MEDICAL SCIENCE MONITOR

REVIEW ARTICLES

e-ISSN 1643-3750
© Med Sci Monit, 2023; 29: e939749
DOI: 10.12659/MSM.939749

Received: 2023.02.07
Accepted: 2023.04.01
Available online: 2023.04.07
Published: 2023.05.06

Exploring the Link Between Attention-Deficit Hyperactivity Disorder and Cannabis Use Disorders: A Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEFG 1 Julia Helena Gujska
ADEF 2 Andrzej Silczuk
BDEF 3 Robert Madejek
BDEF 3 Agata Szulc

1 Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
2 Department of Public Health, Medical University of Warsaw, Warsaw, Poland
3 Department of Psychiatry, Faculty of Health Sciences, Medical University of Warsaw, Pruszków, Poland

Corresponding Author: Andrzej Silczuk, e-mail: silczuk@wp.pl
Financial support: None declared
Conflict of interest: None declared

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder in children and adults. In the substance use disorders (SUDs) population, ADHD prevalence reaches 23.1%, leading to more severe substance abuse progression and reduced treatment effectiveness. Cannabis is the most common illicit drug used among the ADHD population.

The increasing popularity of medical marijuana (MM) has raised concerns about its potential impact on neurocognitive functions, particularly in adolescents. Persistent cannabis use can cause permanent changes in brain structures and circuits. This review aims to overview the comorbidity of ADHD and SUDs, focusing on cannabis use disorders.

Theoretical models of the etiologies of ADHD and SUDs were investigated to establish a framework for analyzing their underlying neurocognitive mechanisms. The reward and motivational brain circuitries involving the default-mode network and the endocannabinoid system were emphasized. The high prevalence of SUDs in the ADHD population has ramifications, including earlier age of onset, self-medication, and reduced performance in various domains. Cannabis use disorders are particularly significant due to the increasingly widespread use of cannabis and its perceived safety.

The review highlights the lack of theoretical background on the therapeutic properties of medicinal cannabis, criticizing its speculated applications in the ADHD population. This article reviews the current understanding of the association between ADHD and cannabis use, emphasizing the need for further research and a cautious approach to MM's potential therapeutic applications.

Keywords: Attention Deficit Disorder with Hyperactivity • Cannabis • Medical Marijuana • Substance-Related Disorders

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/939749

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

ADHD is a prevalent neurodevelopmental disorder affecting children and adults, with prevalence rates of 5% in children and 2.5% in adults [1-3]. Neurodevelopmental disorders often result in cognitive, language learning, and behavioral disturbances [4]. ADHD has been associated with reduced school performance, poorer occupational performance, and an increased risk of comorbid disorders and substance use disorders (SUDs) [1,5-7].

SUDs are highly prevalent in individuals with psychiatric conditions, and their co-occurrence is referred to as "dual disorders" [8-10]. Substance use, particularly cannabis, is common among individuals with ADHD [11,12]. The prevalence rate of ADHD in the SUDs population reaches 23.1% [10]. Cannabis is the most frequent illicit drug of choice in the ADHD population [13].

Cannabis use disorders (CUDs) can alter brain circuitry and cause disturbances in executive functioning [14-17]. The influence of cannabis on executive functioning has been studied extensively, with findings suggesting that strains with high delta-9-tetrahydrocannabinol (Δ9-THC) impair executive functioning, while those with high cannabidiol (CBD) do not [9].

Medical marijuana (MM) has gained popularity in recent years [15]. However, discussions about its potential therapeutic application often lack systematization [18]. Moreover, increasing cannabis use may be rooted in inaccurate perceptions of the compound as safe and non-addictive [20,21]. Data show that MM laws can contribute to increased cannabis use and CUDs in adults, who perceive it as being less harmful than other drugs due to its growing legalization status and interest [22]. Furthermore, individuals with comorbid psychiatric disorders also perceive marijuana as being less harmful [23].

Research shows that more than half of adults with ADHD meet the criteria for SUDs at some point in their lifetime [24]. This review aims to explore the link between ADHD and CUDs, focusing on these disorders' characteristics, diagnostic features, and etiologies. The analysis delves into their common neurocognitive mechanisms and functional consequences, with a particular interest in the endocannabinoid system (ECS) [19], default-mode network (DMN), and motivational and reward circuitry. Additionally, the review assesses the application of MM as an alternative therapeutic intervention for ADHD and CUDs.

Theoretical models on ADHD and CUDs' etiology were investigated to set a framework for further analysis. These models suggest shared fundamentals, such as genetic background, neurobiological substrates, and risk factors [10]. The comorbidity of ADHD and SUDs may result from high levels of sensation-seeking and impulsiveness, shared dopaminergic dysregulation of reward and motivational systems, or the self-medication hypothesis [10].

Epidemiological research indicates a strong correlation between ADHD's polygenic risk scores and CUDs, suggesting a common genetic risk [12]. Cannabis is the most commonly used psychoactive drug in the United States and Europe, with studies showing high prominence among teenagers and adolescents, who are especially prone to cognitive impairment [15-17].

Cannabis sativa (ie, cannabis) contains over 144 differing cannabinoids, of which CBD and Δ9-THC are the most frequently studied [9,18]. The effects of these 2 substances are distinct; Δ9-THC has psychotomimetic properties, while CBD has non-psychomimetic properties [9,18]. Numerous clinical studies have linked ADHD pathophysiology with the ECS, revealing impaired ECS signaling through the CB1R [19].

The topic of cannabis and its potential therapeutic form, medical marijuana (MM), has been gaining popularity in recent years [15]. However, discussions about its potential therapeutic application often lack clarity and differentiation between various forms, such as dry cannabis inflorescence, derivatives like oils or hashish, or synthetic constructs [18]. Moreover, these discussions have serious ramifications, as research indicates that increasing cannabis use may be rooted in inaccurate perceptions of the compound as safe and non-addictive or as a self-medication strategy [20,21].

Data show that MM laws implicate may contribute to increased cannabis use and CUDs in adults, who perceive the substance to be less harmful due to its growing legalization status and interest [22]. Moreover, individuals with comorbid psychiatric disorders also perceive the substance as less harmful [23]. Addressing misconceptions about cannabis as a safe drug, high-potency cannabis varieties and new synthetic ultra-potent cannabinoids can lead to severe intoxication, disrupt neurodevelopmental processes, induce psychotic behavior, and contribute to the rapid onset of CUDs [17].

The literature emphasizes the need for more methodologically rigorous clinical studies that distinguish between the ratio of Δ9-THC and CBD in cannabis [18,19]. A narrative review of selected studies was conducted to explore the association between ADHD and cannabis use.

This review synthesizes findings from previous studies, focusing on the underlying neurocognitive mechanisms and their functional consequences. The main topics of interest regarding neurological mechanisms involve the ECS, with further focus on the default-mode network (DMN), and motivational and reward circuitry. By understanding the comorbidity of

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

ADHD and CUDs, researchers and clinicians can better develop effective interventions and treatments.

Characteristics and Diagnostic Features

ADHD

ADHD is a neurodevelopmental disorder characterized by inattention and disorganization, and is often accompanied by hyperactivity or impulsivity. These difficulties affect individuals' personal, educational, and work-related activities [1]. The disorder usually becomes apparent during early developmental stages, leading to mild motor, language, and social development delays. Individuals with ADHD often exhibit poorer performance in cognitive processes, such as attention, memory, and executive functioning [5].

Individuals with ADHD frequently display low frustration tolerance, irritability, and mood lability [25]. Moreover, they prefer smaller, immediate rewards over larger, delayed ones. This aversion to delayed gratification is related to impulsivity and atypical activity in the brain's limbic regions, which are vital for emotional processing [26]. These reward-system nuances are associated with emotional processing and contribute to emotion regulation challenges in individuals with ADHD [27].

ADHD diagnostic criteria require a persistent pattern of symptoms (lasting at least 6 months, appearing before the age of 12, and interfering with daily life activities) that are inconsistent with typical development. Symptoms usually include lack of attention, difficulty concentrating, disorganization, difficulty completing tasks, forgetfulness, and losing items [28].

Due to ADHD's neurodevelopmental nature, inattention and hyperactivity/impulsivity symptoms must manifest during childhood, before the age of 12 years [1]. The DSM-V and ICD-11 distinguish 3 subtypes of ADHD: 1) combined, 2) predominantly inattentive, and 3) predominantly hyperactive or impulsive. Each subtype corresponds to a mild, moderate, or severe severity level. A complete ADHD diagnosis specifies the disorder's clinical presentation and severity [1].

Diagnosing ADHD can be challenging due to gender differences, symptom manifestations, cultural implications, and confounding symptomatology with other conditions. The DSM-V states that ADHD prevalence is more common in males than females, with a ratio of about 2: 1 in children and 1.6: 1 in adults. Females with ADHD predominantly present inattention features [1]. However, research on gender differences suggests that the varied prevalence rate across sexes may result from differential presentations influenced by biological factors and societal gender roles [29].

ADHD symptomatology often lacks continuity, as symptoms may manifest in altered forms during development. For example, childhood hyperactivity may involve excessive motor activity, while adulthood manifestations may include extreme restlessness or talkativeness [1]. Symptom manifestations also vary across different settings and contexts, including cultural backgrounds, with societal, gender, and cultural roles potentially accounting for these differences [30].

Cannabis Use Disorders

Cannabis use disorders (CUDs) involve a pattern of cannabis use that results in distress or clinically significant impairment, representing a primary public health concern [31]. CUDs impair higher executive functions in a dose- and frequency-dependent manner, leading to decreased prosocial goal-directed behavior (amotivational syndrome), hindered social relationships, and increased risk of harm due to risky behavior.

Cannabis takes various forms, including synthetic, and can be ingested differently, influencing the perceived "high." While often used alone, CUDs frequently co-occur with other substance use disorders (SUDs) involving cocaine, alcohol, or opioids. Regular cannabis use shares markers applicable to other SUDs [1].

Like other SUDs, CUDs are characterized by withdrawal symptoms that persist during detoxification. Common withdrawal symptoms include anxiety, depressed mood, anger, irritability, sleep disturbances, and restlessness. Persistent withdrawal symptoms often cause distress, increasing the likelihood of relapse and making quitting difficult. This is particularly significant considering that, like other SUDs, cannabis is often used as a coping mechanism for psychological or physiological difficulties [1,22]. CUDs are highly prevalent among individuals with comorbid mental conditions, potentially due to self-medication, exacerbating their clinical presentation [10,23].

CUDs prevalence rates vary across age groups, with increasing prominence in adolescents and adults. Moderate differences exist among races and ethnic backgrounds, while gender differences in CUDs mirror those typically observed in other SUDs. Generally, CUDs are more common in males than females, although the gender disparity is smaller in adolescents [1].

A CUD diagnosis requires an individual to experience at least 2 of the following within 12 months: (1) substance use lasting longer than intended, (2) unsuccessful attempts to reduce or discontinue substance use, (3) significant time spent obtaining, using, or recovering from substance use, (4) substance craving, (5) impairments in personal and social functioning, (6) substance use despite persistent or recurrent social and interpersonal problems, (7) reduced or discontinued

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

social, occupational, or recreational activities, (8) continuous substance use in physically hazardous situations, (9) ongoing substance use despite knowledge of its likely psychological and physical consequences, (10) tolerance, and (11) withdrawal. These criteria encompass diagnostic features of SUDs, including impaired control over substance use, social impairment, risky use of the substance, and pharmacological concepts [1].

Etiology: Theoretical Models

Attention-Deficit/Hyperactivity Disorder

ADHD etiology has been extensively researched over the years. In 1996, Pennington and Ozonoff published a pioneering work linking ADHD symptoms with the symptomatology observed in patients with prefrontal cortex lesions. They proposed that the inattention and impulsivity displayed by individuals with ADHD arise from deficits in executive functioning, laying the groundwork for future research [32].

Barkley further investigated the concept, suggesting that central executive deficits in ADHD occur in relation to response inhibition (ie, behavioral inhibition) comprising 3 interrelated processes: (1) inhibiting an automatic or prepotent response likely to result in immediate reinforcement, (2) allowing for the delay or pause of an initiated response, and (3) focusing on interference control, which is the ability to maintain focus while rejecting competing stimuli. Barkley argued that impaired response inhibition disrupts 4 executive processes: working memory, self-regulation, internalization of speech, and reconstitution. These disturbances lead to a reduced ability to execute complex actions and perform goal-directed behaviors, particularly in motor control, fluency, and syntax [33].

Other models explored ADHD's differential presentation, focusing on its 3 subtypes (combined, predominantly inattentive, and predominantly hyperactive or impulsive). In 2005, Diamond proposed that the inattentive presentation stems from impaired working memory, while the combined presentation arises from hindered behavioral inhibition [34]. Castellanos et al (2006) associated 2 ADHD subtypes (inattentive and hyperactive) with executive function pathways. They postulated that the inattentive subtype results from disruptions in the "cool" executive function pathway (regulating tasks without affective involvement), leading to cognitive processing difficulties. In contrast, they suggested that the hyperactive subtype is linked to dysfunction in the "hot" executive function pathway (modulating affective tasks involving rewards and motivation), resulting in problems with emotional stimuli [35].

Some models considered ADHD and its subtypes as products of the same impairments, proposing that the deficits stem from disturbances in cognitive control and affect regulation. One model emphasized impaired executive functioning abilities and the role of delayed gratification and arousal in ADHD symptoms. Another model rejected attributing ADHD symptoms to hindered executive functioning, suggesting that ADHD symptoms arise from poor control of the default-mode network (DMN) when engaging in a task [36]. Despite their theoretical differences, most of these models agreed that individuals with ADHD exhibit distinct neurocognitive profiles identifiable through neuropsychological assessment.

Numerous studies have aimed to investigate the cognitive differences between individuals with ADHD and controls. A 2018 systematic review found consistent results, indicating that neurotypical individuals outperform those with ADHD in various neurocognitive domains such as reaction time variability, intelligence/achievement, vigilance, working memory, and response inhibition. These findings support the DMN model, which attributes ADHD symptoms to hindered abilities to switch from rest mode to active rest mode [32].

Cannabis Use Disorders

The self-medication theory, proposed in 1974, is perhaps the most widely known explanation for increased substance use among individuals with comorbid conditions. This theory suggests that people who have comorbid disorders use illicit substances to alleviate unpleasant or disruptive psychiatric symptoms [9]. Based on principles of behavioral science, specifically negative reinforcement in Skinner's operant conditioning, the theory postulates that individuals resort to substances to relieve uncomfortable symptoms, becoming reinforced to use the substance despite being aware of its adverse consequences [9,37].

Research indicates that individuals experiencing withdrawal (a characteristic marker of substance abuse) often turn to cannabis to alleviate pain and discomfort. In regions where cannabis is legal, people are less likely to use it to address depression and anxiety, but more likely to use it for mitigating social discomfort. Nonetheless, cannabis use is a complex phenomenon that warrants further investigation [22].

The inhibitory control dysfunction theory associates substance abuse with impulsivity, suggesting that such abuse may stem from impulsiveness or perseveration [38]. Substance use disorders reflect impaired decision-making, indicating that higher-order cognitive functions and related behavioral issues could be attributed to inhibitory control disturbances. Cannabis users report inhibitory control as one of the most persistent impairments they experience, along with impaired memory and processing speed. Intriguingly, while inhibitory control could be a consequence of chronic cannabis use, it is also considered a predisposing factor for substance use vulnerability [39].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Default-Mode Network

The default-mode network (DMN) was first identified in 2001 by Raichle et al while studying resting state functional connectivity (rsFC) using neuroimaging techniques [40]. The DMN comprises the posterior cingulate cortex (PCC), hippocampal formation, lateral and medial parietal cortex, lateral temporal cortex, medial prefrontal cortex, and precuneus, and reaches full development by adolescence [16]. The DMN demonstrates a consistent pattern of deactivation across its constituent brain regions during task-related activities, while showing abundant functional connectivity between these regions when the brain is at rest. Default-mode brain activity refers to the state where an individual is awake and alert but not engaged in goal-oriented or attention-demanding tasks [41].

The DMN is associated with self-reflexive thought and attentional- and stimulus-independent control. Research on rsFC shows DMN activations to be negatively related to task-positive networks, while stronger intra-DMN connectivity correlates with better performance on working memory tasks, as does stronger anticorrelation between the DMN and executive control network [16].

A 2006 study by Tian et al analyzed rsFC of the DMN in adolescents with ADHD, revealing increased functional connectivity between the dorsal anterior cingulate cortex (ACC) and bilateral brain regions. This increased connectivity may be attributed to abnormalities within the autonomic control functions of these regions or increased affinity within the DMN [36,42]. Other studies found similar results, suggesting that decreased functional interactions between posterior and anterior DMN regions may contribute to some executive function deficits, such as working memory deficiencies and attentional lapses, associated with ADHD [43,44].

Neuroimaging studies on children with ADHD have found decreased regional homogeneity in the frontal-striatal-cerebellar circuit [45] and altered resting state fluctuation amplitudes in various brain regions [46]. A study by Helps et al examined hyperactive participants who described themselves as inattentive, finding reduced power of low-frequency resting state networks in electroencephalogram data and emphasizing the need for further studies on clinical populations of the disorder [47].

In summary, ADHD appears to involve altered connectivity patterns in the DMN, which may be associated with abnormal circuits in the frontal-striatal-cerebellar regions. These alterations may contribute to the attentional lapses, working memory deficits, and task performance oscillations often exhibited by individuals with ADHD. Consequently, ADHD pathophysiology is speculated to arise from both altered DMN connectivity patterns and atypical antagonism between DMN and task-positive networks [41].

Cannabis Use Disorder

Frequent and persistent cannabis use in adolescents can cause permanent changes in their neurocognitive functions due to alterations in brain structures and corresponding brain circuits [46]. Regular substance abusers, including cannabis users, demonstrate changes in rsFC of the DMN, which may reflect structural connectivity within the network [49].

A study focusing on cannabis use among adolescents and young adults found stronger connectivity between the left PCC and the cerebellum, which was correlated with poorer performance on verbal learning tasks and sustained attention or working memory. In controls, stronger connectivity between the left PCC and left PCC precuneus was associated with quicker speed on both sustained and selective attentional measures. These results were supported by other research, which also found that higher intra-DMN connectivity implies better working memory task performance [16].

Increased activity of the anterior and posterior DMN has been linked to the positive emotionality personality trait (considered a protective factor for SUD) in studies of resting baseline activity using glucose metabolic rate as a brain function marker. Interestingly, studies investigating the withdrawal or detoxification phase of various abused substances found significant reductions in dorsomedial prefrontal cortex activity in cannabis abusers, among others. These findings may be central to disturbances in emotional processing and decision-making observed in addiction, as these processes involve engagement of the medial prefrontal cortex, which is also actively engaged in motivational and reward circuit dysregulation [37].

Research by Bossong et al explored the association between the DMN and Δ9-THC in human executive function. The results showed that Δ9-THC administration was associated with impaired task performance and lower DMN activation during task performance-oriented activities. These findings highlight the role of the ECS in terms of both the DMN and executive functioning, the latter being a core deficit of psychiatric conditions like schizophrenia, ADHD, and Alzheimer disease. The relationship between these conditions and DMN modulation (involving the ECS system) is relevant and warrants further investigation [50].

The Endocannabinoid System

The Endocannabinoid System (ECS) was first discovered in the early 1990s. Research implicates the system in a variety of processes, including synaptic plasticity, memory, stress, emotion regulation, immune function, and psychiatric conditions [17,51]. Most research on natural cannabis constituents, called phytocannabinoids, focuses on Δ9-THC, which produces changes

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

in mood, emotion, perception, and cognition. However, recent years have seen increasing interest in the role of another endocannabinoid, CBD, which demonstrates therapeutic potential with advantages surpassing those observed in Δ9-THC. Despite CBD's uncertain effects, studies show that the phytocannabinoid acts as an agonist on serotonin receptors (5-HT), revealing its antidepressant and cognition-enhancing effects [19,22].

The ECS system is a neuromodulator system involving 2 main receptors: CB1R and cannabinoid receptor type 2 (CB2R). CB1R is implicated in various processes, such as memory, learning, cognition, mood, motivation, emotion, and motor activity. Although CB2R was previously thought to engage primarily within the immune system, recent findings link the receptor to modulating midbrain dopamine (DA) activity. The ECS system's role is important in both ADHD and SUDs or CUDs due to its involvement in emotional regulation and motivational processes [19].

A review by Katzman aimed to explore the role of the ECS system across various psychiatric conditions. Despite numerous preclinical models linking ADHD pathophysiology with ECS dysfunction, little research exists on such dysfunction in ADHD-related impairment [19]. However, research on Δ9-THC's influence on executive functioning by Bossong et al suggests that the ECS system plays an important role in executive functioning, particularly in relation to the DMN [50].

Disorders characterized by DA deficiency, like ADHD and autism spectrum disorder, have been investigated in connection with the ECS system. DA level disturbances observed in ADHD individuals have been linked to the experience of reward and motivation. Experimental research has suggested relationships between the ECS system and DA production, attributing the DA system dysfunction in ADHD clinical manifestation to the interplay between the two [52].

Similar findings were postulated in a review by Dawson and Persad, who concluded that targeting the ECS system in ADHD treatment and understanding its effects on DA system dysfunction could provide insight into the fundamentals of ADHD symptomatology and clinical manifestations. However, despite these promising findings and research directions, ADHD is a complex disorder with roots in both genetic and non-genetic (ie, environmental) factors, as well as their interplay [11,52].

Cannabis Use Disorders

Common neurological mechanisms underlying SUDs involve the ECN, which plays a key role in mediating reward and motivation, particularly concerning substance effects and substance-related cues [51]. These cues can induce drug-seeking responses when conditioned by cannabis use, as the substance elicits phasic DA events, implicating the role of the ECS in the formation of addictive behavior [17]. Persistent substance use leads to constant disturbance of DA activity, resulting in long-lasting changes in plasticity and hindering cessation of substance use, while also contributing to an increased risk of relapse. Functional changes across corticostriatal structures, which modulate reward and motivation in substance use, contribute to cellular adaptations occurring in the transition from substance use to substance dependence [51].

Research highlights the important role of the ECS in emotional learning and memory processes. Memory performance may be modulated by ECS signaling amplification, as demonstrated in animal models. Endocannabinoids appear to induce long-term synaptic strength changes across the hippocampus, which mediates associative memory formation and assists in both negative and positive reinforcement to reward. Meanwhile, phytocannabinoids (Δ9-THC and CBD) have been found to modulate limbic brain activity in functional emotional processing. Animal models show that CB1R agonists and antagonists facilitate and weaken memory extinction in both reward- and fear-conditioning instances. These aspects of the ECS role in emotional memory can contribute to extinction, consolidation, and restoration of substance-related memory [51].

Comorbidity Between ADHD and SUDs, or CUDs

Both SUDs and ADHD are characterized by abnormal reward processing, involving alterations in DA transporter binding, D2 receptor levels, and DA release. The relationship between these is complex, but the high prevalence of SUDs in people with ADHD may be rooted in the fact that distinct substances stimulate neurotransmitter release (mainly DA), reducing ADHD-core symptoms [53,54]. DA mechanisms vary across substances; for example, cannabis or opiates do not increase DA levels as much as other substances [54]. The involvement of the DMN and ECS in reward processing have been described above in previous sections.

Daily cannabis use is more frequent among people with ADHD who have the combined subtype than those with the predominantly inattentive subtype. The relationship between these two was found to be significant, with individuals with the mixed subtype being 10% more likely to develop daily cannabis use than those with the predominantly inattentive subtype. Furthermore, individuals using cannabis as self-medication were more likely to have ADHD, specifically its combined subtype, supporting the self-medication hypothesis [9]. Evidence also indicates that females with comorbid SUDs and ADHD used cannabis for longer durations than those with SUDs and no ADHD, as well as males with SUDs and ADHD, or with SUDs alone [55].

Comorbidity between ADHD and SUDs is associated with increased cannabis use. Numerous studies have shown that

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

individuals with ADHD and SUDs have an earlier onset of substance use and cannabis use [11,24,55,56]. Early cannabis use (ie, during adolescence) is linked to the disruption of functional circuit maturation-refinement [14,56]. Research indicates that 33.19-38.10% of adolescents with CUDs have a comorbid ADHD diagnosis. ADHD is the most common psychiatric comorbidity among cannabis abusers and problematic users, and is the second-highest comorbidity with cannabis dependence [58]. Lifetime cannabis use rates more than triple between the ages of 18 to 25 years, with 15.8% of adolescents using cannabis developing lifetime CUDs, compared to 51.7% of young adults [22].

Data show that the prevalence of ADHD in adults seeking treatment for CUDs is 34-46% [9,59]. ADHD prevalence in SUDs seems to vary across different substances of choice [21]. People with ADHD who abuse cannabis are characterized by higher psychopathology severity, along with increased hostility, activation, suspiciousness, and thought disturbances. These results support other research, which found Δ9-THC to be associated with psychosis, paranoia, and aggressiveness in chronic, heavy users [10,18].

The co-occurrence of ADHD and CUDs poses diagnostic challenges, as frequent cannabis use produces neurocognitive changes in executive functioning, similar to those central to ADHD. Clinicians failing to assess cannabis use or patients failing to admit to such use can lead to possible erroneous (false-positive) ADHD diagnoses. Some research suggests that the high comorbidity between ADHD and CUDs may result from the latter inducing neurocognitive changes that mimic ADHD symptoms [56]. However, other findings argue that cannabis-induced cognitive changes alone cannot explain the relationship between ADHD and CUDs due to their commonalities, such as ECS dysfunction [59].

Cannabis and Its Therapeutic Applications

In recent years, the topic of cannabis, its therapeutic form (MM), and its applications in the treatment of psychiatric disorders has emerged in scientific contexts. Numerous reviews have studied MM's therapeutic potential in psychiatric conditions, but most evidence remains insufficient due to it coming from animal models, while human studies often lack rigor and have small sample sizes [18,19,31,60]. It is worth noting that there is some inconclusive evidence suggesting CBD might be used as an adjunctive treatment in schizophrenia, and a few isolated studies show CBD's efficacy in social anxiety [61].

Individuals with ADHD often use cannabis as a coping strategy (self-medication hypothesis). Analysis of online sources concluded that cannabis is considered efficacious in ADHD symptoms in 25% of the considered posts, as opposed to 8% that indicated it is harmful [62]. Only 1 RCT study assessed nabiximol (a cannabinoid/terpene combination) oromucosal spray effects in 30 adults with ADHD for 6 weeks. The primary endpoint was cognitive performance measured by the Quantitative Behavioural Test, which showed no statistically significant differences (and no impairment of performance) in the active group. Secondary outcomes involved emotional liability symptoms. Nabiximol significantly improved hyperactivity/impulsivity scores on the investigator-rated Conners Adult ADHD Rating Scale in the active group [63]. Despite the limitations of this study, it provides evidence supporting the self-medication theory. However, possible cannabis application in ADHD treatment requires further investigation of the endocannabinoid system, as many studies show that cannabis can worsen symptoms of inattention, hyperactivity, and impulsivity. Reduction in cannabis use might be connected with reduced use of other substances, such as alcohol, which may result in improved ADHD symptoms [64].

MM has both neuroprotective and neurotoxic effects [14]. Applications of MM have been discussed regarding CUDs, but substitutional therapy with MM in CUDs remains questionable [17]. In the best circumstances, evidence suggests that CBD may be beneficial as an adjunct to standard therapy in SUDs, but results pertaining to its efficacy and safety are mixed [31]. According to Brucato, discussions on MM's potential therapeutic applications must not overlook the dangers associated with cannabis use, especially among adolescents [57]. Lastly, it is important to consider that MM's influence on the ECS may have ramifications. The ECS is involved in both secondary reward (like those produced by substances) and primary, natural reward. Interference within the system may affect natural reward mechanisms, which drive daily activities, leading to serious consequences [17].

Limitations

This review has several limitations. The primary drawbacks include: (1) the questionable reliability of evidence (some of the presented results come from research based on self-report measures or longitudinal studies); (2) a limited number of sources in specific sections (particularly the sections about the DMN and ECS); and (3) some data pertaining to SUDs in general, rather than exclusively CUDs. Despite these limitations, this review offers a comprehensive overview of the shared pathophysiology of ADHD, SUDs, and CUDs. Future research should focus on exploring the complex relationship between ADHD, SUDs, and CUDs. Moreover, there is an important need to systematize the knowledge by conducting more human-based research, particularly clinical trials with rigorous methodologies and larger sample sizes.

Future Directions

This review offers an overview of the comorbidity among ADHD, SUDs, and CUDs, focusing on their characteristics, shared

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

symptomatology, and underlying neurocognitive mechanisms. The comorbidity and mutual relationship are significant, as estimates suggest that half of adults with ADHD will meet the criteria for SUDs at some point in their lifetime. Furthermore, reports indicate that cannabis is the most widely used illicit substance in Europe and the United States; in line with population-wide trends, the same phenomenon occurs within the ADHD population. As a result, this topic warrants further in-depth studies in the future.

References:

1. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163(4):716-23
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th Edition. 2013
3. Scandurra V, Emberti Gialloreti L, Barbanera F, et al. Neurodevelopmental disorders and adaptive functions: A study of children with autism spectrum disorders (ASD) and/or attention deficit and hyperactivity disorder (ADHD). Front. Psychiatry. 2019;10:673
4. Cioni G, Inguaggiato E, Sgandurra G. Early intervention in neurodevelopmental disorders: Underlying neural mechanisms. Dev Med Child Neurol. 2016;58:61-66
5. Jones MN, Weber KP, McLaughlin TF. No teacher left behind: Educating students with ASD and ADHD in the inclusion classroom. Journal of Special Education Apprenticeship. 2013;2(2): Article 5
6. Breslau J, Miller E, Joanie Chung W-J, Schweitzer JB. Childhood and adolescent onset psychiatric disorders, substance use, and failure to graduate high school on time. J Psychiatr Res. 2011;45(3):295-301
7. Biederman J, Petty CR, Monuteaux MC, et al. Adult psychiatric outcomes of girls with attention deficit hyperactivity disorder: 11-year follow-up in a longitudinal case-control study. Am. J. Psychiatry. 2010;167(4):409-17
8. Kelly TM, Daley DC. Integrated treatment of substance use and psychiatric disorders. Soc Work Public Health. 2013;28(3-4):388-406
9. Loflin M, Earleywine M, De Leo J, Hobkirk A. Subtypes of attention deficit-hyperactivity disorder (ADHD) and cannabis use. Subst Use Misuse 2013;49(4):427-34
10. Spera V, Pallucchini A, Carli M, et al. Does cannabis, cocaine and alcohol use impact differently on adult attention deficit/hyperactivity disorder clinical picture? J Clin Med. 2021;10(7):1481
11. Knecht C, de Alvaro R, Martinez-Raga J, Balanza-Martinez V. Attention-deficit hyperactivity disorder (ADHD), substance use disorders, and criminality: A difficult problem with complex solutions. Int J Adolesc Med Health. 2015;27(2):163-75
12. Wimberley T, Agerbo E, Horsdal HT, et al. Genetic liability to ADHD and substance use disorders in individuals with ADHD. Addiction. 2020;115(7):1368-77
13. Kelly C, Castellanos FX, Tomaselli O, et al. Distinct effects of childhood ADHD and cannabis use on brain functional architecture in Young Adults. Neuroimage Clin. 2017;13:188-200
14. Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Ther Adv Psychopharmacol. 2012;2(6):241-54
15. Patel D. Cannabis use disorder. Psychiatry Update. 2021;33-40
16. Ritchay MM, Huggins AA, Wallace AL, Larson CL, Lisdahl KM. Resting state functional connectivity in the default mode network: Relationships between cannabis use, gender, and cognition in adolescents and young adults. Neuroimage Clin. 2021;30:102664
17. Spanagel R. Cannabinoids and the endocannabinoid system in reward processing and addiction: From mechanisms to interventions. Dialogues Clin. Neurosci. 2020;22(3):241-50
18. Silczuk A, Smułek D, Kołodziej M, Gujska J. The construct of medical and non-medical marijuana-critical review. Int J Environ Res Public Health. 2022;19(5):2769
19. Katzman MA, Furtado M, Anand L. Targeting the endocannabinoid system in psychiatric illness. J Clin Psychopharmacol. 2016;36(6: 691-703
20. Morie KP, Potenza MN. A mini-review of relationships between cannabis use and neural foundations of reward processing, inhibitory control and working memory. Front Psychiatry. 2021;12:657371
21. van Emmerik-van Oortmerssen K, van de Glind G, van den Brink W, et al. Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: A meta-analysis and meta-regression analysis. Drug Alcohol Depend. 2012;122(1-2):11-19
22. Wallis D, Coatsworth JD, Mennis J, et al. Predicting self-medication with cannabis in young adults with hazardous cannabis use. Int J Environ Res Public Health. 2022;19(3):1850
23. Lowe DJ, Sasiadek JD, Coles AS, George TP. Cannabis and mental illness: A review. Eur Arch Psychiatry Clin Neurosci. 2018;269(1):107-20
24. Dunne EM, Hearn LE, Rose JJ, Latimer WW. ADHD as a risk factor for early onset and heightened adult problem severity of illicit substance use: An accelerated gateway model. Addict Behav. 2014;39(12):1755-58
25. Reimherr FW, Marchant BK, Strong RE, et al. Emotional dysregulation in adult ADHD and response to Atomoxetine. Biol Psychiatry. 2005;58(2):125-31
26. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. Am J Psychiatry. 2014;171(3):276-93
27. Sander D, Nummenmaa L. Reward and emotion: An affective neuroscience approach. Curr Opin Behav Sci. 2021;39:161-67
28. Magnus W, Nazir S, Anilkumar AC, Shaban K. Attention Deficit Hyperactivity Disorder. In StatPearls. StatPearls Publishing, 2022
29. Skogli EW, Teicher MH, Andersen PN, et al. ADHD in girls and boys – gender differences in co-existing symptoms and executive function measures. BMC Psychiatr. 2013;13:298
30. Young S, Adamo N, Ásgeirsdóttir BB, et al. Females with ADHD: An expert consensus statement taking a lifespan approach providing guidance for the identification and treatment of attention-deficit/hyperactivity disorder in girls and women. BMC Psychiatr. 2020;20(1):404
31. Chye Y, Christensen E, Solowij N, Yücel M. The endocannabinoid system and Cannabidiol's promise for the treatment of substance use disorder. Front Psychiatry. 2019;10:63
32. Pievsky MA, McGrath RE. The neurocognitive profile of attention-deficit/hyperactivity disorder: A review of meta-analyses. Arch Clin Neuropsychol. 2017;33(2):143-57
33. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. Psychol. Bull. 1997;121(1):65-94
34. Diamond A. Attention-deficit disorder (attention-deficit/hyperactivity disorder without hyperactivity): A neurobiologically and behaviorally distinct disorder from attention-deficit/hyperactivity disorder (with hyperactivity). Dev. Psychopathol. 2005;17(3):807-25
35. Rubia K. "Cool" inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus "hot" ventromedial orbitofrontal-limbic dysfunction in conduct disorder: A review. Biol Psychiatry. 2011;69(12):e69-87
36. Sonuga-Barke EJS, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. Neurosci Biobehav Rev. 2007;31(7):977-86
37. Zhang R, Volkow ND. Brain default-mode network dysfunction in addiction. Neuroimage. 2019;200:313-31
38. Newton TF, De La Garza R, Kalechstein AD, et al. Theories of addiction: Methamphetamine users' explanations for continuing drug use and relapse. Am J Addict. 2009;18(4):294-300
39. Griffith-Lendering MF, Huijbregts SC, Vollebergh WA, Swaab H. Motivational and cognitive inhibitory control in recreational cannabis users. J Clin Exp Neuropsychol. 2012;34(7):688-97
40. Silberstein RB, Pipingas A, Farrow M, et al. Dopaminergic modulation of default mode network brain functional connectivity in attention deficit hyperactivity disorder. Brain Behav. 2016;6(12):e00582
41. Broyd SJ, Demanuele C, Debener S, et al. Default-mode brain dysfunction in mental disorders: A systematic review. Neurosci Biobehav Rev. 2009;33(3):279-96

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

42. Tian L, Jiang T, Wang Y, et al. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci Lett. 2006;400(1-2):39-43
43. Castellanos FX, Margulies DS, Kelly C, et al. Cingulate-precuneus interactions: A new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol. Psychiatry. 2008;63(3):332-37
44. Uddin LQ, Kelly AMC, Biswal BB, et al. Network homogeneity reveals decreased integrity of default-mode network in ADHD. J Neurosci Methods 2008;169(1):249-54
45. Cao Q, Zang Y, Sun L, et al. Abnormal neural activity in children with attention deficit hyperactivity disorder: A resting-state functional magnetic resonance imaging study. Neuroreport. 2006;17(10):1033-36
46. Yu-Feng Z, Yong H, Chao-Zhe Z, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev. 2007;29(2):83-91
47. Helps S, James C, Debener S, et al. Very low frequency EEG oscillations and the resting brain in young adults: A preliminary study of localisation, stability and association with symptoms of inattention. J Neural Transm. 2007;115(2):279-85
48. Hooper SR, Woolley D, De Bellis MD. Intellectual, neurocognitive, and academic achievement in abstinent adolescents with cannabis use disorder. Psychoph. 2014;231(8):1467-77
49. Ma S-L, Chen LH, Lee C-C, et al. Genetic overlap between attention deficit/hyperactivity disorder and autism spectrum disorder in *SHANK2* gene. Front. in Neurosc. 2021;15:649588
50. Bossong MG, Jansma JM, van Hell HH, et al. Default mode network in the effects of Δ9-tetrahydrocannabinol (THC) on human executive function. PLoS One. 2013;8(7):e70074
51. Chye Y, Christensen E, Solowij N, Yücel M. The endocannabinoid system and Cannabidiol's promise for the treatment of substance use disorder. Front. in Psych. 2019;10:63
52. Dawson DA, Persad CP. Targeting the endocannabinoid system in the treatment of ADHD. Gen Mol Med. 2021;3(1):1-7
53. Silva N Jr., Szobot CM, Shih MC, et al. Searching for a neurobiological basis for self-medication theory in ADHD comorbid with substance use disorders: An in vivo study of dopamine transporters using (99m)Tc-TRODAT-1 SPECT. Clin. Nucl. Med. 2014;39(2):e129-34
54. Luo SX, Levin FR. Towards precision addiction treatment: New findings in co-morbid substance use and attention-deficit hyperactivity disorders. Curr Psychiatry Rep. 2017;19(3):14
55. Coetzee C, Truter I, Meyer A. Differences in alcohol and cannabis use amongst substance use disorder patients with and without comorbid attention-deficit/hyperactivity disorder. S Afr J Psychiatr. 2022;28:1786
56. Martínez-Luna N, Daigre C, Palma-Álvarez F, et al. Psychiatric comorbidity and addiction severity differences in patients with ADHD seeking treatment for cannabis or cocaine use disorders. J. Atten. Disord. 2019;25(7):978-88
57. Brucato R. Nicotine and cannabis use in attention deficit hyperactivity disorder (ADHD) and non-ADHD adolescents: Evidence for gateway drug effects. J. Neurosci. 2018;1(3):20181111
58. DeMaria PA. Cannabis use disorders and ADHD. J Addict Med. 2016;10(1):70
59. Notzon DP, Pavlicova M, Glass A, et al. ADHD is highly prevalent in patients seeking treatment for cannabis use disorders. J Atten Disord. 2016;24(11):1487-92
60. Turna J, Patterson B, Van Ameringen M. Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? Depress Anxiety. 2017;34(11):1006-17
61. Sarris J, Sinclair J, Karamacoska D, et al. Medicinal cannabis for psychiatric disorders: A clinically-focused systematic review. BMC Psychiatr. 2020;20(1):24
62. Mitchell JT, Sweitzer MM, Tunno AM, et al. "I use Weed Foir My ADHD": A qualitative analysis of online forum discussions on cannabis use and ADHD. PLoS One. 2016;11(5):e0156614
63. Cooper RE, Williams E, Seegobin S, et al. Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial. Eur Neuropsychopharmacol. 2017;27(8):795-808
64. Francisco AP, Lethbridge G, Patterson B, et al. Cannabis use in attention – deficit/hyperactivity disorder (ADHD): A scoping review. J Psychiatr Res. 2023;157:239-56

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]