Heavy cannabis use, dependence and the brain

*a clinical perspective*

Kroon, E.; Kuhns, L.; Hoch, E.; Cousijn, J.

**DOl**
10.1111/add.14776

**Publication date**
2020

**Document Version**
Final published version

**Published in**
Addiction

**License**
CC BY-NC-ND

**Link to publication**

**Citation for published version (APA):**
Heavy cannabis use, dependence and the brain: a clinical perspective

Emese Kroon\textsuperscript{1,2}, Lauren Kuhns\textsuperscript{1,2}, Eva Hoch\textsuperscript{3,4} & Janna Cousijn\textsuperscript{1,2}\textsuperscript{a}

Neuroscience of Addiction Lab, Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands, \textsuperscript{1} The Amsterdam Brain and Cognition Center (ABC), University of Amsterdam, Amsterdam, the Netherlands, \textsuperscript{2} Cannabinoid Research and Treatment Group, Department of Psychiatry and Psychotherapy, University Hospital, Ludwig Maximilan University, Munich, Germany \textsuperscript{3} and Division of Clinical Psychology and Psychological Treatment, Department of Psychology, Ludwig Maximilian University Munich, Munich, Germany \textsuperscript{4}

ABSTRACT

Aims: To summarize and evaluate our knowledge of the relationship between heavy cannabis use, cannabis use disorder (CUD) and the brain. Methods: Narrative review of relevant literature identified through existing systematic reviews, meta-analyses and a PubMed search. Epidemiology, clinical representations, potential causal mechanisms, assessments, treatment and prognosis are discussed. Results: Although causality is unclear, heavy and dependent cannabis use is consistently associated with a high prevalence of comorbid psychiatric disorders and learning and memory impairments that seem to recover after a period of abstinence. Evidence regarding other cognitive domains and neurological consequences, including cerebrovascular events, is limited and inconsistent. Abstinence after treatment is only achieved in a minority of cases; treatment targeted at reduction in use appears have some success. Potential moderators of the impact of CUD on the brain include age of onset, heaviness of use, CUD severity, the ratio of 9-tetrahydrocannabinol to cannabidiol and severity of comorbid disorders. Conclusions: Current evidence of long-term effects of daily cannabis use and cannabis use disorder on brain-related outcomes is suggestive rather than conclusive, but use is associated with psychiatric morbidity and with cognitive impairments that recover after a period of abstinence.

Keywords: brain, cannabis use disorder, cognition, neurological disorders, review, treatment.

INTRODUCTION

This narrative review summarizes our knowledge of the relation between heavy cannabis use [defined as (near) daily use], cannabis use disorder (CUD) and the brain. Cannabis contains more than 100 different cannabinoids [1], of which 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most studied. THC is the main psychoactive cannabinoid responsible for the cannabis ‘high’ and addictive potential. CBD has been suggested to ameliorate THC effects while having little psychoactive effect on its own [2]. Aside from plant-based cannabis products, synthetic cannabinoids mimic the effects of THC. Given the scope of this review, the limited evidence on the effects of synthetic cannabinoids and the chemical differences between plant-based and synthetic cannabinoids, we will only discuss the effects of plant-based cannabis products unless otherwise specified.

Although CUD is one of the most common substance use disorders (SUDs), effects of CUD on the brain are still rarely studied. Daily cannabis use has been established as one of the best predictors of CUD. As such, findings from heavy users and, where possible, individuals with a diagnosed CUD will be evaluated. After a brief epidemiological overview, clinical representations, potential causal mechanisms, assessments, treatment and prognosis will be discussed. Table 1 provides a summary of the acute and long-term effects of heavy cannabis use and CUD on brain structure, cognition, psychiatric comorbidities and neurological disorders.

EPIDEMIOLOGY

Cannabis is the most used drug world-wide, with an estimated 188 million recreational users in 2017.
Table 1 Summary of current evidence for the effects of cannabis on the brain.

<table>
<thead>
<tr>
<th>Brain structure</th>
<th>Short-term effects</th>
<th>Long-term effects</th>
<th>Suggested Reading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No evidence to support or refute effects</td>
<td>Limited evidence for reduction hippocampal and pre-frontal cortex volume. <strong>Inconsistent</strong> evidence for other brain structures. <strong>Potential moderators:</strong> heavy history ↑, CUD severity ↑, early onset ↑, sex</td>
<td>[3]</td>
</tr>
</tbody>
</table>

**Cognition**

<table>
<thead>
<tr>
<th>Learning and memory</th>
<th>Sufficient evidence THC/cannabis impairs (non)-verbal learning and episodic memory. <strong>Limited</strong> evidence impairments other types of learning and memory. <strong>Potential moderators:</strong> dose ↑, early onset ↑, heavy history ↓, low THC:CBD ratio ↓</th>
<th>Sufficient evidence for impairments in current heavy users. <strong>Insufficient</strong> evidence for lasting effects after abstinence. Evidence for (partial) recovery. <strong>Potential moderators:</strong> subacute THC/cannabis effects ↑, early onset ↑, heavy history ↑, comorbid psychopathology ↑</th>
<th>Limited evidence impairments in current CUD and lasting effects after abstinence. Preliminary evidence for (partial) recovery. <strong>Potential moderators:</strong> subacute THC/cannabis effects ↑, early onset ↑, heavy history ↑, CUD severity ↑, comorbid psychopathology ↑</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craving</td>
<td>Sufficient evidence THC/cannabis reduces craving. <strong>Potential moderators:</strong> age ↓, heavy history &amp; CUD ↑</td>
<td>Sufficient evidence for increased craving. <strong>Limited</strong> evidence for increased brain activity reward-related areas after exposure to cannabis-related stimuli. <strong>Potential moderators:</strong> heavy history ↑, CUD severity ↑</td>
<td><strong>Sufficient</strong> evidence, increased craving, <strong>limited</strong> evidence increased brain activity reward-related areas after exposure to cannabis-related stimuli. <strong>Potential moderators:</strong> heavy history ↑, CUD severity ↑</td>
</tr>
<tr>
<td>Cognitive biases</td>
<td>Limited evidence cannabis related approach bias and attentional bias</td>
<td><strong>Sufficient</strong> evidence for attentional bias, <strong>insufficient</strong> evidence approach bias in current users. No evidence to support or refute lasting effects after abstinence. <strong>Potential moderators:</strong> heavy history ↑, CUD severity ↑, THC ↑, craving ↑</td>
<td><strong>Limited</strong> evidence attentional bias, <strong>no evidence</strong> to support or refute approach bias in current CUD. No evidence to support or refute lasting effects after abstinence. <strong>Potential moderators:</strong> heavy history ↑, CUD severity ↑, THC ↑, craving ↑</td>
</tr>
<tr>
<td>Emotion processing</td>
<td>Consistent, but <strong>limited</strong> evidence THC/cannabis impairs emotion recognition, particularly negative emotions. <strong>Potential moderators:</strong> low THC:CBD ratio ↓</td>
<td><strong>Limited</strong> evidence for impaired emotion identification/recognition and reduced activity in CB1 rich brain areas during emotional processing in current users. No evidence to support or refute lasting effects after abstinence. <strong>Potential moderators:</strong> heavy history ↑, CUD severity ↑, THC ↑, craving ↑</td>
<td><strong>Limited</strong> evidence impaired emotion identification/recognition and reduced activity in CB1 rich brain areas during emotional processing in current CUD. No evidence to support or refute lasting effects after abstinence</td>
</tr>
<tr>
<td>Attentional control</td>
<td><strong>Sufficient</strong> evidence THC/cannabis impairs attentional control. <strong>Potential moderators:</strong> dose ↑, heavy history ↓</td>
<td><strong>Sufficient</strong> evidence for impairments sustained and divided attention in current heavy users. <strong>Insufficient</strong> evidence for lasting effects after abstinence. Evidence for (partial) recovery. <strong>Potential moderators:</strong> sub-acute THC/cannabis effects ↑, early onset ↑, heavy history ↑</td>
<td>No evidence to support or refute lasting effects</td>
</tr>
<tr>
<td>Working memory</td>
<td><strong>Inconsistent</strong> evidence THC/cannabis impairs working memory</td>
<td>There is <strong>inconsistent</strong> evidence for long-term working memory deficits in heavy users. <strong>Limited</strong> evidence for recovery in heavy users. <strong>Potential moderators:</strong></td>
<td>No evidence to support or refute lasting effects</td>
</tr>
</tbody>
</table>

(Continues)
<table>
<thead>
<tr>
<th></th>
<th>Short-term effects</th>
<th>Long-term effects</th>
<th>Suggested Reading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Heavy cannabis use</strong></td>
<td><strong>Cannabis use disorder</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Suggested Reading</strong></td>
<td><strong>Suggested Reading</strong></td>
<td></td>
</tr>
<tr>
<td>Motor inhibition</td>
<td><strong>Sufficient</strong> evidence THC/cannabis impairs inhibition ongoing responses (stop-signal task). <strong>Inconsistent</strong> results with other inhibition tasks. <strong>Potential moderators</strong>: dose ↑</td>
<td><strong>Limited</strong> and <strong>inconsistent</strong> evidence for impairments</td>
<td>[18–20]</td>
</tr>
<tr>
<td>Decision-making</td>
<td><strong>Insufficient</strong> evidence THC/ cannabis impairs decision-making</td>
<td><strong>Insufficient</strong> and <strong>inconsistent</strong> evidence for impairments</td>
<td>[18–20]</td>
</tr>
<tr>
<td>Intelligence</td>
<td>No evidence to support or refute effects</td>
<td>There is <strong>insufficient</strong> and <strong>limited</strong> evidence for reduced intelligence</td>
<td>[21–24]</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Potential moderators</strong>: CUD duration ↑</td>
<td></td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>No evidence to support or refute effects</td>
<td><strong>Sufficient</strong> evidence statistical association. Causality unclear. <strong>Potential moderators</strong>: early onset ↑, CUD severity ↑</td>
<td>[25,26]</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>No evidence to support or refute effects</td>
<td><strong>Sufficient</strong> evidence statistical association. Causality unclear. <strong>Potential moderators</strong>: CUD duration ↑</td>
<td>[25,27]</td>
</tr>
<tr>
<td>Anxiety</td>
<td><strong>Sufficient</strong> evidence THC/ cannabis increases risk anxiety and panic attacks. <strong>Potential moderators</strong>: dose ↑, low THC: CBD ratio ↓</td>
<td><strong>Sufficient</strong> evidence statistical association. Causality unclear. <strong>Potential moderators</strong>: high THC:CBD ratio ↑, early onset ↑</td>
<td>[28,29]</td>
</tr>
<tr>
<td>PTSD</td>
<td>No evidence to support or refute effects</td>
<td><strong>Sufficient</strong> evidence statistical association. Causality unclear. <strong>Potential moderators</strong>: high THC:CBD ratio ↓, early onset ↑</td>
<td>[30]</td>
</tr>
<tr>
<td>Psychosis and schizophrenia</td>
<td><strong>Sufficient</strong> evidence THC/ cannabis increases risk transient positive symptoms. <strong>Limited</strong> evidence THC/cannabis increase risk negative symptoms. <strong>Potential moderators</strong>: dose ↑, low THC : CBD ratio ↓, schizophrenia diagnosis ↑</td>
<td><strong>Sufficient</strong> evidence statistical association. Causality unclear. <strong>Potential moderators</strong>: heavy history ↑, low THC:CBD ratio ↓, early onset ↑</td>
<td>[31–33]</td>
</tr>
<tr>
<td>Other substance use disorders</td>
<td>–</td>
<td><strong>Sufficient</strong> evidence statistical association. Causality unclear. <strong>Limited and inconsistent</strong> evidence for gateway to illicit, alcohol and cigarette use</td>
<td>[34,35]</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td><strong>Limited</strong> evidence THC/cannabis increases the risk cerebrovascular accidents. <strong>Potential moderators</strong>: heavy history ↑, synthetic</td>
<td>No evidence to support or refute effects</td>
<td>[36,37]</td>
</tr>
<tr>
<td></td>
<td>No evidence to support or refute effects</td>
<td>No evidence to support or refute effects</td>
<td></td>
</tr>
</tbody>
</table>
Brain tumours

CUD = cannabis use disorder; THC = 9-tetrahydrocannabinol; PTSD = post-traumatic stress disorder; CBD = cannabidiol.

Table 1. (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Short-term effects</th>
<th>Long-term effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heavy cannabis use</td>
<td>Cannabis use disorder</td>
</tr>
<tr>
<td>Cannabis use disorder</td>
<td>↑, ↑</td>
<td>↑, ↑</td>
</tr>
<tr>
<td>Comorbidity ↑</td>
<td>↑, ↑</td>
<td>↑, ↑</td>
</tr>
<tr>
<td>Other drug use ↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CUD = cannabis use disorder; THC = 9-tetrahydrocannabinol; PTSD = post-traumatic stress disorder; CBD = cannabidiol.

(approximately 3.8% of the world population [39]). Paralleling population increases, the number of cannabis users has increased 16% between 2006 and 2016 [40]. There are large continental and regional differences in cannabis use trends [40]. Globally, the potency of cannabis (%THC) is increasing. Data from the United States (8.9% in 2008 to 17.1% in 2017) and Europe [herbal cannabis: 5.0% (2006) to 10.2% (2016), cannabis resin: 8.1% (2006) to 17.2% (2016)] indicate more than a twofold increase in potency within the last decade, with the THC : CBD ratio also rising [1]. Past-year use among individuals older than 15 years is currently stable, at approximately 7.4% in Europe [39,41], decreasing in Australia (from 12.6% in 2001 to 10.4% in 2016 [42]), but increasing in Canada (from 9.1% in 2011 to 14.7% in 2015 [39]) and the United States (from 13.5% in 2015 to 13.9% in 2016 [40]). These increases are suggested to parallel trends in legalization and decreases in risk perception [43]. Cannabis use appears less common in Africa, Asia and South and Central America [44]. Nonetheless, the limited data available suggest that the annual prevalence is also increasing in these regions [44].

Prevalence of use is highest for young adults [39] and men [41,45]. Approximately 10% of users become daily users [46]. Daily use is one of the best predictors of CUD, with approximately one in three developing dependence [47]. World-wide, CUD is among the most common SUDs [48]. An estimated 22.1 million people suffer from CUD, two-thirds of whom are male [48]. Most CUDs remain untreated [39,49], but among those seeking treatment, demands are higher for adolescents and young adults [46]. Among those not seeking treatment, the annual remission rate is approximately 17% [50]. Genetic vulnerability, early life trauma, mental health problems, tobacco use, high potency cannabis, early onset and intensity of use are suggested to play an important role in the development and severity of CUD [51–53].

CLINICAL REPRESENTATION

Cannabis use disorder as a brain disease

CUD is defined as problematic cannabis use leading to clinically significant impairments or distress [54]. Although still debated, SUDs including CUD are increasingly referred to as a brain disease. Supporting this, SUDs are associated with changes in brain structure and function that potentially impede recovery [55]. THC binds to the endocannabinoid 1 (CB1) receptor which is densely present in brain areas involved in learning, memory, reward, motivation and control—processes crucial to SUD development, maintenance and recovery. The few existing studies that investigated brain mechanisms underlying CUD suggest that abnormal functioning of CB1 rich brain areas is common (e.g. [6,56]) and linked to increased cannabis use [57], (future) cannabis use problems [6] and craving [56]. Studies investigating brain structure in cannabis users also point towards alterations in CB1 rich brain areas. While results are generally inconsistent, reductions in volume have been most consistently reported in the hippocampus and pre-frontal cortex, including the orbitofrontal cortex [3]. Studies in CUD specifically are missing: however, hippocampal volume appears to be smaller with increasing CUD severity [58]. Additionally, the role of endocannabinoids in cerebral autoregulation and vascular tone, together with acute transient vascular effects of THC (e.g. hypertension), have been proposed as a mechanism for vascular-event-related brain damage in cannabis users (e.g. [59]).

Cognition

Cognition refers to all mental processes that support behaviour and thoughts. Cognition can be subdivided into behaviourally distinct processes with partially overlapping brain mechanisms and encompasses complex cognitive functions, such as decision-making, that rely on the integrity of many lower level functions such as attention, reward processing and memory. The results of research into the effects of cannabis effects on cognition is shaped by impairments of motivation and control-related cognitive functions, known to be impaired in other SUDs [18,19], and clear impairments of learning and memory during cannabis intoxication [4,60]. SUDs are characterized by extremely strong motivations to use and loss of control over use [61]. Repeated cannabis use is thought to sensitise and condition users to the positively experienced effects of...
use [62]. This will subsequently manifest in increased positive affect and reward attribution, craving and cannabis-oriented cognitive biases (e.g. attentional bias, approach bias) in response to cannabis-related stimuli. Impaired control over these motivational processes would be reflected in compromised attentional control, working memory, inhibition and decision-making. Therefore, besides potential short- and long-term effects on learning and memory, evidence for the relation between cannabis use and motivation and control-related cognitive functions will be discussed.

Learning and memory

Cannabis intoxication impairs learning and memory. Episodic memory (autobiographical events) impairments are most prominent [4,5]. Impairments may depend on THC dose and heavy cannabis users are generally only affected at higher dosages [4,5]. Long-term effects are less clear. Impairments are most often found up to a few weeks after cessation (e.g. [63,64]). Although few studies focused on heavy use and CUD specifically, more severe users may experience larger deficits [64,65] and less recovery of cognitive functions after abstinence [66]. Longer lasting subacute effects in heavier users and early onset use have both been linked to poorer recovery [67,68] but other factors such as high THC : CBD ratios [69] and less recovery of cognitive functions after abstinence may also play a role.

Motivation and control-related cognitive functions

Craving. Heavy and dependent cannabis users display craving and increased brain activity in reward-related brain areas after exposure to cannabis-related stimuli [7,71]. Craving is stronger in more severe users [8] and has been found to predict CUD problem severity [6], treatment outcome [72] and withdrawal severity [9] in heavy users. Craving generally decreases during intoxication [10], but adolescents may be less prone to these satiation-induced decreases in craving [11].

Cognitive biases. Although research is limited and replication is warranted, heavy and dependent users consistently show an attentional bias (i.e. fast attentional orientation and maintenance of attention) towards cannabis-related stimuli [12]. Attentional bias is weakly associated with craving [73] and may be higher with increasing CUD severity [74] and use of cannabis with high THC : CBD ratios [75]. Approach bias (i.e. relative automatic approach action tendencies) towards cannabis-related stimuli may also be predictive of cannabis use [76] and has been found to be stronger in intoxicated heavy users [77]. Moreover, higher activity in cognitive control-related brain areas during an approach–avoidance task has been shown to predict reductions in problem severity [78].

Emotion processing. Cannabis intoxication consistently impairs emotion recognition [13]. This effect is attributed to THC, while CBD partially attenuates the effect [14]. Effects may be larger for negative emotions, as the use of THC has been found to selectively impair the normative attentional bias for negative but not positive faces. This impairment was accompanied by reduced activity for negative faces in reward, learning and cognitive control-related brain areas [15]. Heavy and dependent cannabis use have also been associated with emotion identification and discrimination deficits (e.g. [16]). Impairments may mostly be guided by misinterpretation of negative faces [16]. However, both negative and positive emotional stimuli have been linked to reduced brain activity in CB1 rich brain areas such as the anterior cingulate cortex and amygdala in heavy users [17].

Attentional control. Attention refers to the capacity to direct attention towards relevant information and can be measured in a drug relevant (e.g. attentional bias discussed above) or irrelevant context. Cannabis intoxication consistently impairs attention in a dose-related manner and heavy cannabis users seem less affected due to tolerance (e.g. [79,80]). Current evidence suggests long-term impairment of attention in tasks that require focus on a single (e.g. maintenance) or multiple processes (e.g. disengagement and orientation) in heavy cannabis users that resolve after abstinence [20,67]. Moreover, earlier onset has been related to stronger impairments [67,68].

Working memory. Findings on the effects of cannabis intoxication (e.g. [60,81]) and long-term effects of heavy and dependent use (e.g. [82]) on working memory (i.e. temporary memory storage crucial to use, update and manipulate information needed for daily life decision-making) are less consistent than effects on learning, memory and attention. Heavier use (e.g. [64,70]) and increasing task complexity [20] may relate to stronger deficits, but comparability between studies is low. Age may also play a role, with spatial working memory deficits found in adolescents [82] but not adults [83].

Inhibition and decision-making. Inhibition refers to the capacity to over-ride a prepotent response or stop the execution of a response when behavioural goals change [84]. Inhibition is multi-faceted, referring to fast forms of motor inhibition as well as slower decision-making related forms of inhibition (e.g. delayed gratification and decision-making) [85]. Regarding motor inhibition, cannabis intoxication consistently and dose-dependently
decreases the ability to stop behaviour (e.g. [79,86]). However, these effects may be partially driven by the motoric effects of cannabis. Regarding decision-making-related inhibition, results are inconsistent with some studies reporting increased impulsive decision-making (e.g. [81,87]), while others do not (e.g. [86,88]), or only find effects on reaction times [89]. Long-term effects on inhibition and decision-making are unclear due to the mixed results of a limited number of studies with variable research designs [18]. Nonetheless, decision-making deficits may be more pronounced in more dependent users [90] and insensitivity to negative information (e.g. monetary loss) may increase risky decision making in cannabis users (e.g. [91]).

Intelligence

Several longitudinal studies suggest that heavy cannabis use is related to a decline in IQ [21,22]. However, more recent studies suggest that this decline is more probably explained by other confounding variables [e.g. socio-economic status (SES) [23,24] and subacute effects of cannabis intoxication [21]].

Psychiatric comorbidities

US surveys estimate substantial comorbidity of CUDs with mood (39.6%), anxiety (30.5%) and personality (35.9%) disorders [92]. Most evidence points towards a bidirectional relationship, where CUD increases the odds and symptom severity of other psychiatric disorders and vice versa [93]. For example, there is substantial evidence that cannabis use negatively impacts the development of manic symptoms in bipolar disorder (e.g. [27]) and CUD is associated with higher risks for comorbid depression (e.g. [94]). In turn, depression may increase CUD risk [25]. Self-medication may play an important role in explaining these relationships. Although the therapeutic effects of cannabis remain to be confirmed, reduction of anxiety or post-traumatic stress disorder (PTSD)-related sleep problems are commonly reported motives of use [30,95]. However, cannabis intoxication may also trigger anxiety attacks, especially at higher doses [14,28], and increase the risk for an anxiety disorder [28,29].

Although evidence is mixed [96,97], earlier onset and heavier patterns of use may increase risks for comorbid psychiatric disorders. For example, adolescent-onset relative to adult-onset cannabis users had an increased risk of developing depression in mid-life [26]. Early onset has also been associated with an increased likelihood of attempting suicide (e.g. [98]).

The relationship between cannabis and psychosis and schizophrenia is among the most investigated topics in the cannabis literature [31–33]. Intoxication studies show a time-bound, dose-dependent effect of cannabis on positive psychotic symptoms (e.g. paranoia, delusions and fragmented thinking) (e.g. [99]). THC is responsible for these transient effects, which CBD may attenuate (e.g. [100]). Studies investigating negative psychotic symptoms are scarce, but there are indications of THC-induced blunted affect, psychomotor symptoms, and emotional withdrawal (e.g. [101]). For individuals with schizophrenia, cannabis use can aggravate symptoms (e.g. [102]). Age of onset, heavy use and using high-potency cannabis increases the risk for psychosis and schizophrenia [33]. However, more longitudinal studies are needed to establish causality and exclude the possibility of other explanations, such as shared (genetic) risk factors or self-medication of premorbid symptoms.

Other substance use disorders

Co-use of tobacco, alcohol and/or cannabis is common, and individuals with more psychological problems are more likely to be polysubstance users [103]. Regarding brain effects, it is likely that polysubstance use has cumulative or synergistic effects [104]. Cannabis has been proposed as a gateway to harder illicit drugs such as cocaine and opiates, and has indeed been linked to an elevated risk of cocaine and opiate use initiation (e.g. [34]). However, it remains questionable whether cannabis itself, and not social or genetic factors that cause shared liability, explains this sequence of transition [35,105]. In addition, a reversed gateway effect from cannabis to tobacco use has been reported (e.g. [106]).

Neurological disorders

Cerebrovascular accidents

As the endocannabinoid system plays a role in cardiovascular regulation, it is suggested that cannabis use might result in cardiovascular problems that lead to cerebrovascular accidents [107]. Although there are only a handful of reports of haemorrhagic stroke after cannabis use, there have been multiple reported cases of ischaemic strokes and transient ischaemic attacks that were retrospectively associated with cannabis use [36]. In multiple cases of cannabis-associated ischaemic stroke, re-exposure to cannabis resulted in a new ischaemic stroke [36]. Recent reviews indicate a temporal link between cannabis use and ischaemic stroke/transient ischaemic attacks, but most studies fail to control for important confounding variables such as tobacco use [37,108]. Further research is needed to establish a causal relationship [59]. Current evidence indicates that amount of use, the use of synthetic cannabis, age, gender, comorbidities and other drug use may moderate this relationship (e.g. [59,108]).
Brain tumours

There is currently insufficient proof of a relationship between heavy cannabis use/CUD and brain cancer [38]. There are no studies investigating heavy users/CUD specifically and most studies in cannabis users suffer from low power and poor control over tobacco smoking [38]. However, one study in a small sample of monthly cannabis users [109] indicated an increased risk for malignant primary adult-onset glioma, warranting further research.

Causal mechanisms

The causal mechanisms are largely unknown. Most evidence is correlational and based on indirect measures of brain structure and function. Longitudinal studies crucial to evaluate causality are limited. Cognitive deficits and co-morbid psychopathology could be pre-existing or driven by a third shared causal factor. Nevertheless, animal and human pharmacological studies provide insights into the potential working mechanisms.

THC resembles the naturally occurring agonist anandamide in its properties as a partial CB1 and CB2 (though with lower binding affinity) agonist [110]. THC can thereby mediate dopaminergic and serotonergic neurotransmission, including dopamine release in the striatum and ventral tegmental area [111], areas crucial for salience and reward processing. THC-induced striatal dopamine release appears blunted in dependent users [112]. THC-mediated alterations in salience processing may underpin cognitive and psychopathological deficits associated with cannabis use [113]. CBD may play an attenuating role by eliciting effects opposing those of THC in brain areas involved in reward processing and cognitive control [113].

In rodents, chronic THC exposure causes a reduction in the number and signalling efficiency of CB1 receptors (e.g. [114,115]). This down-regulation has been related to withdrawal [116]. Abstinence may restore CB1 density, with more rapid reversal in the striatum and mid-brain than in cortical regions [117]. A more recent study has also found reversible and regionally selective down-regulation of brain CB1 receptors in human heavy cannabis users [117].

Furthermore, heavy cannabis use has been associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is involved in natural stress responses. Dysregulation of the HPA-axis may cause the blunted stress response to negative emotional stimuli [118] and stress-related withdrawal symptoms such as dysphoria, anxiety and irritability [55,118] observed in CUD.

Route of administration also influences the effects of cannabis. When inhaled (e.g. smoking, vaping or dabbing), cannabinoids quickly travel via the lungs into the bloodstream towards the brain. In contrast, cannabinoids in edibles take longer to reach the bloodstream via the digestive system and bind to peripheral cannabinoid receptors (e.g. in the liver) before reaching the brain. THC reaches high levels in plasma very quickly, but is also a lipophilic substance easily absorbed by fat [119]. Although plasma is generally cleared of THC and its metabolites within a week [119,120], THC is still slowly released by fat into the bloodstream [120]. In line with this, heavy compared to occasional users exhibit slower blood clearance of THC, potentially causing longer-lasting subacute effects [119].

Assessments in clinical practice

The DSM and ICD are the golden standards for diagnosing CUD and other psychiatric disorders. According to the DSM-5, CUD can be defined as problematic cannabis use leading to clinically significant impairments or distress [54]. While the ICD-10 [121] and old DSM-4 [122] still differentiated between abuse and dependence, the DSM-5 classifies CUDs as mild (two to three criteria), moderate (four to five criteria) or severe (six or more criteria), depending on the presence of any of 11 diagnostic criteria over a period of 12 months [54]. The diagnostic criteria pertain to loss of control, social problems, use in risky situations and physical dependence. In addition, the DSM-5 includes craving and cannabis withdrawal syndrome as novel diagnostic criteria. Withdrawal symptoms include nausea, headaches, mood changes, aggression, appetite changes and craving. These symptoms normally peak within the first week of abstinence, and severity has been associated with heaviness of cannabis use [123].

Reliable and commonly used DSM- and ICD-based structured interviews to diagnose and assess the severity of CUD include the Structured Clinical Interview for Depression (SCID), Mini-International Neuropsychiatric Interview (MINI), Psychiatric Research Interview for Substance and Mental Disorders (PRISM) and World Mental Health-Composite International Diagnostic Interview (WHM-CIDI). Although used mainly in academic settings, multiple brief questionnaires have been developed to assess and screen the severity of use-related problems [e.g. Cannabis Use Disorders Identification Test Revised (CUDIT-R) [124], Cannabis Use Problems Identification Test (CUPIT) [125], Severity of Dependence Scale (SDS) [126]] and quantity of use; for example, time-line follow-back (TLFB) [127]. These measures have good psychometric properties and are time-efficient, making them a valuable addition in clinical practice to gather helpful information about quantity and patterns of use [128].

Cognitive assessments can be extremely informative in clinical practice. At early stages of treatment, patients may experience cognitive impairments that can result in poorer understanding of therapeutic interventions and materials, hampering learning and change processes. Computerized cognitive assessments and training programmes...
can be helpful, although they are rarely used and evaluated. The Montreal Cognitive Assessment (MoCa [129]) is a short, 10-minute, cognitive battery that can be used to identify mild cognitive impairment in individuals with SUDs [130]. Clinicians are also advised to adapt communication to the individual patient’s cognitive capacities. Repetition of information may be helpful until the patient attains abstinence and cognition improves. Treatment manuals (e.g. [131]) describe such therapeutic procedures. Similar to cognition, comorbid psychopathology has been shown to affect treatment retention, efficacy and prognosis (see section Prognosis; [9,132–134]), warranting assessment in early stages of treatment. In research, a large variety of cognitive tests and psychopathology assessments are used, with choices often guided by the available time and relevance to the subject of investigation. To improve our current knowledge base and clinical practice, more efforts should be made to align and standardize clinical and research assessments.

**Treatment: current practice and new developments**

Cannabis has become the primary reason for first-time treatment entry across all illicit drugs world-wide [44], with a 75% increase in Europe over the past 10 years [39]. Possible explanations for this rise in treatment demands include increasing CUD prevalence, changes in risk perception, increasing cannabis potency, changes in referral practices and increasing availability and accessibility of treatment services [135]. In Europe, 5–10% of daily and near-daily users are currently in outpatient treatment—indicating a large treatment gap [49]. Despite high treatment demands, the number of clinical trials testing mental and psychosocial interventions for CUD specifically is still small [136].

**Psychosocial interventions**

Evidence supports the effectiveness of combinations of cognitive–behavioural therapy (CBT), motivational enhancement therapy (MET) and contingency management (CM) or psychosocial problem solving (PPS) [49,136]. These interventions are usually short (one to 12 sessions) and compared to inactive rather than active control groups [137]. In children and adolescents, family therapy interventions are also promising [49,138]. Most clinical trials assess cessation or a reduction of use as primary outcomes. Rates of cannabis abstinence are low and unstable [136], but comparable to treatments for other SUDs. Interventions aimed to reduce frequency and intensity of consumption appear more successful in reducing CUD severity and cannabis-related psychosocial problems in addition to use [136].

**Pharmacotherapy**

No medications are as yet licensed for CUD treatment. A systematic review [139] indicated that SSRI antidepressants, mixed-action antidepressants, bupropion, buspirone and atomoxetine are probably of little value in the treatment of cannabis dependence. The evidence base for the anticonvulsant gabapentin, oxytocin and N-acetylcycteine is weak. Another systematic review [140] found mixed effects of THC preparations for the reduction of cannabis withdrawal symptoms and treatment retention. A recent randomized controlled trial (RCT) [141] tested the efficacy and safety of the FAAH-inhibitor PF-04457845 in male daily cannabis users and found that those who received the drug, compared to placebo, had fewer withdrawal symptoms and used less cannabis 4 weeks later. More clinical studies are needed to examine the benefits and safety of drugs for the treatment of CUDs.

**New developments and future directions**

Reaching and motivating youth with CUD is difficult, but targeted digital media interventions are beginning to show some benefits in clinical settings [142] and beyond [143]. Cognitive remediation as an adjunct to CBT and MET may also be promising. Little previous research has examined the neuropsychological factors that affect individuals with CUD ability to learn new skills in CBT, but there is initial evidence that lower scores on neuropsychological tests increase the chance of treatment dropout [144]. Exercise during an early treatment phase may accelerate the return of cognitive functioning and have a direct effect on whether patients find treatment useful and complete it [145]. Moreover, add-on training to improve working memory [146] or reduce cognitive biases [147] may also increase treatment success. While the causal neurobiological mechanisms underlying CUD will need to be unravelled, pharmacotherapy [139] and neurostimulation (e.g. Transcranial Magnetic or Direct Current stimulation) aimed to enhance cognition [148] have shown initial success in other SUDs. Considering the heterogeneity of CUD and high comorbidity rates, the potential benefits of individualized treatment options should also be addressed in future research.

**Prognosis**

Despite the unclear and highly variable long-lasting effects of heavy cannabis use and CUD, prognosis can be assumed to be worse for cannabis users with higher CUD severity. As evidence-based CUD treatments are limited and abstinence rates are low (6-month follow up: 24–35% [149,150]), prevention is pivotal. Heavy users in contact with health professionals should therefore always be encouraged to stop or reduce use to prevent further escalation. Among those that seek treatment, cognitive deficits may reduce
treatment attendance [134]. While some cognitive deficits may precede CUD, cognitive deficits appear to recover for those maintaining abstinence [151,152].

Although more studies are needed to confirm this and study its mechanisms, odds for long-term abstinence (with or without treatment) and cognitive recovery may be negatively influenced by withdrawal severity [123,153], use of cannabis with high THC : CBD ratios [152], age of onset [152], CUD severity [68] and comorbid mental disorders [153]. Although increased risk of developing a CUD is highly undesirable, self-medication for anxiety, PTSD, depression and psychosis-related symptoms should be taken into account [93].

While reducing cannabis use might improve treatment for comorbid psychiatric disorders, aggravation of symptoms combined with craving and withdrawal after reducing cannabis use may also cause setbacks in treatment. Importantly, effective pharmacotherapy for comorbid psychiatric disorders may reduce cannabis use as a consequence [154].

To date, no strong causal relationship between cannabis use and neurological disorders, such as brain cancer and stroke, has been established. The effect of continued cannabis use or abstinence on the prognosis of neurological disorders is therefore unclear.

CONCLUSIONS, LIMITATIONS AND FUTURE DIRECTIONS

Despite the growing societal burden, our knowledge of the long-term effects of heavy cannabis use and CUD on brain-related outcomes is extremely limited. Heavy and dependent cannabis use is consistently associated with a high prevalence of comorbid psychiatric disorders and with learning and memory impairments that seem to recover after abstinence. Evidence regarding other cognitive domains and neurological consequences, including cerebrovascular events, is limited and inconsistent. Potential moderators of the impact of heavy cannabis use and CUD on the brain include age of onset, heaviness of use, CUD severity, THC : CBD ratio, and severity of comorbid disorders. The causal direction of the relationship between heavy cannabis use and CUD on cognitive, psychiatric and physical health outcomes remains to be established. The current knowledge base is limited by the use of inconsistent terminology, varying research designs and paradigms causing low comparability across studies, as well as insufficient control of potential confounding factors (e.g. tobacco use). Future studies on individuals diagnosed with CUD are crucial to distinguish between dependence-specific effects and effects of frequency of use. Furthermore, longitudinal studies are needed to unravel the underlying mechanisms and parse the role of shared risk factors (e.g. genetics) and pre-existing cognitive deficits and psychiatric symptoms to establish causality. There is a high need for more effective treatments as abstinence after treatment is achieved by a minority. Currently, treatment targeted at reductions in use appears most successful. To improve our current knowledge base, more efforts should be made to align and standardize clinical and research assessments.

Declaration of interests

None.

Acknowledgements

This review was supported by grant 1R01 DA042490-01A1 from the National Institute on Drug Abuse.

References

Cannabis and the brain: a clinical perspective

569


