairment in multiple studies across a fairly wide variety of experimental circumstances.

Does Cannabis Impair Actual Driving Behaviors?

If So, Which Behaviors, to What Extent and for How Long After an Acute Cannabis Dose?

Table 2 Quantitative measurements of actual driving behavior under either real on-road or simulated driving conditions.

Many of the behaviors were assessed since they are impaired in alcohol-intoxicated drivers.

Table 3 lists examples of translating driving measures altered by cannabis derived from **Table 2** into standard outcome measures for simulated driving tasks of ascending complexity. For example, standard deviation of lane position (SDLP) is a

TABLE 3 | Driving scenarios and key outcome measures for 3 hierarchical driving tasks.

Name	Conventional outcome measures	Cannabis-related impairment	Exploratory time-locked outcome measures	Attention/control manipulation
Road Tracking Task (Operational)	1 – Standard Deviation of Lane Position (SDLP)	(69, 89–94)	Corrections when SLDP ≥1 SD from participant's mean	Unpredictable lateral wind gusts
Car Following Task (Tactical)	1- Coherence, 2- Modulus, and 3- Delay signal analysis indices	(91, 96)	Lead car peak acceleration or deceleration	High rates (g) of lead vehicle speed change
Gap Acceptance Task (Strategic)	1- Size of gap chosen 2- Minimum time-to-contact (TTC)	(97)	Onset of the acceleration through chosen traffic gap	Cross-traffic in opposing directions

measure of lateral position and lane deviation, elicited at a simple, operational level of driving complexity that in this example involves the subject needing to continue driving in a straight line while dealing with unpredictable lateral wind gusts necessitating vehicle correction by steering.

Delays during the car following task incorporate aspects of speed variance and stopping time during more complex tactical driving maneuvers. The task involves the subject maintaining a fixed distance from a lead vehicle that slows down or speeds up unpredictably.

Gap acceptance choice and time to contact measures incorporate measures of slowness in avoiding other vehicles and altered passing behavior cited in **Table 2** during the execution of passing maneuvers, during a complex, strategic-level gap acceptance task. This task involves the subject making the decision when to safely pass a stalled vehicle, necessitating lane change under conditions of variable oncoming traffic.

How Does One Assess Driving Impairment Validly and Reliably?

We describe four separate approaches to answering this question. The most direct way to address this issue is to have research subjects drive a real vehicle on a real road, while acutely intoxicated on cannabis (91). Although this procedure is the gold standard, it is subject to practical and ethical constraints. These include interaction with other on-road vehicles, and the impossibility of enacting certain scenarios (e.g., animal runs onto the road unexpectedly, or a leading car brakes suddenly). As an alternative, a closely-related approach to deal with this set of problems has been to employ real vehicles on closed-course experimental highways such as Virginia Tech's Smart Roads, a set of state-of-the-art, closed test-bed research facilities closely resembling real highways, managed by Virginia Tech Transportation Institute (VTTI) in cooperation with the Virginia Department of Transportation (VDOT)[1] On some of these test roads a series of sensors embedded in the tarmac communicate with computer equipment located inside the test vehicles. Dual-operator controls such as those used in driver education vehicles are available in case of emergencies when the intoxicated subject exhibits dangerous driving. In the case of alcohol, intoxicated driving research using an instrumented vehicle on a simulated test highway (99) has been performed using the Smart Road, and revealed generally similar deficits to those exhibited on a desktop driving simulator.

A third approach is to recognize that under most circumstances, one cannot ethically or practically allow research subjects to drive a real vehicle on a real road. Instead, one can use an extremely high-end driving simulator that can accommodate the chassis and controls from a variety of real vehicles, such as that used in the National Advanced Driving Simulator (NADS) at Iowa, that has been used to assess cannabis-intoxicated driving (100). The NADS is unique in incorporating sufficient technology to provide highly realistic, real-time kinesthetic feedback that closely mimics that of real driving, and an extremely wide and realistic field-of-view. All three of the above approaches score most highly on face validity, but entail various practical hurdles such as being relatively difficult and/or expensive to access.

A fourth approach, and therefore the most practical solution, resembles the set up immediately above, but in a more affordable, lower-tech incarnation. This translates to in-lab testing with sufficient construct/criterion validity to provide useful data. For many investigators, this involves the use of driving simulators, that range anywhere from videogame-like apparatuses linked to a typical desktop -sized computer display screen, steering wheel and gas/brake pedals at one end of the spectrum, to an actual, repurposed, instrumented motor vehicle chassis on a motion base (to provide some form of kinesthetic feedback), situated in front of a wall-sized projection screen (to provide greater field-of-view), at the more sophisticated extreme. The advantages of such setups are obvious: subjects can be intoxicated with the study drug/placebo in the lab and subsequently asked to drive in a number of pre-programmed scenarios to quantify their degree of impairment.

Simulators in general provide a controlled, safe environment that theoretically translates into real-world driving performance. A large number of scenarios can be pre-programmed in order to test driving ability under a wide variety of conditions, and these can be varied sufficiently to avoid learning effects. With driving simulators one can mimic scenarios that are unethical or impractical to test in real life, such as abruptly-appearing road hazards, weather changes, or similar unexpected scenarios. Furthermore, because of the ease of manipulating the

[1]https://www.vtti.vt.edu/facilities/virginia-smart-roads.html

environment, driving scenarios can be easily constructed that would be unsafe or impossible to create on a real roadway. We and others have shown that intoxicated driving under the influence of alcohol compares fairly closely to driving a real vehicle on a real, instrumented road (99), demonstrating validity. Major considerations for simulated driving include the degree of realism and sophistication (and therefore expense) of the relevant hardware, software, driving tasks and measurement capabilities. And underpinning these is the issue of validity, that is the extent to which simulated driving behavior can be used to draw inferences regarding the behavior of real-world highway driving in relevant, representative situations (for example in heavy traffic).

Does Cannabis' Impairment Profile in Terms of Domains Impacted and the Severity of Impairment Resemble That of Alcohol?

As summarized in **Table 4** opposite, while both alcohol and cannabis impair aspects of driving behavior, the two drugs affect driving rather differently, with overlap in deficits mainly for weaving, and possibly for divided attention (although this latter is not well-studied for cannabis). Studies can only point toward generalities in the population, as there might always be exceptions of cannabis-intoxicated people who do not drive more slowly or carefully. Factors including youth, driving experience and substance tolerance may all influence the individual's response to a drug (14). It is worth emphasizing that few studies have directly compared driving impairment due to the two drugs in a head-to-head fashion, and almost none-in a design involving substantial numbers of the same subjects and assessments over a range of doses of both substances. Thus, any conclusions have to be tentative at this point. The conclusions summarized in the **Table 4** are based in part on published work from our own laboratory involving simulated driving and subjects' self-reports, that has involved BAC levels ranging from 0.05 to 0.08 for alcohol (59, 87, 101, 110, 111) and more recent unpublished data (102) involving inhalation of vaporized doses of cannabis ranging from ∼42.5 to ∼65 mg. One major behavioral difference that we observe in our subjects is that cannabis-intoxicated volunteers report not only being aware of their likely driving impairment (see later section on impairment duration), but also overestimate its degree, and consequently tend to drive more slowly in an attempt to compensate for deficits. In contrast, alcohol-intoxicated subjects at a BAC of 0.08% or above are not only more likely to fail to recognize their actual impairment but are also more inclined to make impulsive behavioral choices, and at BAC's equal to or exceeding 0.1, to engage in dangerous driving behaviors such as driving at excessive speed, especially in risky situations such as when navigating their vehicle around curves.

Experiments that have examined brain responses to intoxicated driving, although few in number, also speak to different alterations provoked by the two drugs. As mentioned elsewhere in this article, Hartman et al.'s (100) simulated driving study using the NADS directly compared the two drugs in the same set of individuals. While cannabis only affected weaving behavior (measured by standard deviation of lane position/SDLP), alcohol impaired SDLP in addition to measures of lane departures and maximum acceleration.

TABLE 4 | Contrasting alcohol vs. cannabis effects on simulated and actual driving behavior and associated cognitions.

Impairment domain	Alcohol	Cannabis
Awareness of deficit	Impaired (14)	Unimpaired (14)
Ability to compensate for deficits	Absent (14)	Present/partially present (14)
Tracking/lane position	Impaired [(101)*, (102)]	Impaired (100, 103, 104)
Divided attention	Impaired (87, 105)	Impaired (84)
Concentration	Impaired (81)	Impaired (84)
Reaction time	Increased (106)	Increased/No Change (106, 107)
Impulsive/risky choice making	Impaired (56, 108)	Unimpaired (56)
Excessive driving Speed	Present (109)	Absent (100)

Indicates dose dependent.

Are Alcohol/Cannabis Combinations More Impairing (Synergistic) Than Either Substance Used Alone?

This is important public health question, particularly if "safe" levels of the two substances that do not individually significantly impact driving, have a meaningful impact on decrementing driving behavior when combined. As Dubois et al. (112) note, in the realm of motor vehicle crashes the phenomenon of simultaneous combined alcohol/cannabis intoxication is on the increase, with a 5-fold increase in crashes involving detection of combined THC/alcohol from below 2% in 1991 to above 10% in 2008.

Simulated driving studies that have examined the nature of interactions between cannabis and alcohol are notably inconsistent in detecting synergy between the two substances vs. a purely additive effect, as noted by Hartman et al. (100). For example, Ronen et al. (113) reported that while there were no significant alterations in lane position variability when either 13 mg THC or 0.05% (BAC) alcohol were administered alone, the combination produced a significant increase in weaving behavior. Lenne et al. (69) reported significant independent main effects of both cannabis and alcohol, but found that the combination was purely additive without interaction/synergy. In an on-road study combining different THC doses with a 0.04% target BAC (an alcohol concentration considered insufficient by itself to produce behavioral change), the combination significantly increased SDLP (91). In Hartman et al.'s (100) double-blind, placebo-controlled study, both cannabis and alcohol were individually significantly associated with impaired lateral control (weaving) assessed by measures of SDLP. While cannabis only affected SDLP, alcohol impaired this measure as well as lane

departures and maximum acceleration. In terms of equivalence between the two substances, while lower doses of cannabis administered through vaporization yielding 8.2 μg/L blood THC were associated with SDLP abnormalities similar to breath alcohol (BrAC) values of 0.05% (∼0.05%, SDLP at 13.1 μg/L THC approximated 0.08% BrAC. Combining alcohol and cannabis in this study produced an additive rather than a synergistic effect on SDLP, with no interaction. The authors also noted that these THC concentrations collected during driving in their study were generally higher than those collected typically hours later by law enforcement in traffic-stop situations.

Epidemiologic studies also shed some light on this question Dubois et al. (112) examined combined THC/alcohol crash culpability in fatal car crashes. The study confined itself mainly to victims with a low levels of BAC of 0.08% or less. The authors estimated that each 0.01 BAC unit increased the culpability odds (COs) of a crash by ∼9–11%. Drivers who were positive for THC alone had a 16% increase in COs, while combined THC/alcohol COs were synergistic, exceeding CO values for alcohol or THC alone. The authors stress that further research would be needed to clarify more specifically interactions between cannabis and alcohol concentration levels and driving impairment.

A reasonable overall conclusion from examining the above studies is that while there are many suggestions of a synergistic decrement in driving behavior – particularly for SDLP – when cannabis and alcohol are used together, there is also credible contradictory evidence arguing only for an additive effect. More importantly perhaps, most of the above studies demonstrate that there is a lack of comprehensive investigations exploring the full range of interactions across a variety of both BAC and cannabis doses/blood levels conducted in the same subjects to allow more meaningful comparisons. For example, investigators willing to repeat the rigorous design of the Hartman et al. (100) study across such an expanded range of doses of the two substances would provide a more definitive answer to this important question of synergy. So evidence is lacking to make solid conclusions at this time.

Is Cannabis' Impairment of Driving Related Temporally to Administered Dose or to Blood Levels of THC or Its Metabolites?

Typical of experiments describing a generally poor correlational relationship between performance disruption and serum THC is the study of Ramaekers et.al. (98) who described effects in in 20 cannabis users smoking placebo or doses of 17.5 mg or 35 mg of THC per 70 kg body weight, and subsequently evaluating THC blood levels and various behaviors critical tracking task/perceptual motor control, motor impulsivity (using a stop signal task) and executive function (using the Tower of London paradigm) from 15 min to 5 h post drug challenge. As noted, their findings are in sharp contrast with those reported for alcohol intoxication, where behavioral disruption and BAC track closely. While legislators may wish for data showing straightforward relationships between blood THC levels and driving impairment that parallel those of alcohol, the widely different pharmacokinetic properties of the two substances, leading to a rapid fall in THC levels to a relatively steady, low baseline within ∼20 min of an inhaled dose make this goal unrealistic.

A final consideration is that even if a candidate behavioral/cognitive task or biological measure (such as plasma THC) is sensitive to recent cannabis exposure, it may nevertheless be unrelated to on-road driving ability, and thus not useful as an index of fitness to drive.

What Is the Duration of Cannabis-Related Driving Impairment?

Cannabis' peak impairment on driving performance is evident 20–40 min following inhalation (14), even as THC blood levels are long past their peak and continuing to diminish. By 1–2.5 h post-inhalation, behavioral impairment is still present but already beginning to diminish (14, 114). Because of this fairly time-limited impairment, several sources suggest that following acute use, cannabis consumers should wait a minimum of 3–4 h before attempting to drive (115). A recent paper from Arkell et al. (116) used a double-blind, within-participant randomized clinical trial with an active THC dose of 13.75 mg consumed by inhalation following vaporization, and measurements of driving performance in an actual vehicle on a real road. The major findings were that weaving (assessed by standard deviation of lane position/SDLP) was significantly greater at 40–100 min, but not at 240–300 min post-dose. Subjects' self-rated confidence to drive safely tracked poorly with actual measured SDLP, with participants significantly rating themselves as more impaired 4–5 h following active THC compared to placebo, despite SDLP being unimpaired by that time. It is important to note that consumption of "edibles," with delayed onset and greater persistence of intoxication effects, and dosing via smoking or vaporization at a higher dose than used by Arkell et al. (116) would likely result in a greater period of impairment. Lastly, cannabidiol (CBD) administered simultaneously in vaporized cannabis does not significantly diminish THC-induced driving impairment (117), despite the fact that there is some evidence that CBD may alter either the pharmacokinetics (PK) of THC or modulate behavioral effects of the latter (118, 119). Recently Liu et al. (119) developed population PK models of THC and CBD. When high-dose CBD was inhaled at the same time as THC, the systemic availability of the latter decreased significantly. Interestingly, in the same set of experiments, frequent users of cannabis appeared to have higher systemic availability of both THC and CBD when high-dose CBD was administered.

It is worth drawing attention to the fact that the majority of driving studies have been performed on inhaled cannabis in younger subjects, and there is a paucity of studies on driving performance following oral administration of the drug, where there is likely to be increased variability of both onset and duration of impairment. In addition, despite increasing use of cannabis in individuals aged over 60 (typically to help manage insomnia and chronically painful conditions), there are very few studies quantifying cannabis-related driving impairment in such older individuals following any route of

drug administration, although likely age-related alterations in pharmacokinetics are likely.

Can We Detect Cannabis-Impaired Drivers at the Roadside?

A number of recent papers have surveyed various issues pertaining to roadside detection of putatively cannabis-impaired drivers (120–123). Because roadside detection of alcohol impaired drivers works so well and straightforwardly, this model has undoubtedly biased expectations, procedures, expectations and policies in the case of cannabis. However, we will present evidence that these guiding assumptions fail to carry over from one substance to the other.

How does roadside detection of cannabis-impaired drivers unfold in the real world? Typically, law enforcement personnel will either stop a driver for "probable cause" (that in practice could constitute anything from an observation of vehicle weaving, to a non-functional taillight), or detain them at a random police checkpoint. If the driver appears to be impaired, or cannabis-related paraphernalia is visible within the vehicle for example, then law enforcement personnel will generally administer a battery of roadside tests for impairment detection. If these are abnormal, they will assess the subject's BrAC via a "breathalyzer" device. If the breathalyzer reading is negative, then the police may request that the subject's blood be drawn for drug testing at nearby facility. The average time between the police pulling over such a driver and the blood sample actually being collected in this manner is 90 min (124). It is important to note that roadside tests of driver impairment/intoxication were originally developed for detecting alcohol-impaired drivers, and the extent to which they are applicable to cannabis impairment has not been rigorously examined. For example, common test items that validly screen for alcohol-intoxicated drivers include measurements of postural sway, nystagmus, heel-to-toe walking and repeating a sentence correctly. Many if not all of these items are minimally impaired by cannabis intoxication (14). Similarly, while drug recognition expert's (DREs) are consistently reliable in identifying alcohol-impaired drivers, they are more variable in their ability to correctly identify cannabis-impaired individuals (125–127). A number of current experiments are underway to find the most reliable ways to assess individuals driving under the influence of drugs (DUID) including cannabis.

This raises the issue of whether there are available other, more feasible candidate screens for roadside testing of cannabis-impaired drivers. Ideally, such a test must be simple, quick, and sufficiently robust to test in real-world situations, for example by roadside at night in a situation where there is perhaps little light and noisy traffic passing by. Such a test must be practical to administer at the roadside, e.g., on a tablet computer, must demonstrate accurate prediction (acceptable false-positive/false-negative rates), and have a narrow confidence interval, high reproducibility, generalizability, and acceptable face validity. Ideally it should also display strong criterion-related validity. Several such candidate measures are currently undergoing testing. These include Milburn's DRUID test battery (128–130), assessments of postural instability using electronic devices, measurements of brain state using portable EEG devices (131), pupillary responses to flashes of light, laptop-based cognitive test batteries, and hand-held, instrument-based cognitive testing devices, such as the Intoximeter[2]. It should be emphasized that all of these investigations are preliminary, and no valid, reliable screening paradigm is yet available. Moreover, with any such potentially useful approach there is a need to validate it against a valid and reliable measure of impaired driving, in terms of determining its relevance, then subsequently to conduct extensive field trials.

Other issues with roadside detection of cannabis-impaired drivers include dual or multi-intoxication, for example the individual as consumed small amounts of both cannabis and alcohol which are acting synergistically, mentioned above. It would be useful to know whether one can identify deficits specific to cannabis, or either mimicked by or potentiated by other drugs of abuse (or alcohol). Another potential difficulty is the lack of personal baseline information for police from an individual being tested at the roadside. This presupposes the presence of a large behavioral database for a particular task, normed to age and sex as appropriate. One possibility is that a useful test for screening for cannabis-impaired drivers could involve capitalizing on combinatorial batteries, where several deficits detected are unlikely to co-occur by chance, yielding a "fingerprint" of cannabis impairment.

In the real world, policy determinations might need to choose between (1) detection of recency of use or (2) tests whose results accurately predict driving impairment. There are potential new developments in biological measurements of THC at the roadside that are relevant to this discussion. As mentioned earlier, one major problem with presumptively intoxicated driver testing involves the lag between a driver being examined by police on suspicion of driving under the influence of drugs and the relevant blood sample being obtained. This deficiency is potentially addressed by a "THC breathalyzer" device currently under development or by specific field sobriety tests for cannabis behavioral impairment that reflect impaired driving. The device manufactured by Hound Laboratories (Oakland, CA), that is currently undergoing field testing and validation, is touted as a cannabis "Breathalyzer," that aims to detect trace amounts of THC from cannabis smoked in last 2–3 h. The technology is based on the fact that very small amounts of THC can purportedly be found in exhaled breath up to 3 h after one last inhaled cannabis. Because these quantities are tiny (picograms) as THC is not water-soluble, any successful detection technology has to be ultra-sensitive. If trials of the device are encouraging, it subsequent employment will at least address the current pronounced lag between police roadside testing and THC measurement, but does not fully address in itself the other problems noted above, i.e., does recency of smoking cannabis equate to impaired driving in the individual being tested. The difficulties in addressing the latter approach to find tests sensitive to actual driving impairment are exemplified by the legal issues surrounding "*per se*" laws.

[2]https://www.intox.com/?keyword_session_id=vt$\sim$adwords%7Ckt$\sim$%7Cmt$\sim$b%7Cta$\sim$442241803803&_vsrefdom=wordstream

What Is the Status of "*per se*" Laws for Cannabis-Impaired Driving?

A number of authors have examined issues of biological specimen collection to detect cannabis intoxicated drivers (132, 133). Wong et al. (134) usefully distinguish between three different approaches to identify cannabis-impaired drivers. The first is "effect based" requiring proof that the drug impaired the defendant's driving. This approach pertains in most US states, but its enforcement is complicated by two factors: proving that the drug resulted in impairment, and a paucity of agreed-on and standardized methods to quantify drug-induced driving (135, 136) impairment. If there is no consensus in how to measure driving impairment, attempts to link any type of predictive test to driving becomes problematic. The second approach consists of legislating that any detectable amount of THC or a metabolite is sufficient to convict the driver of drugged driving (137–139). The obvious difficulty with this approach concerns the well-documented lengthy persistence of THC and its metabolites in blood and to some extent oral fluids, particularly in regular users. Some investigators have shown that THC in stays in the body for many days, even up to a month after last use, obviously well-after the period of acute driving-related behavioral impairment (103, 140, 141).

The third approach is the use of "*per se* limits," as adopted by several US states. The intent of such legislative efforts is to set a quantitative threshold for blood THC concentrations that is reliably associated with driving impairment, and thus constitutes an offense "*per se*" (i.e., in and of itself). In part this assumption derives from (or is a supposedly logical extension of), well-established associations between blood alcohol concentrations and driver impairment. In the case of THC, the presumption in establishing such a threshold is that a defined range of blood or saliva THC concentrations exists that reliably separates cannabis-impaired drivers from those who may have residual detectable amounts, but are unimpaired (137–139, 142). Thus, *per se* cannabis DUI laws create a new traffic safety violation defined by state-defined levels of THC or its metabolites, where exceeding this legal limit by itself serves as proof of impairment (62, 137).

Many investigators in the field believe that the current evidence supporting such threshold is slim and that such legislative efforts are premature (138, 143). *Per se* laws vary enormously from state to state in the US. For example, 13 states prohibit driving with any amount of detectable plasma THC, while a handful of states specify a legal THC cutoff level, above which driving is illegal. These cutoff values themselves are also not consistent. In CO, MT, IL and WA, they are set at 5 ng/ml of blood (or in some cases, such as IL, blood breath or urine); in NV and OH the value is 2 ng/ml. The remainder of states prohibit driving while "incapacitated by" or "under the influence of" cannabis, so-called "effect-based DUI laws" as mentioned above, which essentially rely on a subjective judgment. While each such state hews to a slightly different legal standard, both these latter definitions translate to an ill-defined prohibition on "driving while high."

In 2007, an international group of experts met to determine whether a *per se* THC threshold could reasonably be set (138). They concluded that "…a THC concentration in the serum of 7–10 ng/ml is correlated with an impairment comparable to that caused by a blood alcohol concentration (BAC) of 0.05%. Thus, a suitable numerical limit for THC in serum may fall in that range.… (and).… offers an empirical basis for a *per se* limit for THC that allows identification of drivers impaired by cannabis. The limited epidemiological data render this limit preliminary." Further evidence from a variety of sources has cast this initial conclusion in doubt. The essential problem is that because of the distinct pharmacokinetics of THC, leading to a persistence of the drug and its metabolites in blood, and enormous inter-individual variability in metabolism of THC, the establishment of *per-se* limits is much more complex and ill-defined than for alcohol. The worst-case scenarios yield either false positives, resulting in conviction for driving under the influence of drugs (DUID) based on cannabis that the subject may have consumed days to weeks ago, when they are now completely unimpaired, or conversely false negative cases, where an individual's driving is in fact impaired by recently-consumed cannabis, but their THC blood or saliva level is below the *per se* threshold.

Recent publications shed considerable light on these concerns. Logan (143) examined data from 2 sources in ∼ 600 drivers arrested for DUI in which only THC was present compared to ∼ 350 drug-free controls, examined by a drug recognition expert, and ∼4,800 drivers arrested for DUI who tested positive for THC or its metabolites. The key findings were that compared to drug-free controls, the arrestees performed more poorly in psycho-physical tests including the Standardized Field Sobriety Test, but that the finger-to-nose test was the only indicator for which performance differed according to where the subjects were in the >5 ng/ml or < 5 ng/ml THC group (with the former showing more errors). Analysis of alternative cut points ranging from 1 to 10 ng/ml failed to identify any threshold THC level that was useful as a limit and would provide an acceptable level of agreement with the SFST. The authors reported that all of the candidate THC concentration thresholds would have misclassified a substantial number of drivers, producing both large numbers of false positives and false negatives, and concluded that "based on this analysis, a quantitative threshold for *per se* laws for THC following cannabis use cannot be scientifically supported."

Similarly, a 2019 report issued by the Congressional Research Service (144): concluded that "Research studies have been unable to consistently correlate levels of cannabis consumption, or THC in a person's body, and levels of impairment. Thus, some researchers, and the National Highway Traffic Safety Administration, have observed that using a measure of THC as evidence of a driver's impairment is not supported by scientific evidence to date." Finally, a recent study by Arkell et al. (145) concluded that "The blood and oral fluid *per se* limits examined often failed to discriminate between impaired and unimpaired drivers," ….. "Moreover, blood and oral fluid THC concentrations were poorly correlated with driving

impairment. … It is almost impossible to infer how much cannabis was consumed, or when it was consumed, based solely on a given concentration of THC in any biological matrix."….. "Due to erratic and route-dependent differences in THC pharmacokinetics as well as significant inter- and intra-individual variability, blood and oral fluid THC concentrations, unlike BAC (blood alcohol concentrations) for alcohol, provide little information as to the amount of cannabis consumed or the extent to which an individual may be intoxicated. Collectively, these results suggest that the *per se* limits examined here do not reliably represent thresholds for impaired driving."

A final issue is that people who use cannabis regularly may well-develop measurable tolerance to intoxicating and impairing effects of the drug. Although those effects remain to be established for driving performance, they would not translate legally into such individuals being allowed to drive with higher blood THC levels, paralleling the legal status with regard to alcohol tolerance. A separate issue is that the individuals who use cannabis daily or more frequently (e.g., to treat an ongoing medical condition), may always exceed the *per se* limit. This is another challenge that would likely need to be overcome if *per se* laws were to be widely adopted.

In summary, current evidence from the above studies suggests that efforts to establish *per se* limits for cannabis-impaired drivers based on blood THC values are still premature at this time. Considerably more evidence is needed before we can have an equivalent "BAC for THC." The particular pharmacokinetics of cannabis and its variable impairing effects on driving ability currently seem to argue that defining a standardized *per se* limit for THC will be a very difficult goal to achieve. Furthermore, there has been virtually no testing of driver impairment following oral consumption of "edibles," with virtually all testing being performed on inhaled cannabis derived from flower or vaporized liquid, despite the increasing consumption of cannabis in edible forms, and the distinct pharmacokinetic difference in time of onset and duration of intoxication between the oral vs. inhaled dosing methods.

DISCUSSION

It should be clear from the various studies reviewed in this paper, that cannabis-impaired driving is a real public health problem, in that it results in such drivers being significantly more likely to be involved in motor vehicle crashes (134). This is the case despite widespread emerging agreement that the relative risk of such impaired driving is significantly lower than other legislated drug use while driving, such as that resulting from alcohol or cocaine (25). However, the issue posed regarding cannabis legalization is not whether we intend to substitute one drug (cannabis) for another (e.g., alcohol), but that as a society we are deciding whether to legalize a new, previously illegal substance and thereby expose new individuals to the drug's side effects alongside its putative benefits. With increasing legalization of cannabis and therefore rising use rates/availability of the drug, particularly in forms containing higher percentages of THC, it is a mathematical certainty that this problem of cannabis-impaired driving will worsen. It is not possible to predict at this point whether absolute rates of cannabis-involved motor vehicle crashes will approach those seen with other substances, although the numbers of drivers projected to be cannabis users over the next decade will certainly increase significantly. So it would be mistake to conclude the problem of cannabis-intoxicated driving should not be addressed.

Given this context however, a number of conceptual and practical difficulties attend the reliable understanding and detection of such driving impairments, not all of which are widely recognized. Thus, while the intent of legislative efforts to detect and sanction cannabis-impaired driving are well-intended, their execution often falls short. In part this is because of the lack of understanding of the limitations of what the relevant science does and does not support.

What can we conclude to date regarding cannabis-impaired driving, based on available research? We know that the pharmacokinetics of alcohol and cannabis are distinctly different (17), as are for the most part the cognitive/behavioral domains relevant to impaired driving affected by each substance (14). These differences must be properly appreciated and recognized to prevent an unfounded, yet common tendency to elide the two drugs in matters pertaining to time courses of impairment, allocating significance to biological detection of the drug's presence or concentration in bodily fluids or exhaled breath, and developing roadside impairment testing or screening batteries. In terms of an affordable experimental laboratory paradigm with which to quantify impaired driving following acute dosing with cannabis, simulated driving appears overall to be sufficiently valid and reliable to be a reasonable surrogate for on-road driving experiments (100). Investigators have a reasonable idea of the duration of driving impairment following moderate doses of inhaled cannabis (146). We can be moderately confident of these observations tempered by the relatively small numbers of well-controlled studies (and small numbers of participants within those studies) examining cannabis-impaired drivers. Such small-scale studies are necessary because of the complex pharmacokinetics of THC compared alcohol, necessitating rather complicated and necessarily expensive experiments, and their downside is noted below.

As a general point, the literature also suggests that the issue of cannabis-impaired driving is bedeviled by a number of issues. What then are some of these difficulties and unknowns? It is important for both scientists and legislators to identify questions that either have the potential to direct this field forward, or that are needed to prevent it from running astray. In a climate where policymakers are particularly keen to legalize cannabis (amongst other reasons to enhance state revenues), there is appropriate consequent pressure to enact legislation to detect and deal with cannabis intoxicated drivers. This urgency however can lead to development of laws that are insufficiently reliant on the relevant known science, and that make unwarranted assumptions such as inappropriately adopting approaches that are appropriate for alcohol-intoxicated drivers, but not so for cannabis-intoxicated ones.

Thus, there remain many uncertainties and open questions regarding cannabis-intoxicated driving. Some such difficulties include lack of clarity in interpreting body fluid sampling after fatal and non-fatal crashes (the lengthy persistence of THC in the body after an acute dose makes interpretation complex) (140). As a consequence of the more complex pharmacokinetics of THC compared to that of alcohol, there is no straightforward way at the present time to equate measurements of THC levels in blood or saliva and current driving impairment. Related to this issue, there are still open questions regarding the time course of THC-related driving impairment following different acute doses of certain forms of the drug. In particular, duration and characteristics of impairment following increasingly-used cannabis concentrates with very high THC content ("dabs," "shatter" etc) and of edibles at different doses are understudied.

Unlike screening for alcohol impairment, as yet there are no agreed-on reliable and valid roadside sobriety testing paradigms for cannabis-impaired drivers, a lack of agreed-on norms for such testing (124), and approaches to account for a lack of sober baseline testing on presumptively impaired individuals (For example an older driver may be clumsy or exhibit mild psychomotor slowing at their sober baseline; this may yield a false positive on a poorly designed screening test).

Epidemiologic studies are often necessarily uninformative as to specific doses of THC that subjects consumed prior to driving, the drivers' impairment in key psychomotor domains at the time of the crash or assessment by law enforcement, and their biological levels of cannabinoids at the time of incapacitation as opposed to those a significant time later. While experimental laboratory studies can be informative regarding some of these questions, as they are under direct control, such investigations are complex to carry out, labor-intensive, usually expensive and notably difficult to obtain appropriate approval for. For all of those reasons they are often characterized by low subject numbers and thus statistically underpowered as noted above. In addition they lack direct validity, as few of them are conducted in real vehicles on an actual highway. Simulated driving in general is a safe valid substitute approach to test drug-related driving impairment, alongside cognitive & behavioral tests. However, the extent to which behaviors on different types of driving simulators are valid surrogates for on-road driving is underexplored.

Because of their vastly different pharmacokinetics, roadside testing measures and blood drug levels for cannabis impairment are not comparable to those available for alcohol (125), nor as simple to interpret. And because blood THC is still the gold standard, the practical difficulties in obtaining blood sampling and the time lag involved greatly complicate this issue. Standardization of collection times would be greatly desirable. Devices currently under testing that claim to detect the presence of smoked cannabis in breath samples may hopefully provide a reliable index of recent cannabis use, although this does not necessarily equate either to dose consumed or level of intoxication/impairment. Partly as a consequence of the above, and partly due to the complex pharmacokinetics of THC, *per-se* laws as currently construed are based on insufficient information and need to be more data-driven than they are at present (144, 145). The risk from this lack of knowledge is bi-directional: it can result in both under-detection of genuinely cannabis-impaired drivers and unnecessary criminal conviction of individuals with detectable THC in physiological samples who are nevertheless no longer intoxicated or driving-impaired.

A final significantly understudied question is the issue of synergy between impairing effects of alcohol and cannabis, particularly in light of their frequent simultaneous consumption. A particular concern is that low doses of each drug in combination, where neither alone is sufficient to cause manifest driving impairment, will lead to such impairment (147). If such synergy exists (and it is not yet convincingly demonstrated), then the characteristics of such combined intoxication need to be studied and defined as a first step to identifying them so that they can be reliably screened for and detected at the roadside.

RECOMMENDATIONS

Cannabis-impaired driving is an under-appreciated risk, and one with growing public health consequences. The situation is complicated by the somewhat skewed, agenda-driven reporting of this area of inquiry. For example both proponents and opponents of cannabis legalization each interpret statistical reports of motor vehicle crashes in relationship to cannabis legalization differently, hoping that the data can help further their own agenda. Relying on established science can definitely help the debate, particularly in instances where science finds itself bumping up against public policy, with legislators and others needing to be more current/topical about the existing research, so that they can make the best, most informed, policy decisions.

Looking first at the public health issue, because cannabis-intoxicated individuals are relatively aware of their impairment, particularly in comparison to alcohol-intoxicated drivers, many cannabis users erroneously assume that they are therefore safe to drive. Public service announcements emphasizing risks of "stoned driving," such as those used in Australia, would be a useful investment in the US. And although the evidence for synergy of impairment between alcohol and cannabis is still preliminary, this point could be easily incorporated into such PSA's, at least as a means of raising awareness of a potential problem. In the interim though, more research needs to be conducted in this area, given its potential public health importance.

Until there is more evidence-based consensus of opinion on meaningful thresholds for *per se* laws, we would recommend against reliance on such legislation. This is particularly the case given the significant inconsistencies in threshold values currently determined by different states in the US, and the rather weak scientific basis for such decisions. Any such laws cannot claim to be strongly based on current scientific evidence, which suggest collectively that standard based on detectable blood THC levels are not useful. These relatively recently ascertained facts tend to contradict established legislative efforts to demarcate cut offs. A related issue is the still current disconnect between demonstrating the presence of THC in a physiological sample

taken from a putatively intoxicated driver and the assumption of driving impairment.

There is widespread agreement on the dearth of available valid roadside tests that assess cannabis-related behavioral patterns specifically, and an obvious need to develop such screening paradigms that index actual cannabis-related driving impairment, rather than mere intoxication that may be unrelated to such impairment. It is important therefore to first validate experimentally any such putative field sobriety impairment measures in the context of concomitant on-road or simulated driving.

Finally, because cannabis concentrates and edible forms of the drug are becoming more popular (148, 149), and are both potent sources of THC and little-studied in terms of their types and time courses of driving impairment, it would be prudent for the National Institute on Drug Abuse to devote more resources on studying the effects of these forms of cannabis, and developing procedures for making them available to investigators for this purpose.

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