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REVIEW

Acute cognitive and psychiatric effects of cannabinoids

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Summary

Cannabinoids are known to affect cognitive function and to trigger or worsen psychiatric symptoms and disorders. This review aims at providing a comprehensive outline of the existing literature on the acute effects of cannabinoids on these domains. Recent and relevant evidence shows that cannabinoid intake acutely affects several basal cognitive domains such as learning, memory, and attention. As well, clear acute impairing effects on decision-making, sensitivity to reward, and inhibition are consistently reported, whereas evidence on compromised working memory and problem solving is less solid. Cannabinoid consumption leads to euphoria, relaxation, and increased sociability but can also trigger undesirable effects such as psychotic symptoms/disorders, anxiety and panic, dysphoria, and negative affect in both clinical and non-clinical samples. Δ9-tetrahydrocannabinol (THC) seems the main culprit for these acute impairments, while evidence supporting potential protective effects of cannabidiol (CBD) is mixed but continues to grow. Dose and THC:CBD ratio, frequency and chronicity of use, pre-existing vulnerability, and demographic/psychosocial factors may moderate these effects. High-potency cannabis ("skunk") and synthetic cannabinoids ("spice") have stronger adverse effects and are more dangerous. The existing literature is limited by heterogeneity in terms of populations investigated, compounds and doses administered, and route of administration. More research on high-potency and synthetic compounds, less explored domains, and the role of CBD is needed. This review provides crucial insights on the acute effects of cannabinoids on cognition and mental health that may have important clinical, social, and legal implications.

Keywords: anxiety, cannabinoids, cognition, psychosis, review

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BACKGROUND AND AIMS

The use of cannabinoids for both recreational and medicinal purposes is unceasingly increasing, raising concerns about their acute and long-term effects on human health [1,2]. In particular, both occasional and frequent cannabinoid intake has been associated with altered cognitive performance and the development or worsening of psychiatric symptoms [1]. However, there seem to be differences in impairments between acute and chronic use [3]. Besides physical symptoms (such as conjunctival hyperaemia, xerostomia, increased appetite, tachycardia, and elevated blood pressure), acute cannabinoid intake can produce substantial neuropsychiatric effects that are seen during and shortly after the peak of active metabolites in the bloodstream [1,4,5]. Although natural cannabis contains more than 100 phytocannabinoids, its effects are mainly attributed to Δ9-tetrahydrocannabinol (THC), a high-affinity cannabinoid receptors partial-agonist [6,7]. Another important cannabinoid is cannabidiol (CBD), a compound that seems to have the ability to counteract psychotic symptoms and cognitive impairment associated with cannabis use, also possibly having anxiolytic properties [8-11]. Thus, the acute effects of cannabis mainly depend on the concentrations of THC and CBD as well as on the THC:CBD ratio [4,12-14]. In recent years, high-potency cannabis – known as "skunk" – has increasingly taken over the market [15,16]. Skunk typically presents with THC concentrations of 12-18% and

virtually no CBD [17]. Hence, its use is associated with more adverse effects than a typical marijuana/hashish joint and may be especially harmful to mental health [15]. Besides, there is a growing diffusion of synthetic cannabinoids (SCs), which became popular as "legal highs" under brand names such as "Spice" and "K2" [9,18]. Hundreds of different types of SCs have been isolated worldwide [9]. Notably, these compounds have extra ingredients (preservatives, additives, fatty acids, amides, esters, benzodiazepines, and O-desmethyltramadol) that are added purposely to induce greater psychoactive effect and as masking agents [19-21]. SCs generally have more potent effects than THC [6,7,18], with an earlier onset and peak as well as a shorter duration [22]. The acute effects produced by cannabinoids also depend on other factors such as the route of administration (with edibles producing delayed but stronger and longer-lasting effects than smoked cannabinoids), the individual susceptibility to single components, and previous use habits with the subsequent development of tolerance [5,12,13,23]. Over the decades, a substantial body of evidence documenting the acute psychoactive effects of cannabinoids has accumulated. With the aim of providing a well-rounded understanding of the complex interplay between cannabinoids and brain physiopathology, in this review we will synthesise the literature available on how their intake acutely impacts cognitive function and increases the risk of psychiatric symptoms and disorders.

COGNITION

It is well-established that acute cannabinoid use transiently diminishes the ability of the brain to hold and process information, and evidence that cannabis intoxication is associated with short-term impairment across several cognitive domains is substantial [3,13]. Data regarding SCs, albeit suggesting even more severe cognitive impairments, are still sparse [9,24]. Notably, cognitive function emerges as the domain displaying the highest degree of tolerance to the acute effects of cannabinoids in frequent users [3,23].

Verbal learning and memory

The disruption of verbal learning and memory is one of the most frequently observed acute effects of cannabinoids [3,13]. The encoding of new memories is compromised during cannabinoid intoxication, leading to subsequent deficits in recalling them, while the retrieval of old memories consolidated when not under influence seems unaffected [13,25]. Clear data are available regarding the acute impairing effects of THC on immediate and delayed recall and sometimes recognition accuracy [3]. In people using cannabis more than once a week, evidence suggests a development of tolerance to the memory-impairing effects of acute THC intake [26]. Notably, impaired verbal learning and memory are consistently observed across different age groups (including adolescents and young adults) and even in occasional users.[3] Significant associations between poorer performance in regular users and dose, frequency, quantity, duration, early age of onset of cannabis use, THC:CBD ratio, and SC use have been reported, with long-term users experiencing greater impairment [24,27]. Improvement or recovery with abstinence has been observed in some studies, but not consistently [3]. In contrast, CBD seemingly offers protection against the acute memory-impairing effects of THC [3,13,28].

Attention

The compromised ability to focus and sustain attention has long been recognized as a defining feature of cannabinoid intoxication [3,9,12] and documented in several studies in both adolescent and adult users [3]. Acute exposure to cannabinoids impairs focused, divided, or sustained attention, often in a dose-dependent manner [12]. Furthermore, false alarms are increased under influence of THC [29]. Individuals who use cannabinoids daily may develop tolerance, resulting in milder impairments [3], but conversely seem to remain partially impaired when they go abstinent [30].

Executive function

The acute intake of cannabis has notable but differential effects on executive function [31-33]. These effects are mainly due to THC, while research on the effects of CBD is scarce [34]. Evidence on the acute effects of SCs is preliminary and mostly preclinical [34].

Acute cannabis intake causes impairments in working memory [13,31], though inconsistently [32] and differentially across a wide range of tasks [3]. Cannabis-induced deficits in working memory are seen more in the ability to manipulate information while it is "online" (e.g., when doing mental arithmetic) than in the ability to retain it for brief periods (for instance, when remembering a telephone number before dialling it) [13]. Performance accuracy after THC intake seems decreased for moderately high working memory loads only but enhanced for low working memory loads, possibly reflecting a compensational neural mechanism [35]. Interestingly, impairments have been reported in recent or heavy users – with greater frequency and quantity of use correlated with poorer performance – but not in older users [3]. Impaired working memory typically remains after other acute effects have subsided [31] and may persist even for a few weeks, but appears to mostly resolve with longer abstinence [3].

During acute cannabis intoxication, individuals tend to exhibit heightened tendencies towards risky decision-making, impaired inhibition, and increased sensitivity to reward [3], although research findings are somewhat mixed and task-dependent [13]. Acute THC administration putatively affects decision-making by altering sensitivity to reward and punishment [3]. Acute cannabis use has also been associated with poor inhibitory control, with decreased inhibition efficiency and increased inhibition errors in a dose-dependent manner [3,12,31,32]. Interestingly, people who are more susceptible to the psychotogenic effects of cannabis seem more likely to make inhibition errors than those who are not [36]. These alterations comprehensively lead to an increase in risk-taking behaviours, a feature observed in both infrequent and regu-

lar cannabis users [3,37,38]. All these impairments, together with cannabinoid-induced motor function deficits, have implications for activities that demand precise motor coordination and attentional focus, such as driving [3]. Notably, these negative effects on cognitive function seem to be offset when cannabis also contains CBD [12,31].

THC administration was found to impair planning, reasoning, association, task performance, and problem solving, though not in all studies [3]. Interestingly, these effects look consistent across samples of occasional, moderate, and heavy users but generally tend to be relatively mild, possibly because of compensatory neural mechanisms [3,32]. Verbal fluency may also be affected by acute cannabis use, with the existing body of research, albeit narrow, seemingly suggesting that impairments are more likely to occur in older individuals with longer durations of exposure, while in younger users it may depend on factors such as their intellectual capacity and the specific task [3]. Finally, although the subjective effect of cannabis distorting time is well known, objective evidence about cannabinoid intoxication and altered time estimation is extremely limited [3]. Some lines of evidence have suggested that a psychoactive dose of THC increases internal clock speed, with time overestimation and underproduction [39]. This effect seems not to be dose-related and blunted in chronic cannabis smokers [39].

PSYCHIATRIC SYMPTOMS

The intoxication effects of cannabis are described by users as mild euphoria and "high", relaxation, increased sociability, decreased anxiety and boredom, and enhanced sensory-perceptive experiences, all within a general pleasant feeling [9,40,41]. Non-clinical populations consistently rank relaxation high as a reason for use [40]. Nevertheless, a number of undesired psychiatric symptoms can be triggered by acute cannabis consumption in both occasional and frequent cannabis consumers, whether already affected by a psychiatric disease or without a history of mental illness [9,12,42-44]. First-time use, dose, THC concentration and THC:CBD ratio, frequency of use, personality traits, and pre-existing vulnerability are among the main moderating factors [9,12,40]. SCs can induce reactions similar to those occurring with natural cannabis, however they occur more frequently, peak early, are more pronounced, and show more variability, ranging from sedation to agitation [22,45,46]. In studies comparing natural cannabis and SC users, SCs were correlated with more psychotic symptoms, agitation, and longer hospitalizations [47]. Some psychiatric effects may be experienced for days and weeks after consuming SC products [48].

Psychotic symptoms

Cannabinoids can produce acute, transient, dose-dependent psychosis-like effects in people without a history of mental illness, especially at high doses [4,16,43,44,49]. Dose-dependent psychotic experiences have been reported by 15-50% of individuals in community surveys [40]. Symptoms include depersonalization, derealization, dream-like euphoria, disorientation, delusions, hallucinations, paranoia, and psychomotor agitation [4,50]. Some lines of evidence suggest that THC can lead not only to auditory speech hallucinations but also to visual distortions and illusions [4]. These symptoms generally resolve in a short time (few hours) but may last up to a week, and are generally followed by full recovery [51]. Negative symptoms of psychosis, including decreased affective range, spontaneity, and rapport, as well as psychomotor retardation and emotional withdrawal, were also reported in several studies and determined not to be related to self-rated sedation [52,53].

Heavy cannabinoid use may lead to an acute functional psychosis, similar to an acute schizophreniform disorder and lacking the organic features of a toxic psychosis.[4] In some cases, cannabinoid-induced psychotic episodes may persist for a substantial period of time after acute intoxication [54]. This happens especially with SCs, giving rise to the term "spice-ophrenia" [16,19,40,48]. The risk of developing psychotic illness in vulnerable individuals seems to be dose-dependent [16,55]. Beginning cannabis use at a younger age may potentially elevate the susceptibility to experiencing psychotic symptoms or developing full psychotic disorders [43], but this issue remains uncertain [42].

In subjects with pre-existing schizophrenia, the acute use of cannabinoids can lead to re-emergence or worsening of symptoms and even require hospitalization in those who were psychiatrically stable and adherent to medications [40,43,44]. However, although smoking cannabis seems to worsen negative affect and increase hallucinations in individual with psychosis[56], these people describe relief of dysphoria, relaxation, increased socialization, enhancement of positive affect, and, in some cases (10%), amelioration of psychotic symptoms [57-59]. This, together with the fact that the increases in hallucinations are delayed, may explain cannabis use despite the worsening of positive symptoms in this population [56].

The psychotogenic effects of cannabis are largely attributable to THC but the mechanisms through which these occur and which factors predict vulnerability are not completely clear [42]. Some data provide evidence for a modest increase in striatal dopamine transmission after acute administration of THC, although to a far lesser extent than other recreational drugs [13]. Besides dopaminergic transmission, other potential candidate mechanisms of psychosis-like symptoms include excitatory-inhibitory imbalance between GABAergic [60] and glutamatergic [61] systems. The use of SCs may cause even more frequent and more severe psychotic disorders and psychosis-like conditions[6], although their role in psychosis seems more complex than any single chemical component might explain, and these effects may not be a simple extension of the typical effects of natural cannabis [62]. Those experiencing psychotic episodes related to SC use are also reported to present with higher/more frequent levels of agitation and behavioral dyscontrol compared to those psychotic

episodes described in natural cannabis misusers [63]. The moderating role of CBD on the development of psychotic symptoms after acute cannabis intake is less clear: CBD may attenuate psychosis-like symptoms induced by THC in non-clinical samples of healthy volunteers, especially when CBD is administered immediately before THC [11]. Further, at high doses (800-1000 mg), CBD seems potentially effective in reducing positive – but not negative – symptoms of schizophrenia [8]. However, these beneficial effects of CBD are not unequivocal across all available studies [42]. Since the interest in understanding the effects of CBD on psychotic manifestations is rapidly increasing[8], research is likely to provide further insights in the near future.

Anxiety and panic

Anxiety reactions are the symptoms most frequently associated with acute cannabinoid use [51,64]. Cannabinoids can cause acute and short-lasting episodes of anxiety, intense fear, panic, and phobic attacks, especially in those who are not habitual users, at high doses, and/or when SCs are used [9,51]. These effects are less evident among frequent users, who seem to develop some level of tolerance [12]. Individual predisposition to anxiety disorders, history of previous episodes, and context of use are acknowledged risk factors for developing acute cannabinoid-induced anxiety states [51]. The anxiogenic properties of THC have been firmly established and seem to occur especially at higher THC dose and THC:CBD ratio [12,51,64]. On the other hand, CBD shows a consistent anxiolytic action and seems to decrease the anxiogenic effect of THC when the THC:CBD ratio in cannabis is low without having an anxiogenic effect at high doses [10,65]. In view of this, cannabis containing primarily CBD, albeit deserving further investigations, has been suggested as a suitable option to manage anxiety or stress-related disorders [65].

Mood

Euphoria, enhancement of positive affect, and increased openness to others are consistently reported [40,56,66] and are described as some of the main reasons for cannabis use [58], although transient dysphoria may develop instead [49]. However, while prolonged use of both natural and synthetic products is a well-known risk factor for the insurgence and/or the worsening of acute recurrencies in bipolar disorder [67-69], little is known regarding how its acute intake can cause/trigger manic symptoms in both healthy individuals and people already suffering from bipolar disorder. No accounts of frank and enduring mania after a single use of natural cannabis are available in the literature, and only one case of a manic episode triggered by a single dose of a SC was reported [70]. Anyways, grandiosity is often reported among the typical symptoms of acute psychotic episodes induced by cannabinoids [40]. Similarly, while chronic cannabinoid use does not have positive long-term effects on the course and outcome of depression [71], there seems to be no data regarding the possible triggering effect of acute cannabinoid intake on the development of long-lasting depressive symptoms. Anyways, cannabis can acutely bring about transient emotional lability, intense introspection, or sadness [24,51,64].

LIMITATIONS OF THE EXISTING LITERATURE

The body of work published on the acute effects of cannabinoids on cognition and mental health is heterogeneous in several factors. The populations included in these studies are quite variable, especially concerning participants' history of cannabis use, age, and comorbidities. Studies also differ in terms of compounds administered, THC concentration and THC:CBD ratio, and route of administration. In this regard, despite their now widespread use, data about SCs are still limited. Lastly, while the literature is quite substantial with respect to domains such as memory, attention, psychotic symptoms, and anxiety, further research must necessarily be carried out on others in order to provide more consistent evidence.

CONCLUSIONS

The available body of evidence indicates that the intake of cannabinoids – and especially of high-potency or synthetic ones – acutely impairs cognitive function and increases the risk of psychiatric symptoms and disorders. On the other hand, the potential health benefits of CBD suggest that it may have a protective role and might potentially be used to treat different neuropsychiatric symptoms and conditions, although some findings are against this trend and more research is needed.

As high-potency cannabis and ever new SCs become more and more available on the market, interest in the medical use of cannabis grows, and the use of cannabinoids continues to rise as a whole, it becomes increasingly crucial to keep on studying their acute effects and develop evidence-based guidelines for their utilization. Progress in the study of cannabinoids and their psychoactive effects will provide more data relevant to clinical, public health, and legal spheres, ultimately helping optimize the potential benefits and concurrently minimize associated risks.

Conflicts of interest statement

The authors declare no conflicts of interest.

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Authors' contributions

D.C.: conceptualization, methodology, investigation, writing - original draft; F.B.: conceptualization, methodology, writing - review & editing, supervision; C.C.: methodology, writing - review & editing, supervision; G.C.: conceptualization, writing - review & editing, supervision, project administration.

Ethical consideration

This study did not involve human subjects and/or animals.

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