

REVIEW ARTICLE OPEN ACCESS

Attention Deficit Hyperactivity Disorder, Cannabis Use, and the Endocannabinoid System: A Scoping Review

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ABSTRACT

There is emerging evidence that the endocannabinoid system (ECS) plays a significant role in the pathophysiology of many psychiatric disorders, including attention deficit hyperactivity disorder (ADHD). Increasing evidence suggests that a number of neurobiological correlates between endogenous cannabinoid function and cognitive dysfunction are seen in ADHD, making the ECS a possible target for therapeutic interventions. Cannabis use and cannabis use disorder are more prevalent in individuals with ADHD, compared to the general population, and there is growing popular perception that cannabis is therapeutic for ADHD. However, the relationship between cannabis use and ADHD symptomology is poorly understood. Further understanding of the role of the ECS in ADHD pathophysiology and the molecular alterations that may be a target for treatment is needed. To further the science on this emerging area of research, this scoping review describes the preclinical and clinical evidence seeking to understand the relationship between the ECS and ADHD.

1 | Attention Deficit Hyperactivity Disorder (ADHD) and the Endocannabinoid System

ADHD is a common neurodevelopmental disorder characterized by cognitive functional impairment with symptoms of inattention, disorganization, and/or hyperactivity–impulsivity that can have debilitating impacts on all aspects of an individual's life. Estimated prevalence of ADHD for US children and adolescents is 9.8% (Bitsko et al. 2022), and estimated prevalence for US adults is 4.4% (Kessler et al. 2006).

The neurobiological underpinnings of ADHD are still not entirely understood. Common cognitive dysfunctions in ADHD include deficits in motor response inhibition and difficulties with impulse

control, sustained visuospatial attention/concentration, reaction time, and working memory; however, there is considerable heterogeneity in clinical presentation between individuals diagnosed with ADHD (Hoogman et al. 2017). Many structural differences have been noted in areas of the brain in individuals with ADHD known to regulate these functions, including impairment in fronto-striata-cerebellar white matter tracts, abnormalities in ventromedial frontal regions, and volume reductions in the basal ganglia and limbic areas (Norman et al. 2016). A dual pathway neurocognitive model of ADHD posits that inattention and executive function impairments are related to dysfunctional prefrontal-striatal circuits. In contrast, hyperactivity may be related to fronto-limbic-mediated dysfunctional reward and motivation circuits (Chen et al. 2016).

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The prevailing hypotheses behind the role of neurotransmitter functionality in ADHD originate from observed effects of common pharmacologic treatments for the disorder. Stimulants act on dopaminergic D1 receptors in the prefrontal cortex and D2 receptors in the striatum (Solanto 1998). Nonstimulant drugs such as atomoxetine increase presynaptic concentrations of norepinephrine (NE) and dopamine (DA) in the prefrontal cortex. DA transmission is thought to decrease neural noise and thereby weaken inappropriate connections, whereas NE enhances appropriate connectivity (Arnsten 2009). Neurotransmitter functional variability as a pathogenesis for ADHD is further supported by association between prefrontal cortex and caudate nucleus volume with DA transporter (DAT) genotype variants DRD4 and DAT1 (Sonuga-Barke 2005).

The endocannabinoid system (ECS) is a complex biological network widely distributed throughout mammalian tissues and cells, involved in numerous physiological and pathological processes (Di Marzo 2009; Lowe et al. 2021). The primary receptors of the ECS are two G-protein coupled receptors: Cannabinoid 1 receptor (CB1R) and Cannabinoid 2 receptor (CB2R). Although CB2 receptors are largely expressed in immune cells and are implicated in inflammatory and autoimmune responses (Lowe et al. 2021), CB1R receptors are mainly located in the central nervous system (CNS) and appear to play a role in cognition, memory, learning, emotion, mood, motor activity, and motivation (Breivogel and Childers 1998; Katzman, Furtado, and Anand 2016). Through a complex network of interactions, the ECS modulates dopaminergic and serotonergic neurotransmission (Peters, Cheer, and Tonini 2021). CB1R receptors affect dopaminergic responses related to reward and reinforcement and modulate excitatory and inhibitory synaptic plasticity (Covey et al. 2017; Wenzel and Cheer 2018). By regulating serotonin release and serotonin receptor expression, the ECS and serotonin systems have overlapping roles in functions such as appetite, body temperature, sleep, and arousal (Haj-Dahmane and Shen 2011). Furthermore, preclinical evidence suggests that ECS interacts with the endovanilloid system, specifically through the transient receptor potential Vanilloid 1 (TRPV1) and CB1R, to regulate anxiety and depression like behaviors triggered by stress (Norz  and Maldonado-Vlaar 2023). The neuromodulating effects of the ECS are complex, and further understanding is needed. There is emerging evidence that the ECS plays an important role in the pathophysiology of many psychiatric disorders, including ADHD, making the ECS a potential target for therapeutic intervention for psychiatric disorders (Navarro et al. 2022). Although progress has been made in the translational research on the ECS, much more clinical research is needed before cannabinoid therapies can be used to treat these disorders (Navarro et al. 2022).

Attention deficit/hyperactivity disorder is strongly associated with cannabis use and cannabis use disorder (August et al. 2006; Biederman et al. 2008; Katzman, Furtado, and Anand 2016; Kelly et al. 2017; Rasmussen et al. 2016; Tamm et al. 2013). The theory of self-medication has been posited to explain the increased risk of cannabis use associated with ADHD (McDonald et al. 2003; Pani et al. 2013). Clinical studies suggest that the ECS may be involved in the regulation of executive function, inhibition, and impulsivity through modulation of the default mode network (DMN) (Bossong et al. 2013; Breivogel and Childers 1998; Katzman, Furtado, and Anand 2016). However, consumption of the

cannabinoid THC has been associated with acute impairment of learning, memory, and attention (Crean, Crane, and Mason 2011; Volkow et al. 2016). However, it is important to note that THC is only one of many cannabinoids found in the cannabis flower and should not be compared to other non-psychoactive cannabinoids such as cannabidiol (CBD).

Due to its extensive roles, the ECS has become a target for potential therapeutic applications for various disorders (Di Marzo 2009; Lowe et al. 2021). However, much more clinical research is needed to investigate the molecular alterations of the ECS before facilitating the design of novel therapeutic targets toward these alterations (Lowe et al. 2021; Navarro et al. 2022). Despite the lack of clinical evidence, there is a growing popular perception that cannabis can be therapeutic for ADHD, with many individuals seeking information about cannabinoid products for treatment of ADHD symptoms in places like online forums (Mitchell et al. 2016). In light of this growing popularity, this scoping review sought to explore the existent research on potential therapeutic effects of cannabis in relation to ADHD symptomatology and how the ECS may influence symptoms of ADHD.

Although there are several reviews summarizing the research on the ECS involvement in psychiatric disorders (Katzman, Furtado, and Anand 2016; Navarrete et al. 2020; Navarro et al. 2022), there are no reviews specifically examining the relationship between the ECS and ADHD symptomatology. To further the science on this emerging area of research, this scoping review sought to describe the preclinical and clinical evidence seeking to understand the relationship between the ECS and ADHD. The scoping review divides the data into evidence from preclinical studies and clinical studies and concludes with a discussion of findings.

2 | Methods

A systematic search of PubMed, PsycINFO, EMBASE, and the Cochrane Library was conducted for articles up to March 2022. This review was conducted and reported in accordance with the PRISMA reporting guidelines (Tricco et al. 2018). Searches were not limited by publication type. The following search terms and synonyms were used: attention deficit disorder with hyperactivity, endocannabinoid, ECS, cannabis, cannabis/therapeutic use, cannabinoids, CBD, and marijuana. The full search strategy can be found in Supporting Information Appendix 1. Reference lists of identified articles were hand searched for additional relevant studies. In addition, systematic reviews of cannabinoids and psychiatric/mental illness were reviewed for relevant studies. All preclinical and clinical studies were included in the search.

All records were uploaded to Covidence for article screening. Two independent reviewers (JR, MF) performed abstract/title and full-text reviews. A third independent reviewer (BW) acted as a moderator if there was disagreement between the first reviewers. Preclinical studies were included if they examined components of the ECS (e.g., receptors and endocannabinoids) in relation to ADHD traits (e.g., impulsivity, executive dysfunction, and hyperlocomotion). Preclinical studies were excluded if they focused on addiction/substance use disorder. Clinical studies

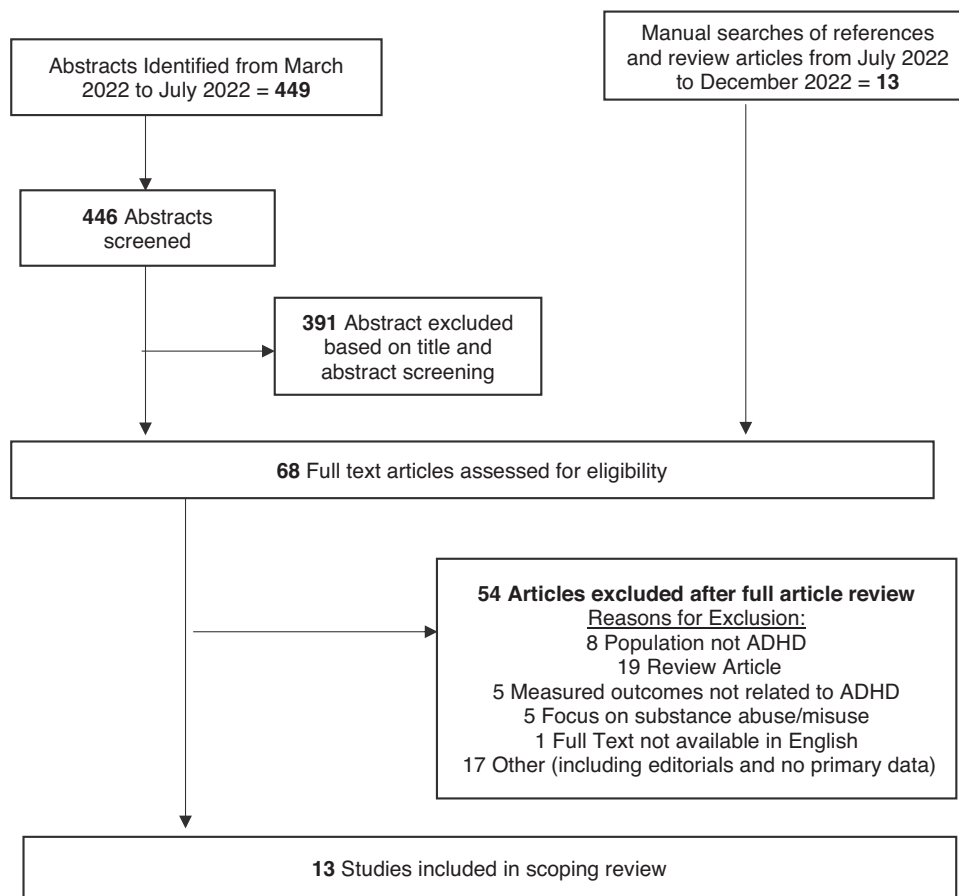


FIGURE 1 | Review process for article inclusion. ADHD, attention deficit hyperactivity disorder.

were included if they (1) examined neuro-pathophysiology in relation to ADHD and cannabis use; (2) examined the role of the ECS in tasks of executive function, inhibition, and impulsivity; or (3) focused on therapeutic use of cannabis for ADHD symptoms. Clinical studies were excluded if they focused on substance use disorder/cannabis use disorder. Clinical studies were also excluded if they focused on a population other than ADHD or if measured outcomes were not related to ADHD symptomatology. In accordance with PRISMA Scoping Review guidelines, no risk of bias assessment was performed (Tricco et al. 2018). A total of 13 articles were included.

3 | Results

A flowchart of the article review process is shown in Figure 1. A total of 449 citation records were identified from searching the four databases. After exclusions, 13 studies were included in the review. Five preclinical studies are presented in Table 1. Five clinical studies examining effects of cannabis on cognition are presented in Table 2. Two clinical studies examining effects of cannabis on ADHD symptoms are presented in Table 3.

4 | Preclinical Studies

Schneider et al. (2015) attempted to understand the role of the CB1R in the persistence of adolescent behavior (i.e., increased

risk/novelty seeking, social play, impulsivity, and reward sensitivity) into adulthood. The investigators hypothesized that the CB1R mediates adolescent behavior in rats through enhanced endocannabinoid (eCB) signaling during adolescence. To study enhanced CB1R signaling, the investigators introduced a missense mutation (F238L) into the rat *Cnr1* gene encoding for CB1R. Mutant and wild-type (MT/WT) adults were compared with WT adolescent rats using striatal binding levels of CB1R agonist, expression levels of CB1R, uptake of CB1R ligand on PET scan, electrophysiologic analysis of glutamate release probability in striatal brain slices, and behavioral measures of risk seeking, social play, impulsivity, and reward sensitivity to food and drugs. Glutamate release probability was used as a measure for CB1R signaling, as CB1R activation inhibits glutamate release probability (Gerdeman and Lovinger 2001). Although brain slices from MT adults showed no differences in concentration of CB1R receptor proteins compared to WT adults, MT adults did demonstrate decreased probability of glutamate release compared with WT adults, suggesting a gain of function in CB1R signaling. WT adolescents showed similar patterns of glutamate release to MT adults; however, the effect was mediated through increased binding of CB1R in WT adolescents, as opposed to a gain of function of CB1R in MT adults. In behavioral measures, MT adults demonstrated significantly greater levels of risk seeking, food and drug reward sensitivity, and social play than their WT counterparts. These behavioral phenotypes were indistinguishable from those demonstrated by WT adolescent rats. WT adolescents did not demonstrate persistence of these behaviors

TABLE 1 | Preclinical studies examining role of the endocannabinoid system (ECS) in modulation of attention deficit hyperactivity disorder (ADHD) symptomatology traits.

Study	Study design	Subject groups	Intervention	Outcome measurements and corresponding exposure conditions	Results
Schneider et al. (2015)	Animal model	Male adult/adolescent Fischer 344 rats and <i>Cnr1</i> F238L mutant and wild-type (MT/WT) littermates	Missense mutation (F238L) into the rat <i>Cnr1</i> gene that encodes for the CB1R induced in MT adults	1. Striatal [³⁵S]GTPγS analysis 2. Whole cell patch clamp recordings of dorsolateral striatal tissue 3. Western Blots for striatal CB1R, FAAH and MAGL 4. AEA and 2-AG levels by mass spectrometry 5. CB1R ligand uptake by PET 6. Risk taking behavior and decision making: – Open field test, elevated plus maze, light/dark emergence test, novelty preference test, novel object exploration test, predator odor risk taking task (PORT) 7. Food and reward intake sensitivity: – Limited access food reward intake test, progressive ratio (PR) test, sweetened condensed milk (SCM) intake 8. Social play behavior	1. MT striatal [³⁵S]GTPγS binding > WT adults 2. Whole cell patch clamp recordings: – No difference in amplitude of synaptic events in MT vs. WT adults – MT adults synaptic inter-event interval > WT adults – Potentiation of synaptic transmission in MT adults with administration of CB1R antagonist 3. Western blots: – No differences in striatal CB1R protein levels in MT vs. WT adults – No differences in levels of MAGL in MT vs. WT adults – MT FAAH levels < WT adults – No difference in levels of AEA and 2-AG in MT vs. WT adults 4. AEA and 2-AG levels: – No difference in levels of AEA and 2-AG in MT vs. WT adults 5. PET: – No difference in CB1R uptake in MT vs. WT adults 6. Risk taking: – MT > WT adults in EPM, open field, EMT, and PORT 7. Food and reward intake: – MT > WT adults – CB1R antagonist reduced SCM consumption in MT to WT levels – Adult MT = adolescent WT SCM intake 8. Impulsive choice: – MT > WT adults 9. Social play behavior: – MT > WT

(Continues)

TABLE 1 | (Continued)

Study	Study design	Subject groups	Intervention	Outcome measurements and corresponding exposure conditions	Results
Pattij et al. (2007)	Animal model	48 male Wistar rat	Administration of selective CB ₁ receptor antagonist rimonabant (SR141716A) and agonist WIN55,212-2	- Premature response prior to visual stimulus (inhibitory control) - Perseverative responses following correct choice (compulsivity) - Accurate choice/correct response/latency/omission errors (attention): - Five choice serial reaction time task - Response inhibition: - Stop signal paradigm - Impulsive choice: - Delayed reward paradigm	- Premature response: - SR141716A produced dose dependent decrease - No change with WIN55,212-2 - Perseverative response: - Not affected by any dose of SR141716A - No change with WIN55,212-2 - Attention: - Increase in accurate choice with SR141716A - No change in accurate choice with WIN55,212-2 - Increase in response latency with SR141716A - Increase in response latency with WIN55,212-2 - No change in omission with SR141716A - Increase in omission with WIN55,212-2 - Response inhibition: - No change with SR141716A or WIN55,212-2 - Impulsive choice: - No change with SR141716A or WIN55,212-2

(Continues)

TABLE 1 | (Continued)

Study	Study design	Subject groups	Intervention	Outcome measurements and corresponding exposure conditions	Results
Castelli et al. (2011)	Animal model	DAT-CI male mice generated by homologous recombination in 129/SvJ embryonic stem cells backcrossed to C57BL/6J mice for 10 or more generations and controls	Administration of CBIR agonist HU210 Administration of GABA(b) receptor agonist baclofen Administration of Type 5 metabotropic glutamate receptors (mGluRs) by DHPG, which mobilizes the endocannabinoid 2-arachidonoylglycerol (2-AG) in the striatum Administration of cocaine Administration of CBIR inverse agonist AM251	1. Motor activity: – Open field test 2. Sensitivity of CBIR(GABA): – Frequency and amplitude of striatal spontaneous inhibitory postsynaptic currents (sIPSCs) – Frequency of striatal spontaneous inhibitory postsynaptic currents (sIPSCs) as % of pre-intervention – Amplitude of striatal evoked inhibitory postsynaptic currents (eIPSCs) as % of pre-intervention – Electrophysiology trace before and during intervention 3. Synaptic modulation of GABA(b) receptor and CBIR (glutamate) by Baclofen: – Frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) as % of pre-intervention/time – Frequency of spontaneous glutamate-mediated excitatory postsynaptic currents as % of pre-intervention/time – Amplitude of evoked excitatory postsynaptic currents (eEPSCs) as % of pre-intervention 4. Effects of DHPG on striatal mIPSCs: – Frequency of mediated inhibitory postsynaptic currents (mIPSCs) as % of pre-intervention/time – Voltage-clamp recordings before and during intervention 5. Effects of cocaine and sucrose on CBIRs _(GABA) in DAT-CI mice: – Frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) as % of pre-intervention/time – Electrophysiological traces of sIPSCs before and during intervention 6. Sucrose sensitivity – Preference of sucrose concentration (as measured by intake)	1. Motor activity: – DAT-CI mice demonstrate greater motor activity than controls 2. Sensitivity of CBIR(GABA): – Baseline sIPSC were the same between WT and DAT-CI – Significant reduction in sIPSC for control mice with administration of HU210 – Effect blocked by AM251 – No reduction in DAT-CI Mice – Depression of eIPSC amplitude in controls with administration of HU210 – No effect on eIPSC in DAT-CI mice 3. Synaptic modulation of GABA(b) receptor and CBIR (glutamate) by baclofen: – Baclofen reduced sIPSC frequency in controls and DAT-CI mice – HU210 agonist inhibited glutamate-mediated sEPSC and ePSC in controls and DAT-CI mice 4. Effects of DHPG on striatal mIPSCs: – DHPG inhibits GABA mIPSCs or eIPSCs in controls but not in DAT-CI mice – Pre-incubation with AM251 blocks inhibition in controls 5. Effects of cocaine and sucrose on CBIRs _(GABA) in DAT-CI mice: – Cocaine and sucrose potentiate effects of CBIR agonist on sIPSC in WT but not in DAT-CI mice – DAT CI mice continue to demonstrate sensitivity to sucrose concentration 6. Sucrose sensitivity – DAT CI mice continue to demonstrate sensitivity to sucrose concentration

(Continues)

TABLE 1 | (Continued)

Study	Study design	Subject groups	Intervention	Outcome measurements and corresponding exposure conditions	Results
Luque-Rojas et al. (2013)	Animal model	C57Bl/6J adult male mice	Administration of selective D2/D3 agonist quinpirole (QNP) (0.1 or 1 mg/kg) Administration of FAAH inhibitor URB597 (1 mg/kg) or MAGL inhibitor URB602 (10 mg/kg) Administration of cocaine (20 mg/kg) Administration of saline vehicle (Veh)	1. Locomotion – Open field test 2. Stereotyped behaviors – Observational cylinders	1. Locomotion – Both doses of QNP enhance immobility compared to control – Cocaine increases locomotion – FAAH and MAGL inhibitors did not modify locomotion when coadministered with cocaine 2. Stereotyped behaviors – Mice administered QNP demonstrate significantly greater numbers of stereotyped behaviors, with the exception of grooming – FAAH and MAGL inhibitors did not modify locomotion, anxiety, habituation or stereotypic behaviors in C57/Bl6J mice – Coadministration of FAAH or MAGL inhibitors and quinpirole reversed quinpirole-induced hyperactivity and stereotyped behavior

(Continues)

TABLE 1 | (Continued)

Study	Study design	Subject groups	Intervention	Outcome measurements and corresponding exposure conditions	Results
Tzavara et al. (2006)	Animal model	Dopamine transporter wild-type (WT), heterozygous (HZ), and KO mice of B6x129F1-background	Administration of CB1R antagonist AM251 (1, 3, and 10 mg/kg) or saline vehicle Administration of anandamide uptake inhibitor AM404 (0.3, 1, and 3 mg/kg), anandamide uptake inhibitor VDM11 (2 and 5 mg/kg), or FAAH inhibitor AA5HT (2 and 5 mg/kg), or vehicle Administration of TRPV1 antagonist capsazepine	1. Anandamide tissue levels in striatum, hippocampus, cortex, and cerebellum 2. Locomotion – Horizontal locomotor activity 3. TRPV1 VRI receptor binding – Quantitative receptor autoradiography	1. Anandamide tissue levels – Anandamide levels reduced by 30% in striatum of DAT KO mice – No difference in anandamide levels in other brain regions 2. Locomotion – No effect on locomotion with administration of AM251 in WT or DAT KO mice – AM404 reduced spontaneous locomotion in DAT KO mice at all doses tested in a dose dependent manner – VDM11 and AA5HT similarly reduced hyperlocomotion in DAT KO mice in a dose dependent manner and did not affect locomotion in WT mice – Coadministration of AM251 with AM404 did not prevent hypolocomotor effects – Coadministration of AM404 and capsazepine, VDM11 and capsazepine, and AA5HT and capsazepine counteracted hypolocomotor effects in DAT KO mice while capsazepine alone had no effect on locomotion in WT or DAT KO mice 3. TRPV1 VRI receptor binding – Selective increase of VRI receptor binding in striatum of DAT KO mice – No difference in CB1R binding in the striatum

Abbreviations: CB1R, cannabinoid 1 receptor; DAT-CI, dopamine transporter cocaine insensitive; KO, knockout mice; TRPV1, transient receptor potential Vanilloid 1.

TABLE 2 | Clinical studies examining effects of cannabis on cognition.

Study	Study design	N	Subgroups	ADHD diagnosis	Cannabis use measurement	THC	Outcome measurement	Results
Bossong et al. (2013)	Placebo controlled, cross-over	20	Healthy male volunteers without history of psychiatric disease	NA	Self-report Subjects refrained from use for at least 2 weeks prior to study	6 mg THC via vapor, titrated up to CNS effects	Neuroimaging: pharmacological fMRI Executive function: CPT-IP	Task performance was impaired after THC administration. Impaired performance linked to reduced deactivation in DMN regions. Less deactivation significantly correlated with lower performance after THC
Tamm et al. (2013)	Cross-sectional with comparison group	128	MTA subsample 87 ADHD (42 CU/45 Non-CU) 41 LNCG (20 CU/21 Non-CU)	DSM-IV using the DISC parent report, version 3.0	Self-report CU: ≥monthly use over the past year Non-CU: use <4 times during previous year	NA	Tests of cognition: Verbal learning: HVLT Response inhibition: GNG Decision making: IGT Cognitive interference: D-KEFS-CWI Working memory: PASAT Processing speed: TMT	No significant effects for cannabis use emerged. Interactions between ADHD and cannabis were nonsignificant
Rasmussen et al. (2016)	Cross-sectional with comparison group	88	MTA subsample 62 ADHD (31 CU/31 Non-CU) 26 LNCG (21 CU/14 Non-CU)	DSM-IV using the DISC parent report, version 3.0	Self-report CU: ≥monthly use over the past year Non-CU: use <4 times during previous year	NA	Neuroimaging: Task-based fMRI	Cognitive function: no significant main effects of diagnosis, CU, or interactions for response times and errors of omission on the Go/NoGo tasks fMRI: Cannabis-by-ADHD interaction in the hippocampus and cerebellar vermis, with higher activation during inhibition in CU compared to non-CU, but only amongst non-ADHD subjects

(Continues)

TABLE 2 | (Continued)

Study	Study design	N	Subgroups	ADHD diagnosis	Cannabis use measurement	THC	Outcome measurement	Results
Kelly et al. (2017)	Cross-sectional with comparison group	129	MTA subsample 44 ADHD-CU 44 ADHD Non-CU 20 LNCG CU 21 LNCG Non-CU	DSM-IV using the DISC parent report, version 3.0	Self-report CU; At least weekly in past year or month Non-CU; use <4 times during previous year	NA	Neuroimaging: Structural and fMRI	No significant interactions between ADHD diagnosis and cannabis use, but significant main effects detected in four intrinsic connectivity networks in the ADHD sample. Significant main effects of cannabis use within the DMN including stronger iFC in the right superior temporal sulcus, and stronger iFC in the left fusiform gyrus in the lateral visual network
McDonald et al. (2003)	Double blind, placebo controlled within subjects	37	Healthy volunteers with lifetime history of cannabis use. No history of major DSM-IV diagnosis	NA	Self-report of CU >10 times in lifetime	Marinol 7.5mg or 15 mg	Performance measures: Psychomotor: DSST Verbal recall: HLV Memory: digit span Impulsivity measures: Stop task, Go/No-go task, time test, delay discounting task Personality: Barratt impulsiveness scale-II	THC increased impulsive responding on the stop task. No effect on Go/no-go, delay, or probability discounting tasks. THC increased estimates of short intervals in the time reproduction task. Estimates of longer intervals were unaffected. No significant correlations between tasks before or after drug administration

Abbreviations: ADHD, attention deficit/hyperactivity disorder; CNS, central nervous system; CPT, continuous performance task with identical pairs; CU, cannabis use; DISC, diagnostic interview schedule for children; D-KEFS-CWI, Delis-Kaplan executive function system color word interference task; DMN, default mode network; DSST, the digit symbol substitution test; fMRI, functional magnetic resonance imaging; GNG, Go/NoGo response in inhibition task; HVL, Hopkins verbal learning task; iFC, intrinsic functional connectivity; IGT, Iowa gambling task; LNCG, local normative comparison group; MTA, multimodal treatment study of ADHD; Non-CU, cannabis nonusers; PASAT, paced auditory serial addition test; THC, tetrahydrocannabinol; TMT, trail making task.

TABLE 3 | Clinical studies examining effects of cannabis use on attention deficit hyperactivity disorder (ADHD) symptoms.

Study	Study design	N	Subgroups	ADHD diagnosis	Cannabinoid administered	Cannabis use measurement	Outcome measurement	Results
Cooper et al. (2017)	Randomized Control Trial	30	15 Active group 15 Placebo group	DSM-V using the DIVA and CAARS	Sativex (THC: CBD ratio 1:1) titrated to optimal dose	NA	Cognitive performance: QbTest, SART ADHD symptoms: CAARS Emotional dysregulation: WRAADS Emotional lability: CNS-LS, ALS-SF Functional impairment: WFTS-S	No significant difference was found in ITT analysis Sativex associated with a nominal improvement in hyperactivity/impulsivity and inhibition. Trend toward improvement for inattention and emotional lability
Strueber and Cutter (2022)	Online Survey	1738		Self report	NA	Cannabis use patterns: DFAQ-CU Cannabis use disorder: CUDIT-R	ADHD symptoms: BAASR-IV Dysexecutive syndrome: DEX Personality: PPI	ADHD participants using cannabis noted acute symptom relief, including hyperactivity and impulsivity. They also observed cannabis alleviating medication side effects, such as irritability and anxiety. Cannabis usage frequency significantly influenced the relationship between symptom severity and executive dysfunction

Abbreviations: ALS-SF, affective lability scale-short form; BAASR-IV, the Barkley adult attention-deficit/hyperactivity disorder rating scale-IV; CAARS, Conners' adult ADHD rating scale; CBD, cannabidiol; CNS-LS, Center For Neurologic Study Lability Scale; CUDIT-R, the cannabis use disorder identification test-revised; DEX, the dysexecutive questionnaire; DFAQ-CU, daily sessions, frequency, age of onset, and quantity of cannabis use inventory; DIVA, diagnostic interview for ADHD in adults; ITT, intention to treat; PPI, psychopathic personality inventory; QbTest, quantitative behavioral test; SART, sustained attention to response task; THC, tetrahydrocannabinol; WFTS-S, Weiss functional impairment rating scale self report; WRAADS, Wender-Reimherr adult attention deficit disorder scale.

into adulthood, suggesting a distinct phenotype of the adolescent brain. Administration of a cannabis antagonist produced extinction of these behaviors in MT adults and had no effect on WT adults, further suggesting a relationship between this adolescent behavioral phenotype and CB1R function. Findings suggest that enhanced CB1R signaling may be implicated in the pathogenesis of persistent adolescent behavioral in adulthood, characterized by persistent risk seeking, impulsive choice, and greater sensitivity to food and drug rewards.

Pattij et al. (2007) investigated the effect of CB1R inverse agonist/antagonist rimonabant (SR141716A) and agonist WIN55,212-2 on various paradigms of impulsivity in WT rats using the five-choice serial reaction time task (5-CSRTT), a measure of impulsivity and visuospatial attention, the delayed reward paradigm, a measure of impulsive choice, and response inhibition in a stop signal paradigm. SR141716A demonstrated a dose dependent decrease in premature responses as well as improved visuospatial attentional function and decreased correct response latency in the 5-CSRTT. WIN55,212-2 did not affect inhibitory control in 5-CSRTT but did increase correct response latency and errors of omission. Neither SR141716A, nor WIN55,212-2, demonstrated an observable effect on impulsive choice. The difference of effect in CB1R antagonism on inhibitory control versus impulsive choice suggests that the ECS may have variable effects on separable components of impulsivity, where inhibitory control is suppressing brain functions irrelevant to a task and impulsive choice reflects a cognitive decision where subjects have to weigh immediate versus delayed outcomes. These results suggest a role for CB1R and the ECS in the regulation of visuospatial attention and suggest antagonism of CB1R as a neurobiological target for regulation of attention deficits resulting from problems of inhibitory control (Solanto, Arnsten, and Castellanos 2001), but not for those characterized by motivational style or delay aversion deficits (Sonuga-Barke 2002).

4.1 | ECS and ADHD

Castelli et al. (2011) examined the role of the ECS in modulation of signaling at GABA-mediated synaptic currents and glutamate transmission to striatal synapses by studying the effects of activation of the CB1R pathway in DAT cocaine insensitive (DAT-CI) mice, representing an animal model of ADHD. DAT-CI mice have a point mutation in the DAT, displaying a hyperactive phenotype in the open field test (OFT) that can be reversed by psychostimulant administration like in human ADHD subjects.

Application of CB1R agonist HU210 significantly reduced spontaneous inhibitory signaling in WT striatum, whereas CB1R inverse agonist AM251 prevented this effect. However, striatal neurons from DAT-CI mice demonstrated absence of HU210 effects. Application of GABA(B) receptor agonist Baclofen significantly reduced spontaneous striatal inhibitory signaling in both WT and DAT-CI mice. HU210 similarly inhibited glutamate-mediated excitatory signaling in controls and DAT-CI slices. Application of group 1 metabotropic glutamate receptor agonist DHPG significantly inhibited striatal GABA(A) signaling in control mice, but not in DAT-CI mice. Preincubation of control striatal slices with AM251 fully prevented these inhibitory effects, confirming the role of CB1Rs in inhibited GABA(A) signal-

ing. Together these results indicate that experimental ADHD selectively alters regulation of GABA synapses through a loss of sensitivity of CB1Rs_(GABA) in the striatum of DAT-CI mice. This dysfunctional DA-CB1Rs_(GABA) coupling in ADHD mice may be partially responsible for the hyperactivity and emotional lability characterizing certain subtypes of ADHD, as striatal CB1Rs_(GABA) have been implicated in motor control and emotional regulation (Carriba et al. 2007; De Chiara et al. 2010; Martin et al. 2008), and GABAergic dysfunction has been hypothesized as a mechanism for problems with working memory, cognitive flexibility, inhibitory control, and impulsivity in humans with ADHD (Ferranti, Luessen, and Niswender 2024).

Luque-Rojas et al. (2013) investigated the effect of inhibition of eCB degradation on the behavioral effects of DA D2/D3 receptor agonist quinpirole (QNP) in WT mice to understand how the ECS mediates locomotion and anxiety. Effects of QNP, fatty acid amide hydrolase (FAAH) inhibitor URB597, and MAGL inhibitor URB602 on locomotion were evaluated using the OFT, whereas anxiety was assessed by observation of stereotyped behaviors in observational cylinders. QNP administration produced a biphasic locomotion response, characterized by initial depression followed by marked activation, as well as dose dependent increased stereotyped behaviors. When FAAH or MAGL was inhibited, the hyperlocomotion produced by high-dose QNP was abolished, and induction of stereotyped behaviors was suppressed. These results indicate that inhibition of eCB degradation results in significant suppression of stimulatory behavioral effects induced by DA D2/D3 receptor activation. Additionally, increasing the concentration of endogenous eCBs anandamide and 2-arachidonoylglycerol was sufficient to abolish the stimulatory component derived from DA D2/D3 receptor activation. These data suggest a relationship between the ECS and the regulation of hyperactive behaviors through dopaminergic D2/D3 signaling.

Tzavara et al. (2006) studied DAT knockout mice (DAT KO) and WT mice to uncover the role of the ECS in the normalization of hyperlocomotion. Mice were compared in terms of horizontal locomotor activity and tissue levels of anandamide in striatum, hippocampus, cortex, and cerebellum sections, as well as quantitative receptor autoradiography. DAT KO mice show hyperlocomotion and reduced levels of anandamide in the striatum compared to WT mice. In one experiment, WT and DAT mice were injected with AM251 or control to study effects on spontaneous hyperlocomotion. AM251 produced no effect on horizontal locomotor activity in either WT or DAT KO mice. In another experiment, mice were injected with AM404, an uptake inhibitor of anandamide or control. AM404 attenuated spontaneous hyperlocomotion in the DAT KO mice at doses that had no effect on WT mice. Coadministration of AM251 did not prevent AM404-induced hyperlocomotion in the DAT KO mice, suggesting that attenuation of hyperlocomotion in DAT KO mice was not mediated through CB1R signaling. In a separate experiment, mice were injected with control, AM404, or one of two indirect eCB agonists: anandamide uptake inhibitor VDM11 or FAAH inhibitor AA5HT. The indirect agonists reduced spontaneous hyperlocomotion in the DAT KO mice at all doses and had no effect on locomotion in WT mice. Transient receptor potential cation channel subfamily V member 1 (TRPV1) antagonist capsaizine administered in conjunction with AM404 counteracted

the hypolocomotor effects of anandamide in the DAT KO mice, whereas capsazepine alone had no effect on locomotor activity in DAT KO or WT mice. Administration of capsazepine but not AM251 also prevented the hypolocomotor effects seen with injection of both VDM11 and AA5HT. A selective increase in VRI receptor binding in the striatum of the DAT KO mice was observed, with no difference seen for CB1 receptor binding in the same region. These results indicate that hyperlocomotion in these DAT KO mice is attenuated via activation of eCB signaling by binding of anandamide to TRPV1 receptors.

5 | Clinical Studies

As summarized above, several preclinical studies have suggested a role for the ECS in the pathophysiology and symptomatology of ADHD. There is increasing evidence that the ECS is involved in cognitive functions including attention and executive function through modulation of the DMN; however, clinical research in this area is scarce, and further investigation is warranted. In addition, our search yielded only a few clinical studies assessing effects of cannabinoids on symptoms of ADHD, and results should be interpreted with caution as all clinical studies are limited by methodological restraints.

5.1 | Executive Function

Bossong et al. (2013) used function magnetic resonance imaging (fMRI) to investigate the effects of the eCB agonist THC on domains of executive function. The study aimed to elucidate the role of the ECS in executive functioning by observing performance and brain activity in both the DMN and task-related networks. The study used a placebo controlled cross-over design and a continuous performance task paradigm with identical pairs (CPT-IP) in 23 healthy male subjects. Placebo and THC were administered via vaporization, and THC dose was titrated to maintain CNS effects. Results showed that THC administration decreased the percentage of correctly identified targets and enhanced the percentage of false alarms. Furthermore, brain regions that were deactivated during the task showed less deactivation after THC than after placebo, but there was no significant difference in task-induced activation. These results suggest that the ECS may be a factor in abnormal DMN activity associated with ADHD.

Several studies have examined effects of cannabis use on executive function in young adults with ADHD using subsamples from the multimodal treatment of ADHD (MTA) study (The MTA Cooperative Group 1999). Tamm et al. (2013) assessed whether aspects of executive function deficits were specific to ADHD or cannabis use and whether co-occurring ADHD and cannabis use had additive effects on executive function deficits. Executive function was measured using the six standardized tasks, including Go/NoGo response inhibition task. In this subsample of 87 individuals with ADHD (42 cannabis users/45 nonusers) and local normal comparison group (LNCG) (20 cannabis users/21 nonusers), they found a significant effect for ADHD but not for cannabis use for almost all tasks of executive function, and no significant ADHD by cannabis use interactions.

Using a similar subsample from the MTA, Rasmussen et al. (2016) used a Go/NoGo task fMRI to examine the effects of cannabis use history on inhibition circuitry. In a sample of 62 ADHD (31 cannabis users/31 nonusers) and 26 LNCG (21 cannabis users/14 nonusers), they found no significant main effects of diagnosis, cannabis use, or interactions for response times and errors of omission on the Go/NoGo tasks. In analyses of fMRI data, they found a cannabis-by-ADHD interaction in the hippocampus and cerebellar vermis, with higher activation during inhibition in cannabis users compared to non-cannabis users, but only amongst non-ADHD subjects. The cerebellum and hippocampus regions comprise a significant part of the ECS, and the cerebellum plays an important role in response inhibition circuitry (Rubia et al. 2007).

Kelly et al. (2017) also used a subsample of MTA subjects, with MRI and intrinsic functional connectivity (iFC) analyses to examine large-scale functional networks in cannabis and non-cannabis users with and without ADHD. They found no significant interactions between ADHD diagnosis and cannabis use, but significant main effects were detected in four intrinsic connectivity networks in the ADHD sample. Furthermore, they found significant main effects of cannabis use within the DMN including stronger iFC in the right superior temporal sulcus, and stronger iFC in the left fusiform gyrus in the lateral visual network. Within the DMN, iFC in the right superior temporal sulcus (cannabis users > nonusers) exhibited a positive correlation with HVLT delayed recall, both across all participants and in the nonuser group. This relationship suggests that those with stronger iFC in this region exhibited the best delayed recall performance. In summary, they observed weaker iFC in subjects with ADHD, compared to LNCG, in networks supporting somatomotor and executive function, and stronger iFC in cannabis users in networks supporting the DMN.

Although findings from the MTA subsamples suggest that mild-moderate cannabis use does not exacerbate neuro-vulnerabilities in young adults with ADHD, they should be interpreted with caution due to several limitations of these studies including self-reported cannabis use and small sample sizes, which may have limited the ability to detect effects of cannabis use (Kelly et al. 2017; Rasmussen et al. 2016; Tamm et al. 2013). Furthermore, findings from the fMRI studies may represent Type 1 errors (Eklund, Nichols, and Knutsson 2016), as they were conducted before significant statistical method changes were widely adopted in the field.

5.2 | Inhibition Control and Impulsivity

Deficits in inhibitory control are a feature of ADHD, common in both inattention and hyperactive subtypes (Pani et al. 2013). Substance use is commonly thought to induce impulsive (i.e., risky and maladaptive) decision-making; however, there are few controlled studies to investigate this. To address this, McDonald et al. (2003) used a double blind, placebo controlled within subjects design to examine the acute effects of THC on 4 measures of impulsivity (stop task, Go/NoGo task, time test, delay discounting task) in a sample of 37 adult recreational cannabis users. Participants received placebo, 7.5 mg THC or 15 mg THC. They found that THC administration affected some but not all tests of impulsivity. THC significantly impaired performance on

the time reproduction task but did not affect performance on the Go/NoGo task and the delay discounting task. On the stop task, they found that administration of 15 mg THC significantly decreased stop reaction time but did not affect go reaction time suggesting that the observed effect was specific to response inhibition. In discussion of their findings, the authors note the difference between the stop task and Go/NoGo task, noting that the later involves greater cognitive inhibition, whereas the former requires greater motor inhibition (Rubia et al. 2001).

5.3 | ADHD Symptomatology

In the only randomized control trial (RCT) to date, Cooper et al. (2017) evaluated effects of cannabinoid medication (Sativex, 1:1 THC:CBD) on ADHD symptoms. The study found no statistically significant difference between groups on activity levels, emotional lability, or cognitive performance, as measured by the quantitative behavioral test (QbT) and Sustained Attention to Response Task (SART). Although trends toward improvement were seen in the active group compared to placebo on many of these tests, the study was underpowered which limited the ability to detect significant effects and provide accurate estimates of effect size (Cooper et al. 2017).

Stueber and Cuttler (2022) surveyed 1738 individuals to examine the impacts of cannabis use on people with ADHD. Among individuals with ADHD who endorsed use of cannabis to manage their ADHD symptoms ($N = 169$), a majority (91.93%) reported that cannabis use improved their symptoms compared to those who reported it made their symptoms worse (4.35%) or had no affect (3.73%). Significantly more people reported that cannabis use improved symptoms of hyperactivity, impulsivity, restlessness, and mental frustration. Results also revealed that cannabis use status did not moderate any of the associations between ADHD symptom severity and executive dysfunction, although frequency of use did. This study was limited by use of a convenience sample (primarily white and female, with high prevalence of self-reported ADHD diagnosis and cannabis use) and retrospective self-report.

6 | Discussion

In this scoping review, our aim was to synthesize the existing literature to elucidate the relationship between the ECS and ADHD symptomatology. Our search yielded limited findings, indicating a paucity of literature. Moreover, research in this emerging field is limited by several methodological restraints. Although evidence from preclinical studies suggests a role for the ECS in regulating neurocognitive functions that are characteristically dysregulated in ADHD, data from clinical studies are sparse, impeding the ability to draw meaningful conclusions. More extensive investigations are needed to deepen our understanding of this complex relationship.

Results from preclinical studies indicate that animal models with increased ECS signaling are characterized by preservation of an adolescent-like phenotype into adulthood, which is mediated by a gain of function in the ECS through striatal CB1R enhancement. However, notably, WT adolescents with the same behavioral

phenotype demonstrate a different mechanism of action in the ECS than the adult mutants, namely, increased binding of CB1R. Both result in a behavioral phenotype characterized by increased risk taking, impulsive choice, reward hypersensitivity, and hyperlocomotion. In humans, these behaviors also peak in adolescence, which is posited as a result of preferential action of the limbic system (ventral striatum, medial prefrontal cortex, and amygdala) over the cognitive control system (lateral prefrontal cortex and lateral parietal cortex) due to earlier maturation of the prior (Dekkers, de Water, and Scheres 2022). Meanwhile, individuals with ADHD display similar trajectory of these behaviors during adolescence, however, with greater frequency and with deficits in executive control that often persist into adulthood. This phenomenon has been hypothesized to originate from a different mechanism whereby there is a deficit, rather than an imbalance, in cortical cognitive control (Dekkers, de Water, and Scheres 2022; Sonuga-Barke 2003). The observed persistence of an adolescent behavioral phenotype into adulthood with upregulated CB1R function coupled with preclinical evidence suggesting CB1R-mediated striatal dysfunction producing deficits in executive function reveals an area of future investigation into a potential link between the ECS and executive dysfunction in ADHD (Biederman et al. 2007; Dekkers, de Water, and Scheres 2022). Activation of the CB1R pathway with administration of eCB agonists results in increased impulsivity and lack of inhibitory control, whereas antagonism produces the opposite effects. Conversely, activation of the ECS through the TRPV1 in the striatum of animal models with ADHD attenuates hyperactivity; however, its role in impulsivity is largely unknown. A link between this ECS pathway and ADHD is further supported by the observed role of anandamide in the regulation of dopaminergic D2/D3 pathways as discussed above. Anandamide does not directly bind to DA neurons but instead modulates dopaminergic signaling indirectly. CB1 receptors are not expressed on DA neurons themselves; however, anandamide can influence the dopaminergic system through its action on CB1 receptors located on GABAergic and glutamatergic neurons, which in turn modulate the activity of DA neurons (Peters, Cheer, and Tonini 2021). This indirect regulation can impact D2/D3 receptor pathways, contributing to the overall dopaminergic signaling processes. D2 receptors are known to play a role in the regulation of locomotor activity in humans with movement disorders (Picetti et al. 1997) and have been suggested to play a role in motivation deficits observed in individuals with ADHD (Dekkers, de Water, and Scheres 2022). Additionally, hyperlocomotion and fidgeting in ADHD have been suggested as a compensatory mechanism for correcting striatal dopaminergic dysfunction based on evidence showing exercise increases striatal DA levels in a similar manner to stimulant medications (Bastoli et al. 2022). Meanwhile, D3 receptors have been shown to play a role in regulating prefrontal cortical function and governing the reward process for addictive behaviors and incentive-based learning in humans (Beninger and Banasikowski 2008; Black et al. 2002), with dysregulated striatal dopaminergic signaling having been implicated in the aberrant processing of reward observed in individuals with ADHD (Volkow et al. 2012).

These results suggest a distinct but variable role for different eCB pathways in mediating impulsivity, dysregulated inhibitory control, and hyperactivity. Results suggest both potential therapeutic and harmful drug interactions for patients with ADHD who use cannabinoids, depending on how cannabinoids activate

the pathways. It is therefore essential to understand what types of cannabinoids patients with ADHD are using as well as how this affects their symptom management.

Results from clinical studies conflict with preclinical studies with regard to effects of cannabinoids on impulsivity and inhibition. In their placebo-controlled study, McDonald et al. (2003) found that eCB agonist (THC) affected some but not all measures of impulsivity. They found that THC administration decreased stop reaction time but had no effect on go reaction time. Stop reaction time requires greater motor inhibition and go reaction time requires more cognitive inhibition, so it is possible that the THC administration has varying effects on motor and cognitive inhibition. Furthermore, in the only RCT to date, Cooper et al. (2017) found no statistically significant effect of cannabinoid administration (1:1 THC:CBD) on symptoms of hyperactivity/impulsivity and inattention, compared to placebo. These findings conflict with the preclinical studies that show increased impulsivity and decreased inhibition with administration of eCB agonists.

Three clinical studies used a subsample from the MTA to examine the extent to which cannabis use affects executive function (Tamm et al. 2013), brain functional organization (Kelly et al. 2017), and neural networks associated with response inhibition (Rasmussen et al. 2016) in individuals with and without ADHD. Two studies showed no difference between ADHD subjects with or without cannabis use (Kelly et al. 2017; Tamm et al. 2013). In their study utilizing task-based fMRI, Rasmussen et al. (2016) found higher activation during inhibition in the hippocampus and cerebellar vermis in cannabis users compared to non-cannabis users, but only among non-ADHD subjects. The cerebellum and hippocampus are key components of the ECS. The cerebellum and basal ganglia have the highest concentration of cannabinoid receptors (Jiang et al. 2005), and the cerebellum plays a crucial role in response inhibition (Rubia et al. 2007). It is therefore plausible that the hippocampus and cerebellum exhibit significant plasticity in response to cannabis use, given their roles in the ECS (Rasmussen et al. 2016). In explaining the difference between individuals with ADHD and those without, Rasmussen et al. (2016) hypothesized that cannabis may have different effects on individuals with ADHD compared to those in the control group. However, it is important to note that all studies from the MTA subsample have methodological limitations, as described above, and therefore, results should be interpreted with caution.

Although findings thus far from clinical and preclinical studies are informative, a significant amount of research is still required to fully elucidate the efficacy and safety of treatments targeting the ECS as a therapeutic agent for symptoms of ADHD. Clinical research in this field is limited by many factors, including lack of RCTs and limited variety in cannabinoid products studied. Among clinical studies in this review, two studies used THC only (Bossong et al. 2013; McDonald et al. 2003), one study used a ratio of 1:1 THC:CBD (Cooper et al. 2017), and all MTA subsamples used self-report of cannabis use. It is likely that different cannabinoids will have different effects on symptoms of ADHD. For instance, cannabinoid products high in CBD do not produce impairments in executive functioning, whereas products high in THC do (Crean, Crane, and Mason 2011; Ramaekers et al. 2006; Tamm et al. 2013). Furthermore, CBD has been shown to attenuate the

psychoactive impairments induced by THC (El-Remessy et al. 2006; Hayakawa et al. 2007; Morgan et al. 2010).

7 | Concluding Remarks

In this scoping review, we aimed to synthesize the existing literature to elucidate the relationship between the ECS and ADHD symptomatology. Our search revealed a limited number of studies, highlighting a significant gap in the literature. The research in this emerging field is constrained by various methodological limitations. Although preclinical studies indicate a potential role for the ECS in regulating neurocognitive functions commonly dysregulated in ADHD, clinical data remain sparse, making it challenging to draw definitive conclusions. Findings from this review suggest both potential therapeutic benefits and detrimental drug interactions for individuals with ADHD using cannabinoids. Despite the growing popular opinion that cannabis and cannabinoids may be a therapeutic agent for ADHD symptoms, several critical questions remain unanswered. More rigorous and comprehensive studies are needed to fully understand the safety and efficacy of cannabinoid therapies in individuals with ADHD. Addressing these methodological issues and expanding the evidence base are crucial steps toward clarifying the therapeutic potential of the ECS in ADHD and developing innovative treatments.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.