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Chapter 8

Cannabis Use Disorder

Iris Balodis and James MacKillop

Additional information is available at the end of the chapter

Abstract

Extensive changes in cannabis regulation accompany changing public attitudes toward cannabis use and legalization. Cannabis use is more prevalent when the drug is legal; therefore, there is a substantial need for an evidence-based understanding of the risks associated with cannabinoids. The current chapter reviews the definition of CUD, its prevalence and associated conditions, and the contemporary understanding of its causes to inform policy, prevention efforts, and treatment of CUD in a dynamic and evolving legislative landscape. Studies are currently limited by an absence of standardized methods to characterize cannabis consumption levels as well as compound composition. Understanding the harms associated with cannabis use and CUD will be fundamental in informing policy and supporting clinicians.

Keywords: cannabis, addiction, withdrawal, prevalence, neurobiology, neurocognition, motivation, comorbidities

1. Introduction

The term 'cannabis' refers to any product from plants of the *cannabis* genus, including marijuana and hashish, which are used primarily for their reinforcing effects. The main psychoactive compound in cannabis is Δ^9-tetrahydrocannabinol (THC); however, more than 100 other cannabinoids have been identified [1]. Other compounds include cannabidiol, cannabinol and cannabigerol; there is some evidence for protective effects of cannabidiol on THC's effects [2–4]. In a major shift from the 'war on drugs' campaigns that characterized the 1980s, legalization of cannabis for medicinal and recreational purposes is spreading across Canada and the United States. These extensive changes in cannabis regulation accompany changing public attitudes toward cannabis use and legalization [5]. Cannabis use is more prevalent when the drug is legal [5], therefore with the widespread social and legislative changes, there is a

substantial need for an evidence-based understanding of the risks associated with cannabinoids. Of particular concern is a potential rise in the development of cannabis use disorder (CUD), the psychiatric diagnosis of addiction to cannabis, and it is still unclear how legalization of the drug relates to the prevalence and severity of CUD [6]. Here we review the definition of CUD, its prevalence and associated conditions, and the contemporary understanding of its causes to inform policy, prevention efforts and treatment of CUD in a dynamic and evolving legislative landscape.

2. Definition of CUD

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [7] defines CUD as any 2 of 11 diagnostic criteria (**Table 1**), which include hazardous use of the drug (e.g. driving while under the influence), taking the drug in larger/longer amounts than intended, preoccupation with cannabis, unsuccessful efforts to cut down, drug tolerance, neglecting major roles to use, and social/interpersonal problems related to use. While the DSM-IV included two categories, including both abuse (putatively lower severity) and dependence (putatively higher severity), research supports a dimensional one-factor model, indicating that CUD can best be described as a unidimensional construct [8]. The number of endorsed criteria serves as a disorder severity marker: mild (2–3 criteria), moderate (4–5 criteria) and severe (6+ criteria) CUD [7]. Criteria for craving as well as withdrawal were added in the DSM-5, with 60% endorsement of craving and over 30% reporting withdrawal symptoms in past-year individuals with CUD [9].

3. Cannabis withdrawal syndrome

While it is popularly reported that there are no withdrawal effects from cannabis, there is evidence for withdrawal symptoms in CUD that are comparable to nicotine withdrawal in magnitude and consequences [10, 11]. The DSM-5 now includes a Cannabis Withdrawal Syndrome [7] which consists mostly of emotional and behavioral symptoms including anxiety, irritability, restlessness, depression, anger, as well as sleep, weight and appetite disturbances [12]. Less common physical symptoms include stomach pain, shakiness and sweating [12]. The clinical significance of the withdrawal syndrome was originally questioned; however, those symptoms are linked with increased functional impairment in normal daily activities [13]. The delayed onset of the withdrawal syndrome may explain why it is often overlooked: symptoms peak 2–3 days after cessation of heavy cannabis use and can last 2–3 weeks [12, 14]. Given the daily use of many individuals with CUD, they may not notice the symptoms. Withdrawal symptoms are nevertheless closely linked to relapse: most abstinent individuals experiencing withdrawal symptoms will take the drug to alleviate symptoms, thereby perpetuating cannabis use [15, 16]. The withdrawal syndrome is also important in medicinal cannabis use. Notably, cannabis withdrawal symptoms overlap with mood and anxiety disorder symptoms [7]—the very symptoms that some cannabinoid products are posited to treat. Many individuals cite mood modification as a motivation for cannabis use and are unaware that their short term use for symptomatic relief may result in a long-term withdrawal syndrome [17]. More

A.	A problematic pattern of cannabis use leading to clinically significant impairment or distress.

B. Two (or more) of the following occurring within a 12-month period:

1. Cannabis is often taken in larger amounts or over a longer period than was intended.
2. Persistent desire or unsuccessful effort to cut down or control cannabis use.
3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
4. Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to cannabis use; substance-related absences, suspensions, or expulsions from school; neglect of children or household).
5. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
6. Important social, occupational, or recreational activities are given up or reduced because of cannabis use.
7. Recurrent cannabis use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired).
8. Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
9. Tolerance, as defined by either or both of the following:
    a. a need for markedly increased amounts of cannabis to achieve intoxication or a desired effect;
    b. markedly diminished effect with continued use of the same amount of the substance.
10. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for cannabis (anxiety, irritability, restlessness, negative affect, as well as sleep and appetite disturbances);
    b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
11. There is craving or a strong desire or urge to use cannabis.

Table 1. Diagnostic criteria for cannabis use disorder in the Diagnostic and Statistical Manual of the American Psychiatric Association (5th edition).

generally, medicinal cannabis can be thought of as no different than other medications for which the pharmacology results in physiological dependence including a withdrawal syndrome (e.g., benzodiazepines and opioids), requiring clinical consideration and management. Indeed, the same is true for its abuse liability in the context of CUD.

4. Prevalence of cannabis use and cannabis use disorder (CUD)

Cannabis remains the most commonly used illicit* (*state/country-dependent) psychoactive drug. Large epidemiological studies show that ~43% of individuals in the US and Canada report having tried cannabis, with ~35% having tried it more than once [18–20]. Cannabis use

is highest in adults (ages 18–44), with just over half reporting using cannabis [18]. Past-year cannabis use in emerging adult populations (18–24 years-olds) is around 33.3%, with daily use almost 4% in this age group [18, 19].

Cannabis use prevalence rates from 2002 to 2012 show overall increases across North America [5, 18, 19, 21] and, increases in use and frequency of use coincide with declining risk perceptions of the drug [5]. Nevertheless, cannabis use trends differ longitudinally across specific age groups. For example, since 2002, prevalence rates appear to have increased in adults aged 25–44 (from 14 to 15.6%), remained stable in 18–24 year olds (around 33%) and decreased in the 15–17 age range (from 28.5 to 20%) [18, 19].

Prevalence rates for cannabis use disorder (CUD) range from 2.9% up to 19%—with approximately 13 million individuals worldwide meeting criteria [9, 22, 23]. Severe lifetime CUD rates are around 2%, with rates peaking during the emerging adulthood period (~21 years of age) [9]. There are also sociodemographic differences in prevalence rates—lifetime CUD rates are almost twice as high in males versus females, in adults 18–29, with a mean age of onset in the early twenties [9]. Unmarried individuals and those with lower socio-economic status report higher CUD prevalence rates; however, education appears largely unrelated [9].

One large epidemiological study in the United States also suggests that CUDs doubled between 2002 and 2012 [21], but not all longitudinal studies report the same prevalence trends in CUD [5, 20, 21, 24]. Discrepant prevalence rates may relate to underreporting in earlier studies as social acceptance of cannabis use increases [25]. Indeed, there are notable sociocultural influences on harm perception and willingness to acknowledge CUD symptoms varies between legal cultures [26]. Endorsement of CUD criteria can differ between countries and may relate to legalization status. For example, reports of failed quit attempts and withdrawal symptoms differ between the US and Netherlands [26, 27].

Importantly, CUD is associated with high levels of disability, including social and emotional functioning and greater CUD severity is associated with increasing levels of disability [9]. Information on cannabis-related disability is fairly new, as many previous studies did not include cannabis when studying disease burdens, but newer studies demonstrating that CUD can produce more years with disability [28]. Disability can persist even after CUD remission, although the reason for this is not yet clear [29]. It is also important to note that cannabis use and misuse (more broadly than just CUD) are associated with significant economic costs. In Canada, the estimated economic burden of cannabis use was 2.8Bn in 2014 and cannabis costs exhibited the largest increase among substances from 2007 to 2014, a 19.1% increase [30].

Finally, it is important to contextualize cannabis with other psychoactive drugs. One way to quantify addiction liability across substances is to examine the proportion of individuals who develop a substance use disorder, such as CUD, relative to the number of individuals who have at least tried a given substance. Using this metric in the large National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) cohort, fewer than one in ten (8.9%) individuals transitioned from any cannabis use to cannabis dependence (pre-DSM-5), which was lower than tobacco, alcohol, and cocaine [31]. Another way to contextualize relative risk is to consider the conditional probability between use and misuse (i.e., the proportion of active users of a given drug that have a diagnosable problem). Again,

drawing on large-scale NESARC data, 7.96% of cannabis users met criteria for cannabis dependence, which was higher than alcohol (5.82%) but substantially lower than tobacco (46.13%), heroin (26.96%), and cocaine (23.91%) [32]. In an interesting study of addiction experts using a multi-criteria decision analysis to judge substance use harms, cannabis was ranked 8th out of 20, behind alcohol, heroin, crack cocaine, methamphetamine, cocaine, tobacco, and amphetamine (in that order). Collectively, these findings suggest that although cannabis is far from without risk, it can also be thought of as lower risk than a number of other psychoactive drugs, both legal and illegal.

5. Common comorbidities

Other comorbid conditions are common in CUD; in particular, high rates of depression, anxiety, substance use and personality disorders are consistently associated with CUD [5, 9]. Understanding associations between CUD and other disorders is important as it provides more information on course and progression of the disorder.

Other substance use disorders (SUDs) are most commonly associated with CUD, with greater lifetime use of illicit drugs, including sedative/tranquilizers, painkillers, cocaine stimulants, club-drugs, hallucinogens, inhalant/solvents, heroin and other prescription drugs [33]. Recent epidemiological studies suggest increasing links with stimulant-based substances including MDMA, methamphetamine and prescription stimulants such as Ritalin [33]. It is possible that cannabis and stimulant co-abuse patterns represent individuals counterbalancing each drug's pharmacokinetic effects; for example applying sedative effects of cannabis following stimulant use [33]. Individuals with CUD are also more likely to also be current smokers and report high rates of alcohol use [9, 33]. Longitudinal studies are now providing more support for a causal relationship between early cannabis use and CUD as well as substance use and other psychiatric disorders. One large study demonstrated consistent, dose-response characteristics between early cannabis use and the development of CUD, other illicit substance use, depression and suicide attempts [34]. Altogether consistent data show polydrug use with CUD even when controlling for other health and psychiatric factors present before or during adolescence [33, 34].

In terms of other conditions, personality disorders are highly comorbid, in particular increased rates of antisocial and borderline personality disorder are noted [9]. Anxiety disorders are also linked to CUD, with Post Traumatic Stress Disorder (PTSD) most highly associated, followed by general anxiety and panic disorder [9, 21]. Applying the CUD severity specifiers (mild, moderate, severe) shows that increasing CUD severity is associated with the increasing strength of associations with these psychiatric conditions [21]—similar to CUD, clinical problems also exist on a severity continuum [5].

Converging lines of preclinical, epidemiological and experimental studies demonstrate strong links between cannabinoids and psychosis. The exogenous cannabinoid hypothesis posits that cannabinoid exposure is linked to the development of psychosis [35]. In controlled human laboratory settings, THC and cannabis extract administration produces increased positive symptoms, (including delusions, suspiciousness and perceptual alterations), negative

symptoms (including blunted affect, psychomotor retardation, reduced rapport), cognitive deficits (including learning, memory and attention),—some of which are related to schizophrenia including verbal recall impairment with increased "false positives" and "intrusions" [36]. In healthy individuals, these acute laboratory effects of cannabis are time-locked to drug administration, dose-related and transient [36].

Consistent with acute intoxication experiments, epidemiological studies also provide strong evidence for cannabis use increasing the risk for psychosis, even after adjusting for covariates [37]. While these studies have difficulty demonstrating a causal relationship with psychotic disorders, a growing number of longitudinal prospective studies are beginning to demonstrate these links [37]. There is still more research needed integrating neurobiology, epidemiology and psychopharmacology with particular compounds and potencies (including synthetic cannabinoids) to determine the magnitude and mechanisms of a causal effect [37]. Nevertheless, many individuals who use cannabis regularly do not develop psychotic disorders, therefore understanding those subgroups most at risk to propsychotic effects still needs to be clarified [35].

These findings have significant implications for treatment; high comorbidity rates underscore the fact that clinicians should screen for other conditions as these are likely present. Additionally, treatment approaches may need to target concurrent conditions. The co-relationship between CUD and other conditions is also important if CUD prevalence increases with legislative changes. While the causal relationship between these co-occurrences is not yet definitive, the close association nonetheless highlights important vulnerabilities and speaks to the importance of prevention and early intervention efforts.

6. Contemporary biopsychosocial model of etiology

Most individuals who try cannabis do not use it regularly or progress to CUD; therefore cannabis use alone is not sufficient to develop a CUD. Modern etiological theories of CUD emphasize neurophysiological adaptations that occur with persistent cannabis use, resulting in changes in cognition and motivation that recursively sustain drug-seeking, and important developmental features in which early cannabis use can create vulnerabilities for subsequent misuse and CUD.

6.1. Neurobiology and neurocognition

The endocannabinoid system in the brain modulates the activity of multiple neurotransmitters, including dopamine, through the cannabinoid receptor 1 (CB1) [38].

Most of the rewarding effects of cannabis are mediated through THC at the cannabinoid CB1 receptor in the brain [39–41]. These feelings of high relate to THC concentrations and can be blocked by a CB1 antagonist [42]. Additionally, there is evidence for the CB1 receptor in the development of dependence and in the withdrawal syndrome [39]. The brain responds to persistent cannabis consumption and the resulting circulating THC by homeostatically

downregulating CB1 receptors [43]; full recovery of CB1 receptor density has been detected after one-month abstinence and substantial recovery has been detected as soon as 72-hours [43, 44].

Both the acute and chronic effects of cannabis on the central nervous system are not well-understood in humans. CB1 receptors are heavily expressed in the striatum, hippocampus, amygdala and prefrontal cortex (PFC) and it is mostly in these regions that regular cannabis users show altered neuroanatomy [45]. Understanding neuroanatomic alterations with cannabis use is complicated by this drug's composition changes in recent years including different cannabinoid compounds with unique neural effects [45]. Since the 1990s, THC potency has increased from 4 to 12%; simultaneously, the average concentration of THC to cannabidiol has increased almost 80 times, suggesting plants are now bred with much higher THC concentrations (based on confiscated cannabis materials) [46]. These compound alterations are important as preclinical evidence suggests neurotoxic effects of THC on CB1 rich areas [45]. In humans, volumetric reductions and gray matter density alterations are consistently noted in the hippocampus, which relate to duration of use and cannabis dosage [45, 47, 48]. There are also links with compound composition; THC levels are inversely related to volumetric reductions while higher THC/cannabidiol ratios are associated with reduced volume and gray matter [45]. There is some evidence for neuroprotective cannabidiol effects as individuals with high cannabidiol levels do not show hippocampal volume reductions, however the mechanisms by which cannabidiol might offset THC effects are currently unknown [45].

Outside of the hippocampus, neuroanatomic alterations are additionally noted in high-density CB1 areas including the amygdala and striatum, PFC, parietal cortex, insula and cerebellum [45]. Altogether, these neuroanatomic alterations may result from THC metabolites accumulating and producing neurotoxic effects, cannabinoid receptor adaptations and/or changes in cells or vascularity [45]. All of these CB1-rich areas serve core functions in memory, attention, learning and reward and cognitive control. The hippocampus, PFC and amygdala are central in cognitive processing, indeed behavioral/functional impairments are noted in memory, attention and learning in CUD [49].

6.2. Cognitive functioning

Although the findings are mixed, overall subtle neurocognitive deficits in executive function, memory and learning are found with cannabis exposure, however, long term cannabis effects, and whether they are reversible, are still unclear [49, 50]. The ability to hold and manipulate information is consistently impaired with acute cannabis administration, although few studies report long-term working memory problems [50–53]. Diminished prefrontal cortex and hippocampal activity are noted during memory tasks in heavy cannabis users [54].

Of particular relevance to cannabis is the role of impulsivity—a systematic review provides support for alterations in inhibitory control in heavy cannabis users [55].

There are mixed behavioral findings when examining attention and concentration in CUD as well as impulsive behaviors following acute administration, short-term and long-term abstinence [50]. Nevertheless several neuroimaging studies demonstrate reduced prefrontal,

anterior cingulate and dorsolateral PFC activity during inhibitory control tasks [56–58]. Delay discounting, a behavioral economic measure of impulsivity reflecting preferences for smaller immediate rewards relative to larger delayed rewards, has been inconsistently associated with CUD, although a recent meta-analysis detected an overall small magnitude association [59]. This is consistent with greater impulsivity on this measure in relation to other forms of addiction, ADHD, and obesity [60–62].

Decision-making and risk-taking appear altered following acute cannabis administration as well as after short-term and longer-term abstinence [50]. It is yet unclear whether these effects are short-term or long-lasting or if these represent an exposure effect; while some studies report reversible findings following abstinence [63, 64] others report deficits even years after drug cessation, suggesting cumulative drug effects [65, 66]. Mixed findings again may relate to the changing compound profile of cannabis—most findings reported from acute intoxication experiments to date administer cannabis concentrations ~3% THC—significantly lower levels than the 12% rate often found in current samples [46]. Longitudinal studies with more potent drugs and more systematic control for cannabis use will be critical to clarify the effects. It is also possible that neurocognitive alterations exist prior to cannabis use; however, few longitudinal studies exist testing this hypothesis.

Clarifying neurocognitive impairments associated with CUD is important for understanding how the disorder progresses and impacts specific functions. To date, few studies examine how these impairments relate to recovery and abstinence. Understanding these impairments is also important for clinicians; particular deficits may put into question the usefulness of cognitive therapy [67] as specific cognitive functions may underlie learning adaptive responses and skills in behavioral therapies and avoiding relapse [50].

To date, functional neuroimaging studies examining the underlying neural substrates of these executive functions provide some evidence for altered processing [2, 50, 54, 56–58, 66]. Mixed findings may relate to the neuroimaging techniques employed, the constructs examined and the heterogeneity of characteristics in the samples studied.

6.3. Motivation and cannabis

One of the effects of chronic cannabis use in popular culture is changes in motivation. A recent longitudinal study showed cannabis use predicted lower persistence and initiative in college students [68]. Nevertheless, only a handful of studies have systematically examined cannabis' effects on motivation under controlled conditions. Laboratory studies of cannabis on motivation have found pro-motivational effects [69, 70], amotivational effects [71], or no effect [72]. These mixed findings may relate to problematic methodology, including differing cannabis doses (even within the same study), small sample numbers (e.g. N = 5), cross sectional designs, and differing compound composition over time. The heterogeneity of the cannabis users sampled in the studies is quite diverse; indeed, most human studies in cannabis users compare groups of cannabis users with varying levels of cannabis related problems (e.g. heavy, regular, occasional, light) to controls without assessing CUDs with rigorous diagnostic instruments. Additionally, some of the simple finger-tapping tasks that participants are asked to perform in the laboratory may not adequately capture the affected motivated behavior.

A recent study examining chronic effects of cannabis on reward learning, found that non-intoxicated individuals with CUD did not develop a response bias to reward-paired cues over time, suggesting an impaired ability to learn new rewards [73]. The neurobiology underlying impaired reward learning in CUD is currently not clear, including whether this is a predisposing factor or a result of heavy cannabis use. Nevertheless, the inability to form new reward associations lies at the core of an amotivational syndrome.

There is also evidence for heterogeneity of effects of different active cannabis concentrations and compounds. On another task examining effort-related decision-making, acute administration of cannabis with or without cannabidiol reduced the number of effortful choices for monetary reward compared to placebo [73]. Although the effortful choices were not differentially affected by the presence of cannabidiol in the compound, the investigators found that following cannabis administration with cannabidiol, the expected value of the reward (measured as the outcome value X the probability of receiving that outcome) increased the likelihood of making a high-effort choice. These results suggest that the presence of cannabidiol may affect THC's effects on processing expected value [73].

Amotivation in CUD may reflect that cannabis itself becomes a predominant motivator over other stimuli. One study investigated neural sensitivity to hedonic stimuli and showed that long-term daily users showed greater neural responses in reward networks to cannabis cues, relative to natural reward (fruit) cues [74]. Moreover, activity in frontostriatal temporal regions correlated with subjective reports of craving, THC metabolite levels as well as cannabis withdrawal scores. These findings suggest a hyper-responsivity and specificity of the brain's response to cannabis cues in heavy users. Additionally, the positive relationship between THC levels and neural response suggests that the latter may relate to cannabis use [74]. Another large longitudinal fMRI study prospectively examined striatal changes following cannabis use in youths at the ages of 20, 22, to 24 [75]. The striatum is a key node of the reward network that signals the motivational significance of a stimulus [76]. The results in youths showed that past-year cannabis use at each of the 3 scans related to striatal activation during reward anticipation, even when covarying for binge drinking or other drug use [75]. At the first scan, past-year cannabis use negatively correlated with striatal activation at Time 2, while past-year cannabis use at Time 2 was negatively associated with striatal activation at Time 3. Importantly, blunted striatal response was only present in those individuals with escalating drug use, suggesting that cannabis may be triggering these changes. Overall, this is the first study to show longitudinal associations between cannabis use and striatal activation during a nondrug reward anticipation task. More prospective studies are needed to evaluate whether an amotivational syndrome exists and the mechanisms by which it might develop.

6.4. Developmental influences

Given their increased drug experimentation, combined with a developing endocannabinoid system, adolescents represent a population particularly vulnerable to cannabis' effects [77, 78]. A meta-analysis of cognitive functioning in adolescents reported reduced cognitive functioning with frequent or heavy cannabis use, however, abstinence greater than 72 hours appears to diminish this effect [79].

To date, few neuroimaging studies examine adolescent populations with CUD. Adolescent chronic cannabis use is associated with greater performance-related activation in fronto-temporal areas, despite similar performance, suggesting neuroadaptations, or greater neural effort to perform memory and inhibition tasks [56]. A recent prospective cohort study scanned adolescents as they performed a working memory task prior to and after their first cannabis exposure [80]. The researchers found that those youths that would go on to use cannabis by the age of 15 (follow up), showed increased frontoparietal activity at baseline relative to the non-using group—these neural differences remained unchanged or increased when examined longitudinally. This is the first study to demonstrate frontoparietal and neurocognitive alterations prior to cannabis use. The researchers also found that at 12 years of age (baseline), the adolescents who would go on to use cannabis by the age of 15 (follow-up) had significantly lower scores on the cognitive battery. The difference scores on the cognitive battery from baseline to follow-up did not change, suggesting no significant neurocognitive changes following cannabis initiation. This prospective cohort study is one of the first to demonstrate specific neurocognitive features that may exist prior to cannabis exposure.

Given the changing compound composition of cannabis, combined with increasing THC levels and availability, understanding the effects of cannabis use on the brain and on memory, learning and reward processing should be a priority in adolescents. Accordingly, the Adolescent Brain Cognitive Development (ABCD) study recently launched by the National Institute of Health in the United States will follow 10,000 children longitudinally with multiple measures of neural, cognitive and emotional functioning [81]. This prospective cohort study will provide much-needed information on the long-term effects of cannabis use.

7. Other harms from cannabis

With the exception of nicotine, smoked cannabis includes many of the same chemicals and carcinogens found in tobacco that can damage lung tissue [82]. Heavy cannabis smoking is associated with chronic bronchitis and inflammation/injury in the larger airways [82]. Findings for other types of lung diseases and cancers are mixed, given high rates of comorbid tobacco use in regular cannabis users. Some of the chronic respiratory effects appear reversible, particularly in those individuals who only smoke cannabis [83, 84]. The impact of cannabis use on lung health may also change, as other methods of intake are gaining popularity, such as vaping or edibles [82].

One of the largest public health concerns with legalization of cannabis use is the effect of the drug on driving. Driving simulation studies show a relationship between blood THC levels and impaired performance, particularly with reaction time and lane position variability (i.e., weaving) [85]. One study had occasional cannabis smokers perform a visuomotor tracking task while undergoing fMRI after taking low-dose THC and found decreased psychomotor skills as well as reduced activity in fronto-parietal areas [86]. After alcohol, cannabis is the most commonly reported drug in driving accidents and fatalities [87]. There is current

ongoing research to better understand drug interactions, particularly with alcohol, as psychomotor impairments appear more severe when alcohol and cannabis are combined [85]. Indeed, greater information on the pharmacokinetic effects of cannabis on driving is needed, together with other drug interactions. One difficult problem for roadside testing remains that current cannabis detection through breath, saliva, blood or urine does not provide a reliable measure of recency or potency of use.

8. Future directions in CUD research

A fundamental question in cannabis research is whether observed alterations in neurobiology and cognition with heavy cannabis use persist with abstinence or whether they are reversible. The neurobiological studies are currently limited by an absence of standardized methods to characterize cannabis consumption levels as well as compound composition. The varying compounds in cannabis samples present a challenge to conducting systematic cannabis research; it is unknown how all of these might interact [28] and varying cannabinoid levels across studies may account for the diverse findings reported in the literature. Most studies rely on self-report measures of cannabis use and those that do toxicology analyses provide poor measures for quantifying exposure or the timeframe. Additionally, different measures of intake (i.e., inhaling, vaping, with/without tobacco) can also influence THC release/metabolism. Given all of the uncertainty between exposure parameters and neural substrates, many researchers are now calling for standardization of cannabis use metrics, particularly as the drug's effects appear more closely linked to dosage than duration of use [49]. Questions for future research include: (1) understanding CB1 receptor changes and relationships with reward, motivation, craving and abstinence, (2) clarifying cognitive and motivational alterations and whether these are precursors or consequences of CUD and (3) understanding the links between cannabis use and psychotic disorders. In this changing political, social, psychopharmacological and compositional landscape of cannabis, understanding the harms associated with cannabis use and CUD will be fundamental in informing policy and supporting clinicians.

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