HHS Public Access

Author manuscript

Curr Addict Rep. Author manuscript; available in PMC 2023 December 15.

Published in final edited form as:

Curr Addict Rep. 2022 December ; 9(4): 473–485. doi:10.1007/s40429-022-00450-7.

THC, CBD, and Anxiety: A review of recent findings on the anxiolytic and anxiogenic effects of cannabis' primary cannabinoids

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Abstract

Purpose of review: In the context of ongoing decriminalization and legalization of cannabis, a better understanding of how THC and CBD impact anxiety is critical to elucidate the risks of recreational cannabis use as well as to establish the therapeutic potential of cannabis products for anxiety-related applications.

Recent findings: Recent literature supports anxiogenic effects of THC administration, which may be attenuated among regular cannabis users. Data regarding anxiolytic effects of CBD administration are mixed. Most newer studies contradict earlier findings in reporting no effects of CBD on anxiety in healthy participants, whereas inconsistent results have been reported among individuals with anxiety disorders, substance use disorders, and other clinical populations.

Summary: Future research is needed to reconcile heterogenous findings, explore sex differences in the effects of THC and CBD on anxiety, as well as to assess how effects change with extended exposure, the impact of different CBD doses, and interactions between THC, CBD, and other cannabis compounds.

Keywords

delta-9-tetrahydrocannabinol; cannabidiol; sex differences; dosing; risks; therapeutic potential

Introduction

Cannabis is the most widely used illicit drug worldwide [1] and 49% of US adults report lifetime use [2]. In the context of ongoing decriminalization and legalization of cannabis [3, 4], both recreational and medicinal use of cannabis and its constituents is rapidly expanding [5–7]. Notably, a majority of individuals using cannabis products report that they use them to treat anxiety: anxiety is among the most frequently cited motivations for the use of both medical marijuana [8–10] and cannabidiol (CBD) products [11, 12]. Nonetheless, research on the relationship between anxiety and cannabis' two primary constituents, THC and CBD, remains mixed. A better understanding of how THC and CBD impact anxiety is critical to elucidate the risks of recreational cannabis use as well as to establish the therapeutic potential of cannabis products for anxiety-related applications. While prior

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reviews and meta-analyses have addressed earlier literature on the effects of cannabis and its primary constituents on anxiety [e.g., 13, 14–18], recent studies have continued to elucidate anxiogenic and anxiolytic effects of THC and CBD in humans, examining different routes of administration, different doses, and sex differences, as well as assessing these effects in different populations. Therefore, the current review aims to synthesize the latest research on this topic within the context of the broader literature.

Methods

Several databases were explored to identify recent studies examining the effects of THC and/or CBD administration on anxiety, including Pubmed, Ovid MEDLINE, PsycINFO, and Embase. Additional studies were also identified from reference lists. Studies were included if they were published in the last 5 years, included human participants, and administered known doses of THC and/or CBD (vs. cannabis administration studies in which cannabinoid composition is unknown).

Narrative Review

Delta-9-tetrahydrocannabinol (THC) and Anxiety

Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive component of cannabis [19]. It is a partial agonist at CB1 and CB2 receptors [20], and its effects on anxiety are thought to be driven primarily by CB1 receptor binding, as well as interactions with serotonin 1A receptors and the opioid system [14]. Preclinical literature suggests that THC has dose-dependent effects on anxiety, with anxiolytic effects observed at lower doses and anxiogenic effects seen at higher doses, although findings have not been entirely consistent [reviewed in 14]. The human literature has diverged from preclinical findings – as well as epidemiological and consumer survey data – in reporting exclusively anxiogenic effects of THC administration [14]. Nonetheless, some data suggest that the anxiogenic effects of THC may be blunted among regular cannabis users [21], and when THC is co-administered with CBD [22].

THC: Recent Findings

A number of recent studies have continued to assess the effects of THC on anxiety in healthy volunteers, examining a variety of doses and modes of administration among individuals with different levels of prior cannabis exposure (see Table 1). Among individuals with minimal current cannabis use, studies converge in reporting anxiogenic effects of THC [23–25]. A within-subject, double-blind, crossover study examined the effects of vaporized and smoked cannabis with 0mg, 10mg, and 25mg THC among healthy adults (n=17) with a lifetime history of cannabis use but no current (past month) use [23]. Both doses were associated with a significant increase in visual analogue scale (VAS) ratings of “heart racing” and the higher THC dose was associated with a significant increase in ratings of “anxious and/or nervous” relative to placebo, regardless of mode of administration (smoked vs. vaporized cannabis).

Another study pooled data from 4 double-blind, placebo-controlled studies to examine effects of vaporized and oral cannabis containing low dose (5 or 10mg) or high dose (20 or

25mg) THC among healthy adults (n=50) with no current (past month) cannabis use [24]. The authors found a significant main effect of dose on anxiety, such that VAS ratings of "heart racing", "anxious/nervous", and "restless" all increased in a dose-dependent manner. Notably, there was also a significant dose by sex interaction whereby female participants reported greater increases in all three anxiety ratings relative to male participants, and this remained significant when controlling for weight, blood THC and metabolite levels. Another double-blind, placebo-controlled study examined effects of intravenous administration of 0.015mg/kg THC, 0.03mg/kg THC or placebo among healthy adults (n=42) with minimal cannabis use (~90% no use in past month) [25]. Consistent with prior reports, a significant main effect of dose was found for VAS ratings of "anxious", with greater anxiety reported following the higher THC dose. Contrary to the previous study, no dose by sex interaction was observed.

Three studies have examined effects of THC on anxiety among current cannabis users [26–28]. One within-subject, double-blind study examined effects of oral administration of 7.5mg THC, 15mg THC or placebo among female occasional cannabis users (<11 uses in past month; n=37) [27]. Again, THC administration was found to increase anxiety in a dose-dependent manner, although the increase in anxiety was only significant for the higher 15mg dose relative to placebo. Another study pooled data from two within-subject, randomized, placebo-controlled trials assessing the effects of vaporized cannabis with 13.75mg THC (THC condition), 13.75mg THC and 13.75mg CBD (THC/CBD condition), 13.75mg CBD (CBD condition), and placebo among occasional cannabis users (<2x/week for past year; n=40) [26]. They found a main effect of condition, with participants reporting increased anxiety in the THC condition, which was attenuated in the THC/CBD condition. However, contrary to an earlier study of individuals with no current cannabis use [23], there was no sex by condition interaction in this sample of occasional current users. Finally, one randomized, double-blind, placebo-controlled study examined effects of cannabis containing 12.5% THC or placebo among current regular cannabis users (1–4 days/week; n=91) [28]. Participants were allowed to smoke ad libitum for 10 minutes, resulting in an average dose of 86mg for men and 73mg for women in the active condition. Interestingly, the authors found no main effect of THC administration on anxiety and no sex by condition interaction, although men consumed more THC.

Overall, recent studies largely converge in finding anxiogenic effects of THC administration in healthy adults [23–27], although these effects may be blunted among regular cannabis users [28]. However, findings regarding sex differences in THC's anxiogenic effects have been inconsistent. Current data suggest that oral and vaporized THC administration is associated with more substantial increases in anxiety for women relative to men among individuals with no past month use [24], whereas sex differences were not found when THC was administered intravenously [25] or among current cannabis users [26, 28]. Notably, in the one study in which participants could smoke freely (vs. a fixed dose of THC), women were found to smoke less and to have lower peak concentrations of THC and its metabolites, even after adjusting for differences in THC dose consumed. Therefore, although the authors found no sex differences in the effects of THC on anxiety, women had significantly less THC exposure [28], providing further support for important sex differences in the effects and pharmacology of THC administration.

Cannabidiol (CBD) and Anxiety

Unlike THC, CBD has minimal psychoactive effects [20] and does not bind strongly to endogenous cannabinoid receptors [29]. Rather, CBD is hypothesized to have a modulatory effect on a range of systems in the brain and periphery, impacting endocannabinoid, opioid, serotonergic, and adenosine transmission [30], and promoting hippocampal neurogenesis and synaptic plasticity while downregulating glial reactivity [31]. Several mechanisms have been proposed to underlie CBD's anxiolytic effects, including indirect agonism of CB1 receptors, allosteric modulation of serotonin 1A (5-HT1A) receptors, and interactions with the transient receptor potential vanilloid (TRPV) ion channel receptor family [17, 30, 31]. Animal literature suggests that acute CBD administration significantly attenuates anxiety [see 17, 18 for review], and a bell-shaped response curve has been reported such that low/moderate doses are effective whereas higher doses are not [17, 31]. This response pattern is thought to reflect TRPV1 activation at higher CBD doses, which blocks the anxiolytic effects observed at intermediate doses [32]. Preliminary human studies have also demonstrated anxiolytic effects of acute CBD administration while participants undergo anxiety-producing experimental procedures [33–35]. Therefore, there has been significant interest in CBD's therapeutic potential for treating anxiety in a variety of clinical populations.

CBD: Recent Findings

In addition to examining the impact of CBD administration in clinical populations that typically present with anxiety symptoms (e.g. individuals with anxiety disorders and substance use disorders), several recent studies have also examined CBD's effects on anxiety among healthy volunteers [36–40] (see Table 2). One randomized, double-blind, placebo-controlled trial administered 150mg, 300mg, 600mg or placebo to healthy men (n=57) 1.5 hours prior to a simulated public speaking task [38]. Individuals in the 300mg CBD group (n=15) reported significantly lower VAS ratings of "anxiety" during the task relative to the placebo group (n=15), whereas anxiety ratings did not differ significantly from placebo for the 150mg (n=15) and 600mg (n=12) CBD groups. A second randomized, double-blind, placebo-controlled study used a very similar design to examine whether CBD (150, 300, or 600mg) would improve test anxiety among healthy college students (n=32) taking a statistics exam [40]. Contrary to the previous study, VAS ratings of "test anxiety", "anxiety", and self-reported state anxiety did not differ across groups, demonstrating that none of the doses examined had a significant impact on participants' test anxiety.

Similarly, another randomized, double-blind, placebo-controlled trial administered 2 different 150mg CBD formulations (CBD powder and CBD dissolved in corn oil) or placebo to healthy men (n=45) 1 hour prior to a simulated public speaking task [39]. Again, no significant group differences were observed in anxiety, demonstrating that neither formulation had a significant effect on task-induced anxiety. Another study involved four, double-blind, double-dummy, drug administration sessions, in which 18 healthy adults self-administered 100mg oral CBD, 100mg vaporized CBD, vaporized CBD-dominant cannabis (100mg CBD, 3.7mg THC), and placebo [36]. None of the active conditions were associated with changes in VAS ratings of "Anxious/Nervous" over the 8-hour period following drug administration. However, CBD-dominant cannabis administration only was associated with

increased VAS ratings of “Heart racing”. Given that only the formulation containing THC produced effects on anxiety-related ratings, these results align with literature reporting anxiogenic effects of THC administration (see above) and do not strongly support effects of CBD on anxiety in healthy volunteers. Finally, another recent randomized, double-blind, placebo-controlled, crossover study examined the effect of acute administration of 600mg CBD among 24 healthy volunteers [37]. The authors reported no significant effects of CBD administration on VAS ratings of “anxiety” following a stress induction paradigm (mental arithmetic task). Overall, it is notable that these recent data largely diverge from earlier reports of anxiolytic effects of CBD among healthy volunteers.

CBD for Anxiety Disorders—Several recent studies have examined whether CBD can ameliorate anxiety symptoms among individuals with anxiety disorders, either as a stand-alone treatment [41, 42] or as an augmentation strategy in combination with another evidence-based treatment approach [43, 44]. One double-blind, placebo-controlled study administered 300mg CBD daily to 17 Japanese teenagers with social anxiety disorder and found that individuals in the CBD condition (n=17) displayed a significant reduction in their anxiety symptoms across the 4-week treatment period relative to those in the placebo condition (n=20) [41]. Another open-label trial assessed the efficacy of 12-weeks of CBD (titrated up to 800mg) as an add-on treatment among 31 young people (12–25 years old) with a DSM-5 anxiety disorder who had not responded to a standard anxiety disorder treatment (CBT and/or antidepressant) [44]. Anxiety symptoms decreased significantly across the 3-month treatment period, with 40% of participants showing a 50% symptom reduction. However, this study did not include any control condition, so causal inferences regarding CBD administration are limited.

Conversely, another study examining 300mg CBD to augment *in vivo* exposure treatment for treatment refractory patients with anxiety disorders including social anxiety disorder and panic disorder with agoraphobia failed to detect any effect of CBD on treatment outcomes [43]. In this case, participants received an acute dose of 300mg CBD (n=39) or placebo (n=41) 2 hours prior to 8 therapist-assisted exposure therapy sessions. Anxiety was assessed before, during, and after the 8-session treatment course, as well as 3- and 6-months later. Although anxiety symptoms were found to improve significantly with treatment, there was no significant difference between the CBD and placebo groups. Finally, a randomized, placebo-controlled study assessed whether 300mg CBD would ameliorate anxiety among individuals with PTSD while recalling the details of their traumatic event [42]. Across all participants, the authors again found no significant effect of CBD administration (n=17) on change in anxiety before and after trauma recall relative to placebo (n=16). However, when participants were stratified based on the nature of their trauma, sexual (n=14) versus nonsexual (n=19) trauma, CBD was found to lessen trauma recall-induced anxiety among the nonsexual trauma group, whereas no effect was seen in the sexual trauma group.

Collectively, recent data provide very mixed support for the efficacy of CBD among individuals with anxiety disorders. Notably, existing studies suggest that CBD may be more efficacious among individuals with less severe anxiety (adolescents with SAD [41] vs. patients with treatment-refractory anxiety disorders [43], nonsexual trauma vs. sexual trauma [42]), although one study with no control group did find CBD to be effective among

youth with treatment-refractory anxiety disorders [44]. Therefore, future well-controlled studies are needed to further assess the efficacy of CBD for the treatment of anxiety disorders and to systematically assess whether efficacy varies based on symptom severity.

CBD for Substance Use Disorders—Four recent studies have examined the utility of CBD for treating anxiety in the context of heroin [45], cannabis [46], and cocaine use disorders [47, 48]. In one double-blind, randomized, placebo-controlled trial of CBD for individuals with heroin use disorder [45], CBD (400mg, n=14 or 800mg, n=13) or placebo (n=15) was administered for 3 consecutive days and drug-cue induced anxiety was measured on the first day of CBD administration, 24 hours after CBD administration, and 7 days after the 3-day course of CBD administration. Individuals in the CBD groups reported significantly less drug-cue induced anxiety at all 3 testing sessions relative to the placebo group. Although anxiety symptoms were reduced in a dose-dependent manner, the difference between the 400mg and 800mg groups was not statistically significant.

A second study conducted a double-blind, placebo-controlled, randomized, adaptive Bayesian trial aimed at assessing the efficacy of CBD for cannabis use disorder, identifying effective CBD doses for reducing cannabis use, and assessing a range of secondary endpoints including anxiety symptoms [46]. Across two separate phases of the trial, participants were randomized to receive 200mg (n=12), 400mg (n=24), 800mg (n=23) CBD or placebo (n=23) for 4 weeks, and the 800mg dose was found to reduce anxiety symptoms both during treatment and at follow-up.

Finally, 2 randomized, double-blind, placebo-controlled trials examined the efficacy of CBD for reducing anxiety among individuals with cocaine use disorder [47, 48]. In the first trial, men with crack-cocaine dependence were randomized to receive 300mg CBD (n=14) or placebo (n=17) for 10 days and anxiety was assessed at baseline and at the end of the 10-day treatment period. Contrary to the prior two studies, the authors found no effect of CBD administration on anxiety symptoms during treatment for cocaine use disorder. A second trial examined the efficacy of chronic CBD administration (800mg) for reducing anxiety symptoms, as well as acute anxiety induced by stressful or cocaine-cue-related scenarios among individuals with cocaine use disorder [47]. In this case, participants were randomized to receive 800mg CBD (n=40) or placebo (n=38) for 92 days, anxiety symptoms were measured throughout the treatment period, and cue-induced anxiety was assessed on day 8 based on change in anxiety before and after stress-inducing, cocaine-use-related, and neutral scenarios. Again, the authors found no significant effect of CBD administration on any measure of anxiety. Similar to the recent literature on CBD for anxiety disorders, the evidence for the efficacy of CBD for anxiety in substance use disorders is mixed. Preliminary data suggests that 800mg CBD (both acute and chronic administration) may reduce anxiety symptoms among individuals with heroin [45] and cannabis [46] use disorders, whereas both 300 and 800mg doses were found to be ineffective for treating anxiety in the context of cocaine use disorder [47, 48].

CBD for Other Clinical Populations—A number of recent studies have also assessed the efficacy of CBD for treating anxiety symptoms in other clinical populations. One randomized, double-blinded, placebo-controlled, crossover trial evaluated the efficacy of

300mg CBD to reduce anxiety induced by a simulated public speaking task among 24 individuals with Parkinson's disease [49]. Acute CBD administration (90 minutes prior to stress-induction) was found to significantly reduce anxiety in anticipation, during, and following the simulated public speaking task in this population. Another randomized, placebo-controlled, double-blind study examined whether short-term CBD treatment (600mg/day for 1 week) would reduce anxiety induced by the trier social stress test (TSST) among individuals at clinical high risk (CHR) for psychosis [50]. State anxiety was measured following the TSST among CHR individuals in the CBD (n=16) and placebo (n=17) groups, as well as a comparison group of healthy volunteers (n=25; no medication treatment). There was a significant effect of group on anxiety, such that CHR individuals in the placebo group reported the greatest anxiety, followed by those in the CBD group, and controls reported the lowest anxiety. Although this pattern suggests that CBD may attenuate anxiety induced by a social stressor among CHR individuals, the difference between the CBD and placebo groups was not statistically significant.

Another study assessed the use of CBD among individuals with high paranoid traits and found that acute administration of 600mg CBD (n=16) 130 min prior to a 3D virtual-reality paradigm simulating the experience of being on a London Underground train was not found to effectively reduce anxiety relative to placebo (n=16) [51]. Finally, a retrospective chart review examined the impact of adjunctive CBD treatment for improving anxiety symptoms among a diverse sample of adult psychiatric patients (n=72) [52]. Overall, patients treated with CBD were characterized by decreased anxiety across a 3-month follow-up period. However, this study did not include any control group, so it is difficult to conclude whether the clinical improvements were attributable to CBD administration.

Open Questions and Future Directions

THC and Anxiety—Overall, existing literature strongly supports anxiogenic effects of THC administration in healthy adults [14, 23–27]. However, these findings stand in stark contrast to epidemiological and consumer data suggesting that a majority of medical marijuana users report using cannabis to treat anxiety [8–10, 14]. One recent study suggests that anxiogenic effects of THC may be blunted among regular cannabis users [28]. Therefore, regular users may be less susceptible to the anxiety-inducing effects of THC. Nonetheless, contrary to animal literature suggesting anxiolytic effects of THC at low doses, no human studies have reported anxiolytic effects of THC administration [14].

One potential explanation for this discrepancy is that THC may have distinct effects when administered with other cannabinoids, including CBD and terpenes [14]. Indeed, comparing the same dose of THC administered with and without CBD, Arkell *et al.* [26] found the anxiogenic effects of THC to be attenuated by CBD co-administration. Additionally, although THC and CBD are the dominant cannabinoids in the cannabis plant and have received the most research attention to date, cannabis contains over 140 pharmacologically active cannabinoids [53]. Therefore, behavioral effects of whole-plant cannabis use result from complex interactions between an array of cannabis components. Recent research suggests that terpenes [54], another group of cannabis compounds, may also have anxiolytic effects [14, 55]. Therefore, future research is needed to elucidate how THC interacts with

other cannabinoids to impact anxiety, as well as to better understand how these effects change with extended cannabis exposure.

Additionally, preclinical literature suggests that THC's effects on anxiety vary by age (adolescent vs adult) [56], brain region (injection into hippocampus vs prefrontal cortex) [57], and stress exposure [58], and recent clinical data has reported inconsistent results regarding sex differences in THC's anxiogenic effects [24–26, 28]. Sex differences in endocannabinoid receptor density and changes in receptor density across development have been reported [59], as well as significant sex differences in cannabinoid metabolism [60]. Therefore, future studies are needed to establish whether women are indeed more susceptible to the anxiogenic effects of THC and elucidate the mechanisms underlying sex differences in THC's effects on anxiety.

CBD and Anxiety—Recent literature on the anxiolytic effects of CBD has yielded inconclusive results. Among healthy volunteers, recent literature largely does not support the efficacy of CBD for reducing experimentally induced anxiety [36, 37, 39, 40]. However, it is important to note that the timing of drug administration and testing varied substantially across published reports. Whereas peak plasma levels typically occur 2–3 hours after drug administration [61], one study conducted their stress induction 1 hour following medication administration [39] and in another the stress-induction task took place 5.5 hours after drug administration, Therefore, it is difficult to determine whether the null findings in these studies are attributable to a true lack of anxiolytic effects of CBD in healthy volunteers or rather may be better explained by a sub-optimal latency between drug administration and testing.

Additionally, CBD dosing varies substantially across recent studies. Whereas Linares *et al.* [38] report 300mg to be effective relative to 150 and 600mg doses, only one other study tested the efficacy of a 300mg dose [40], with most studies administering doses found to be ineffective among healthy volunteers [36, 37, 39]. Nonetheless, the second study did not support earlier findings that 300mg was effective for reducing experimentally-induced anxiety [40]. Therefore, the dose-response relationship between CBD and anxiety remains poorly understood [62] and future studies with larger samples are needed to establish optimal dosing to evaluate anxiolytic effects of CBD in healthy volunteers and clinical populations.

Current literature on the efficacy of CBD for improving anxiety symptoms among clinical populations is also mixed. Among individuals with anxiety disorders, recent data supports the efficacy of CBD among teens with social anxiety disorder [41], young people with treatment resistant anxiety disorders [44], and individuals with PTSD from non-sexual trauma [42], whereas a lack of efficacy has been reported when CBD is used as an adjunct to *in vivo* exposure treatment for treatment refractory anxiety disorder patients [43] and individuals with PTSD from sexual trauma [42]. Overall, these studies provide preliminary evidence that chronic dosing may be more effective [41, 44] relative to acute CBD administration [42, 43] for individuals with anxiety disorders. However, future research is needed to establish optimal dosing (amount and acute versus chronic administration), as well as to assess whether the efficacy of CBD varies based on age (teens [41]/young adults

[44] versus adults [42, 43]) or symptom severity [41–43] among individuals with anxiety disorders.

Inconsistent results have also been reported regarding the efficacy of CBD for reducing anxiety symptoms among individuals with substance use disorders. Two studies found that both short-term (3-day) [45] and longer term (4-week) [46] administration of 800mg CBD significantly reduced anxiety symptoms among individuals with heroin [45] and cannabis [46] use disorders. In contrast, 2 studies failed to find any significant effect of chronic CBD administration on anxiety among individuals with cocaine use disorders [47, 48]. Therefore, future research is needed to continue to explore CBD's potential for treating anxiety symptoms among individuals with substance use disorders and to assess whether CBD's therapeutic value may be specific to certain substance use disorders. Research on the application of CBD to treat anxiety in the context of other clinical populations remains preliminary, and future studies are needed to corroborate early evidence it may be effective for individuals with Parkinson's disease [49] and those at high clinical risk for psychosis [50].

Additionally, recent data has failed to address sex differences in CBD's effects on anxiety. Preliminary pharmacokinetic data indicate that the same dose of CBD is associated with higher peak concentrations and greater exposure for women relative to men [60]. This has important implications given CBD's bell-shaped response curve, which has been observed in both clinical [33, 38] and pre-clinical [17, 31] studies. Furthermore, animal research suggests that TRPV1 expression is upregulated by estrogen [63]. Given that TRPV1 activation is hypothesized to block the anxiolytic effects of CBD at higher doses, thess data strongly support the need to investigate sex differences in CBD's effects, as doses that are effective in men be ineffective in women due to higher CBD exposure and greater TRPV1 availability and activation [64]. Therefore, it is essential that future studies address sex differences in CBD's effects on anxiety to adequately establish its efficacy and optimal dosing in both sexes.

Conclusions

Both medical marijuana and CBD products are widely used to treat anxiety, but relationships between THC, CBD, and anxiety are not yet fully understood. Recent evidence consistently supports anxiogenic effects of THC administration, which may be blunted among regular cannabis users. Future research is needed to better understand sex differences in the effects of THC and to elucidate how other cannabinoids interact with THC to impact anxiety. Recent data provides very mixed support for anxiolytic effects of CBD among healthy volunteers, individuals with anxiety and substance use disorders, and other clinical populations. Additional research is needed to address optimal dosing and sex differences in CBD's anxiolytic effects, as well as to assess whether age, symptom severity, or patient population moderates these effects. Further data bridging these remaining gaps in the literature is essential to adequately evaluate the therapeutic potential of CBD for anxiety-related applications.

Declarations

Funding and/or Conflicts of interest/Competing interests

Funding for this work was provided by NIDA K08DA051667 and Women's Health Research at Yale (WHRY). The author does not have existing conflicts of interest.

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Table 1.

Recent Studies Assessing the Effects of THC on Anxiety in Humans

Citation	Participants	THC Dose/Route	Anxiety Outcome Measures	Anxiety Effects	Main Findings	Sex Differences
Spindle *et al.* 2018 [23]	Healthy adults (n=17), no past month cannabis use	10mg, 25mg THC vs placebo; vaporized and smoked	VAS anxious and/or nervous, heart racing, restless, relaxed, paranoid	↑	Both 10mg and 25mg doses (both inhalation methods) increased mean ratings of heart racing relative to placebo. The 25mg dose (both inhalation methods) also increased mean ratings of anxious and/or nervous relative to placebo.	Not assessed
Sholler *et al.* 2021 [24]	Healthy adults (n=50), no past month cannabis use	Low dose (5mg, 10mg) and high dose (20mg, 25mg) THC vs placebo; oral and vaporized	VAS anxious and/or nervous, heart racing, restless, relaxed	↑	Dose-dependent increase observed in VAS ratings of anxious/nervous, heart racing, and restless	VAS ratings of anxious/nervous, heart racing, and restless were significantly higher for female versus male participants, after controlling for body weight and peak blood cannabinoid concentrations
Bassir Nia *et al.* 2022 [25]	Healthy adults (n=42), minimal cannabis use (~90% no use in past month)	0.015 mg/kg, 0.03 mg/kg THC vs placebo; IV	VAS anxious	↑	Significant main effect observed for dose on VAS scores for anxious	ns
Arkell *et al.* 2022 [26]	Healthy adults (n=40), occasional cannabis use (<2 times/week and >10 lifetime exposures)	13.75mg THC (with and without 13.75 mg CBD) vs placebo; vaporized	VAS anxious	↑	Significant main effect of condition observed for VAS ratings for anxious	ns
Pabon *et al.* 2022 [27]	Healthy adult women (n=37), occasional cannabis use (>4 lifetime uses and <11 past month uses)	7.5mg, 15mg THC vs placebo; oral	POMS anxiety subscale	↑	Significant increase in anxiety observed for 15mg dose relative to placebo.	N/A
Matheson *et al.* 2020 [28]	Healthy adults (n=91), regular cannabis use (1–4x/week)	750mg cannabis cigarette with 12.5% THC vs placebo; smoked ad libitum for 10 mins	POMS anxiety subscale	-	No main effect of condition on anxiety	Significant effects of sex observed for amount smoked, estimated THC dose, THC concentration, and AUC of THC, with females displaying less consumption and exposure. No significant sex differences in anxiety observed.

Abbreviations: ↑=anxiogenic; -=no effect; AUC=area under the curve; CBD=cannabidiol; DEQ=drug effects questionnaire; IV=intravenous; mg=milligrams; ns=not significant; N/A=not applicable; POMS=Profile of Mood States; THC= Delta-9-tetrahydrocannabinol; VAS=visual analogue scale.

Table 2.

Recent Studies Assessing the Effects of CBD on Anxiety in Humans

Citation	Participants	CBD Dose/Route	Drug Admin-Anxiety Rating Interval	Stress Induction	Anxiety Outcome Measures	Anxiety Effects	Main Findings	Sex Differences
Spindle *et al.* 2020 [36]	Healthy adults (n=18)	100mg CBD vs placebo; oral and vaporized. CBD-dominant cannabis (100mg CBD, 3.7mg THC) vs placebo; vaporized	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8h after oral dosing (vapor dosing occurred 1 hour after oral dosing)	N/A	VAS anxious/ nervous, heart racing, relaxed, paranoid, restless	↑	CBD-dominant cannabis produced higher peak ratings for heart racing relative to placebo and vaporized CBD	ns
Bloomfield *et al.* 2022 [37]	Healthy adults (n=24)	600mg CBD vs placebo; oral	6 hours	Mental arithmetic task	VAS anxious, HR, BP	-	No significant drug effects found for ratings of anxiety, HR or BP	Not assessed
Linares *et al.* 2019 [38]	Healthy adult men (n=57)	150mg, 300mg, 600mg CBD vs placebo; oral	90, 104, 117, 125 and 155 mins	Simulated public speaking test (SPST)	VAMS anxiety factor, HR, BP	↓	300mg CBD was associated with significantly lower anxiety during stress induction relative to placebo	N/A
Crippa *et al.* 2022 [39]	Healthy adult men (n=45)	150mg CBD (Powder and dissolved in corn oil) vs placebo; oral	30, 60, 90, 120, 150, 180, and 240 mins	Simulated public speaking test (SPST)	VAMS anxiety factor, HR, BP	-	No significant differences observed across groups	N/A
Stanely *et al.* 2022 [40]	Healthy college students (n=32)	150mg, 300mg, 600mg CBD vs placebo; oral	66, 84, and 104 mins	Statistics exam	VAS state test anxiety, VAMS, STAI-state, somatic anxiety symptom scale	-	No significant effects of CBD on anxiety measures	Not assessed
CBD for Anxiety Disorders								
Masataka *et al.* 2019 [41]	Japanese teenagers with social anxiety disorder and avoidant personality disorder (n=37)	300mg CBD vs placebo; daily oral admin for 4 weeks	4 weeks	N/A	Fear of Negative Evaluation Questionnaire, Liebowitz Social Anxiety Scale	↓	Individuals in the CBD group reported significantly lower anxiety on both scales	Not assessed
Bolsoni *et al.* 2022 [42]	Adults with PTSD (n=33)	300mg CBD vs placebo; oral	90 mins	Trauma recall paradigm	VAMS, BP, HR, cortisol	↓/-	Among individuals with nonsexual trauma (n=19), differences in VAMS anxiety before and after trauma recall were significantly smaller following CBD vs placebo; this difference was not significant	ns

Citation	Participants	CBD Dose/Route	Drug Admin-Anxiety Rating Interval	Stress Induction	Anxiety Outcome Measures	Anxiety Effects	Main Findings	Sex Differences
							among individuals with sexual trauma (n=16)	
Kwee *et al.* 2022 [43]	Adults with SAD or PD with agoraphobia (n=80)	300mg CBD vs placebo 2 hours prior to 8 90-min therapist-assisted augmented exposure *in vivo* sessions; oral	Change from baseline to post-treatment	N/A	FQ, BAI	-	No difference in treatment outcome between individuals receiving CBD vs placebo	Not assessed
Berger *et al.* 2022 [44]	Young people (aged 12–25) with an anxiety disorder and no clinical improvement from CBT and/or antidepressant (n=31)	Fixed-flexible dosing schedule from 200–800mg/d CBD as add-on treatment for 12 weeks; oral	Change from baseline to post-treatment	N/A	OASIS	↓	OASIS scores decreased significantly across 12-week treatment period; no placebo control	Not assessed
CBD for Substance Use Disorders								
Hurd *et al.* 2019 [45]	Adults with heroin use disorder (n=42)	400mg, 800mg CBD vs placebo for 3 days; oral	118 mins, ~24 hours, 7 days after 3rd daily dose	Drug-cue exposure paradigm on day 1, 2 and 7	VAS anxiety, BP, HR, cortisol	↓	CBD associated with significant reduction in drug-cue induced anxiety	Not assessed
Freeman *et al.* 2020 [46]	Adolescents and adults with cannabis use disorder (n=82)	200mg, 400mg, 800mg CBD vs placebo daily for 4 weeks; oral	4 weeks (post-treatment), 24 weeks (end of follow-up)	N/A	BAI	↓	800mg CBD associated with significant reduction in anxiety during treatment and follow-up	Not assessed
Mongeau-Perusse *et al.* 2022 [47]	Adults with current cocaine use disorder (n=78)	800mg CBD vs placebo for 92 days; oral	Every 2 days for 10 days, every 2 weeks for another 12 weeks	N/A	VAS anxiety, BAI	-	No group differences in anxiety	Not assessed
Meneses-Gaya *et al.* 2021 [48]	Adult men with crack-cocaine dependence (n=31)	300mg CBD vs placebo for 10 days; oral	10 days (post-treatment)	N/A	BAI	-	No group differences in anxiety	N/A
CBD for Other Clinical Populations								
de Faria *et al.* 2020 [49]	Adults with Parkinson's disease (n=24)	300mg CBD vs placebo; oral	90 mins	Simulated public speaking test (SPST)	VAMS, BP, HR, Self-Statements During Public Speaking Scale	↓	CBD associated with significantly lower task-induced anxiety	Not assessed
Appiah-Kusi *et al.* 2020 [50]	Individuals at clinical high risk for psychosis (n=32)	600mg CBD vs placebo for 1 week; oral	8 days	Trier Social Stress Test (TSST)	STAI (state), cortisol	-	No significant difference in anxiety between CHR groups following CBD vs placebo treatment	Not assessed
Hundal *et al.* 2018 [51]	Individuals with high paranoid traits (n=32)	600mg CBD vs placebo; oral	130 mins	3D virtual-reality paradigm that simulates being on London	BAI, University of Wales Mood Adjective Checklist, cortisol, HR, BP	-	No group differences in anxiety	Not assessed

Citation	Participants	CBD Dose/Route	Drug Admin-Anxiety Rating Interval	Stress Induction	Anxiety Outcome Measures	Anxiety Effects	Main Findings	Sex Differences
				Underground train				
Shannon *et al.* 2019 [52]	Diverse psychiatric patients presenting with primary anxiety and/or sleep concerns (n=72)	25–175mg CBD daily (majority on 25mg dose) as adjunct to treatment as usual; oral	Monthly	N/A	Hamilton Anxiety Rating Scale	↓	Anxiety scored decreased within first month and remained decreased for duration of study for majority of patients; no control condition	Not assessed

Abbreviations: ↑=anxiogenic; ↓=anxiolytic; -=no effect; AUC=area under the curve; BAI=Beck Anxiety Inventory; BP=blood pressure; CBD=cannabidiol; CBT=cognitive behavioral therapy; DEQ=drug effects questionnaire; FQ=fear questionnaire; HR=heart rate; IV=intravenous; mg=milligrams; ns=not significant; N/A=not applicable; OASIS=Overall Anxiety Severity and Impairment Scale; PD=panic disorder; POMS=Profile of Mood States; PTSD=post-traumatic stress disorder; SAD=social anxiety disorder; STAI=state-trait anxiety inventory; THC= Delta-9-tetrahydrocannabinol; VAMS=visual analogue mood scale; VAS=visual analogue scale