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REVIEW

Cannabidiol as a Potential Treatment for Anxiety Disorders

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Abstract Cannabidiol (CBD), a *Cannabis sativa* constituent, is a pharmacologically broad-spectrum drug that in recent years has drawn increasing interest as a treatment for a range of neuropsychiatric disorders. The purpose of the current review is to determine CBD's potential as a treatment for anxiety-related disorders, by assessing evidence from preclinical, human experimental, clinical, and epidemiological studies. We found that existing preclinical evidence strongly supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder when administered acutely; however, few studies have investigated chronic CBD dosing. Likewise, evidence from human studies supports an anxiolytic role of CBD, but is currently limited to acute dosing, also with few studies in clinical populations. Overall, current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

Keywords Cannabidiol · Endocannabinoids · Anxiety · Generalized anxiety disorder · Post-traumatic stress disorder

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Introduction

Fear and anxiety are adaptive responses essential to coping with threats to survival. Yet excessive or persistent fear may be maladaptive, leading to disability. Symptoms arising from excessive fear and anxiety occur in a number of neuropsychiatric disorders, including generalized anxiety disorder (GAD), panic disorder (PD), post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), and obsessive–compulsive disorder (OCD). Notably, PTSD and OCD are no longer classified as anxiety disorders in the recent revision of the Diagnostic and Statistical Manual of Mental Disorders-5; however, excessive anxiety is central to the symptomatology of both disorders. These anxiety-related disorders are associated with a diminished sense of well-being, elevated rates of unemployment and relationship breakdown, and elevated suicide risk [1–3]. Together, they have a lifetime prevalence in the USA of 29 % [4], the highest of any mental disorder, and constitute an immense social and economic burden [5, 6].

Currently available pharmacological treatments include serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, benzodiazepines, monoamine oxidase inhibitors, tricyclic antidepressant drugs, and partial 5-hydroxytryptamine (5-HT)$_{1A}$ receptor agonists. Anticonvulsants and atypical antipsychotics are also used to treat PTSD. These medications are associated with limited response rates and residual symptoms, particularly in PTSD, and adverse effects may also limit tolerability and adherence [7–10]. The substantial burden of anxiety-related disorders and the limitations of current treatments place a high priority on developing novel pharmaceutical treatments.

Cannabidiol (CBD) is a phytocannabinoid constituent of *Cannabis sativa* that lacks the psychoactive effects of Δ^{9}-tetrahydrocannabinol (THC). CBD has broad therapeutic properties across a range of neuropsychiatric disorders, stemming from diverse central nervous system actions [11, 12]. In recent

years, CBD has attracted increasing interest as a potential anxiolytic treatment [13–15]. The purpose of this review is to assess evidence from current preclinical, clinical, and epidemiological studies pertaining to the potential risks and benefits of CBD as a treatment for anxiety disorders.

Methods

A search of MEDLINE (PubMed), PsycINFO, Web of Science Scopus, and the Cochrane Library databases was conducted for English-language papers published up to 1 January 2015, using the search terms "cannabidiol" and "anxiety" or "fear" or "stress" or "anxiety disorder" or "generalized anxiety disorder" or "social anxiety disorder" or "social phobia" or "post-traumatic stress disorder" or "panic disorder" or "obsessive compulsive disorder". In total, 49 primary preclinical, clinical, or epidemiological studies were included. Neuroimaging studies that documented results from anxiety-related tasks, or resting neural activity, were included. Epidemiological or clinical studies that assessed CBD's effects on anxiety symptoms, or the potential protective effects of CBD on anxiety symptoms induced by cannabis use (where the CBD content of cannabis is inferred via a higher CBD:THC ratio), were included.

CBD Pharmacology Relevant to Anxiety

General Pharmacology and Therapeutic Profile

Cannabis sativa, a species of the *Cannabis* genus of flowering plants, is one of the most frequently used illicit recreational substances in Western culture. The 2 major phyto- cannabinoid constituents with central nervous system activity are THC, responsible for the euphoric and mind-altering effects, and CBD, which lacks these psychoactive effects. Preclinical and clinical studies show CBD possesses a wide range of therapeutic properties, including antipsychotic, analgesic, neuroprotective, anticonvulsant, antiemetic, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic properties (see [11, 12, 16–19] for reviews). A review of potential side effects in humans found that CBD was well tolerated across a wide dose range, up to 1500 mg/day (orally), with no reported psychomotor slowing, negative mood effects, or vital sign abnormalities noted [20].

CBD has a broad pharmacological profile, including interactions with several receptors known to regulate fear and anxiety-related behaviors, specifically the cannabinoid type 1 receptor (CB_1R), the serotonin 5-HT_{1A} receptor, and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptor [11, 12, 19, 21]. In addition, CBD may also regulate, directly or indirectly, the peroxisome proliferator-activated receptor-γ, the orphan G-protein-coupled receptor 55, the equilibrative nucleoside transporter, the adenosine transporter, additional TRP channels, and glycine receptors [11, 12, 19, 21]. In the current review of primary studies, the following receptor-specific actions were found to have been investigated as potential mediators of CBD's anxiolytic action: CB_1R, TRPV1 receptors, and 5-HT_{1A} receptors. Pharmacology relevant to these actions is detailed below.

The Endocannabinoid System

Following cloning of the endogenous receptor for THC, namely the CB_1R, endogenous CB_1R ligands, or "endocannabinoids" (eCBs) were discovered, namely anandamide (AEA) and 2-arachidonoylglycerol (reviewed in [22]). The CB_1R is an inhibitory $G_{i/o}$ protein-coupled receptor that is mainly localized to nerve terminals, and is expressed on both γ-aminobutryic acid-ergic and glutamatergic neurons. eCBs are fatty acid derivatives that are synthesized on demand in response to neuronal depolarization and Ca^{2+} influx, via cleavage of membrane phospholipids. The primary mechanism by which eCBs regulate synaptic function is retrograde signaling, wherein eCBs produced by depolarization of the postsynaptic neuron activate presynaptic CB_1Rs, leading to inhibition of neurotransmitter release [23]. The "eCB system" includes AEA and 2-arachidonoylglycerol; their respective degradative enzymes fatty acid amide hydroxylase (FAAH) and monoacylglycerol lipase; the CB_1R and related CB_2 receptor (the latter expressed mainly in the periphery); as well as several other receptors activated by eCBs, including the TRPV1 receptor, peroxisome proliferator-activated receptor-γ, and G protein-coupled 55 receptor, which functionally interact with CB_1R signaling (reviewed in [21, 24]). Interactions with the TRPV1 receptor, in particular, appear to be critical in regulating the extent to which eCB release leads to inhibition or facilitation of presynaptic neurotransmitter release [25]. The TRPV1 receptor is a postsynaptic cation channel that underlies sensation of noxious heat in the periphery, with capsacin (hot chili) as an exogenous ligand. TRPV1 receptors are also expressed in the brain, including the amygdala, periaqueductal grey, hippocampus, and other areas [26, 27].

The eCB system regulates diverse physiological functions, including caloric energy balance and immune function [28]. The eCB system is also integral to regulation of emotional behavior, being essential to forms of synaptic plasticity that determine learning and response to emotionally salient, particularly highly aversive events [29, 30]. Activation of CB_1Rs produces anxiolytic effects in various models of unconditioned fear, relevant to multiple anxiety disorder symptom domains (reviewed in [30–33]). Regarding conditioned fear, the effect of CB_1R activation is complex: CB_1R activation may enhance or reduce fear expression, depending on brain locus and the eCB ligand [34]; however, CB_1R activation potently enhances fear extinction [35], and can prevent fear reconsolidation. Genetic manipulations that impede

CB_1R activation are anxiogenic [35], and individuals with eCB system gene polymorphisms that reduce eCB tone—for example, FAAH gene polymorphisms—exhibit physiological, psychological, and neuroimaging features consistent with impaired fear regulation [36]. Reduction of AEA–CB_1R signaling in the amygdala mediates the anxiogenic effects of corticotropin-releasing hormone [37], and CB_1R activation is essential to negative feedback of the neuroendocrine stress response, and protects against the adverse effects of chronic stress [38, 39]. Finally, chronic stress impairs eCB signaling in the hippocampus and amygdala, leading to anxiety [40, 41], and people with PTSD show elevated CB_1R availability and reduced peripheral AEA, suggestive of reduced eCB tone [42].

Accordingly, CB_1R activation has been suggested as a target for anxiolytic drug development [15, 43, 44]. Proposed agents for enhancing CB_1R activation include THC, which is a potent and direct agonist; synthetic CB_1R agonists; FAAH inhibitors and other agents that increase eCB availability, as well as nonpsychoactive cannabis phytocannabinoids, including CBD. While CBD has low affinity for the CB_1R, it functions as an indirect agonist, potentially via augmentation of CB_1R constitutional activity, or via increasing AEA through FAAH inhibition (reviewed in [21]).

Several complexities of the eCB system may impact upon the potential of CBD and other CB_1R-activating agents to serve as anxiolytic drugs. First, CB_1R agonists, including THC and AEA, have a biphasic effect: low doses are anxiolytic, but higher doses are ineffective or anxiogenic, in both preclinical models in and humans (reviewed in [33, 45]). This biphasic profile may stem from the capacity of CB_1R agonists to also activate TRPV1 receptors when administered at a high, but not low dose, as demonstrated for AEA [46]. Activation of TRPV1 receptors is predominantly anxiogenic, and thus a critical balance of eCB levels, determining CB1 *versus* TRPV1 activation, is proposed to govern emotional behavior [27, 47]. CBD acts as a TRPV1 agonist at high concentrations, potentially by interfering with AEA inactivation [48]. In addition to dose-dependent activation of TRPV1 channels, the anxiogenic *versus* anxiolytic balance of CB_1R agonists also depends on dynamic factors, including environmental stressors [33, 49].

5-HT_{1A} Receptors

The 5-HT_{1A} receptor (5-$HT_{1A}R$) is an established anxiolytic target. Buspirone and other 5-$HT_{1A}R$ agonists are approved for the treatment of GAD, with fair response rates [50]. In preclinical studies, 5-$HT_{1A}R$ agonists are anxiolytic in animal models of general anxiety [51], prevent the adverse effects of stress [52], and enhance fear extinction [53]. Both pre- and postsynaptic 5-$HT_{1A}Rs$ are coupled to various members of the $G_{i/o}$ protein family. They are expressed on serotonergic neurons in the raphe, where they exert autoinhibitory function, and various other brain areas involved in fear and anxiety [54, 55]. Mechanisms underlying the anxiolytic effects of 5-$HT_{1A}R$ activation are complex, varying between both brain region, and pre- *versus* postsynaptic locus, and are not fully established [56]. While in vitro studies suggest CBD acts as a direct 5-$HT_{1A}R$ agonist [57], in vivo studies are more consistent with CBD acting as an allosteric modulator, or facilitator of 5-HT_{1A} signaling [58].

Preclinical Evaluations

Generalized Anxiety Models

Relevant studies in animal models are summarized in chronological order in Table 1. CBD has been studied in a wide range of animal models of general anxiety, including the elevated plus maze (EPM), the Vogel-conflict test (VCT), and the elevated T maze (ETM). See Table 1 for the anxiolytic effect specific to each paradigm. Initial studies of CBD in these models showed conflicting results: high (100 mg/kg) doses were ineffective, while low (10 mg/kg) doses were anxiolytic [59, 60]. When tested over a wide range of doses in further studies, the anxiolytic effects of CBD presented a bell-shaped dose–response curve, with anxiolytic effects observed at moderate but not higher doses [61, 90]. All further studies of acute systemic CBD without prior stress showed anxiolytic effects or no effect [62, 65], the latter study involving intracerebroventricular rather than the intraperitoneal route. No anxiogenic effects of acute systemic CBD dosing in models of general anxiety have yet been reported. As yet, few studies have examined chronic dosing effects of CBD in models of generalized anxiety. Campos et al. [66] showed that in rat, CBD treatment for 21 days attenuated inhibitory avoidance acquisition [83]. Long et al. [69] showed that, in mouse, CBD produced moderate anxiolytic effects in some paradigms, with no effects in others.

Anxiolytic effects of CBD in models of generalized anxiety have been linked to specific receptor mechanisms and brain regions. The midbrain dorsal periaqueductal gray (DPAG) is integral to anxiety, orchestrating autonomic and behavioral responses to threat [91], and DPAG stimulation in humans produces feelings of intense distress and dread [92]. Microinjection of CBD into the DPAG produced anxiolytic effects in the EPM, VGC, and ETM that were partially mediated by activation of 5-$HT_{1A}Rs$ but not by CB_1Rs [65, 68]. The bed nucleus of the stria terminalis (BNST) serves as a principal output structure of the amygdaloid complex to coordinate sustained fear responses, relevant to anxiety [93]. Anxiolytic effects of CBD in the EPM and VCT occurred upon microinjection into the BNST, where they depended on 5-$HT_{1A}R$

Table 1 Preclinical studies

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Silveira Filho et al. [59]	WR	i.p.	**100** mg/kg, acute	GSCT	No effect	NA
Zuardi et al. [60]	WR	i.p.	**10**mg/kg, acute	CER	Anxiolytic	NA
Onaivi et al. [61]	ICR mice	i.p.	0.01, 0.10, **0.50**, **1.00**, **2.50**, **5.00**, **10.00**, **50.00**, 100.00 mg/kg, acute	EPM	Anxiolytic	Effects ↓ by IP flumazenil, unchanged by naloxone
Guimaraes et al. [61]	WR	i.p.	**2.5**, **5.0**, **10.0** and 20.0 mg/kg, acute	EPM	Anxiolytic	NA
Moreira et al. [62]	WR	i.p.	2.5, 5.0 and **10.0**mg/kg, acute	VCT	Anxiolytic	Effect unchanged by IP flumazenil
Resstel et al. [63]	WR	i.p.	**10**mg/kg, acute	CFC	Anxiolytic	NA
Campos et al. [64]	WR	dlPAG	15.0, **30.0**, 60.0 nmol/0.2 μl, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra-dlPAG WAY100635 but not intra-dlPAG AM251
Bitencourt et al. [65]	WR	i.c.v.	**2.0** μg/μl 5 min before extinction, acute	CFC extinction EPM before and 24 h after CFC	Anxiolytic No effect before CFC Anxiolytic following CFC	Extinction effect ↓ by SR141716A but not capsazepine
Campos et al. [66]	WR	dlPAG	**30**, 60 mg/kg, acute	EPM	Anxiolytic	Intra-dlPAG capsazepine renders 60 mg/kg anxiolytic
Resstel et al. [67]	WR	i.p.	1, **10** or 20 mg/kg, acute	RS EPM 24 h following RS	Anxiolytic, ↓ Pressor ↓ Tachycardia Anxiolytic	All effects ↓ by systemic WAY100635
Soares et al. [68]	WR	dlPAG	15, **30** or **60**nmol, acute	ETM PAG E-stim	Anxiolytic Panicolytic Panicolytic	All effects ↓ by intra-dlPAG WAY100635 but not AM251
Long et al. [69]	C57BL/6 J mice	i.p.	**1**, 5, 10, **50**mg/kg, chronic, daily/21 d	EPM L-DT SI OF	No effect 1 mg/kg anxiolytic No effect 50 mg/kg anxiolytic	NA
Lemos et al. [70]	WR	i.p. PL IL	**10**mg/kg IP, **30**nmol intra-PL and intra-IL, acute	CFC	IP and PL anxiolytic IL anxiogenic	NA
Casarotto et al. [71]	C57BL/6 J mice	i.p.	15, **30**, and 60 mg/kg, acute, or subchronic, daily/7 d	MBT	Anticompulsive	Effect ↓ by IP AM251 but not WAY100635
Gomes et al. [72]	WR	BNST	15, **30**, and 60 nmol, acute	EPM VCT	Anxiolytic Anxiolytic	Both effects ↓ by intra BNST WAY100635
Granjeiro et a l. [73]	WR	Intracisternal	15, **30**, and 60 nmol, acute	RS EPM 24 h after RS	Anxiolytic, ↓Pressor ↓Tachycardia Anxiolytic	NA
Deiana et al. [74]	SM	i.p. Oral	**120**mg/kg, acute	MBT	Anticompulsive	NA
Uribe-Marino et al. [75]	SM	i.p.	0.3, **3.0**, **30.0**mg/kg, acute	PS	Panicolytic	NA

Table 1 (continued)

Study	Animal	Route	Dose	Model	Effect	Receptor Involvement
Stern et al. [76]	WR	i.p.	3, **10**, 30 mg/kg immediately after retrieval, acute	Reconsolidation blockade	Anxiolytic 1 and 7 d old fear memories disrupted	Effect ↓ by AM251 but not WAY100635
Campos et al. [77]	WR	i.p.	**5** mg/kg, subchronic, daily/7 d	EPM following PS	Anxiolytic	Effects ↓ by IP WAY100635
Hsiao et al. [78]	WR	CeA	**1** μg/μl	REM sleep time EPM OF	↓ REM sleep suppression Anxiolytic Anxiolytic	NA
Gomes et al. [79]	WR	BNST	**15**, **30**, **60**nmol, acute	CFC	Anxiolytic	Both effects ↓ by intra-BNST WAY100635
El Batsh et al. [80]	LE-H R	i.p.	**10**mg/kg, chronic, daily/14 d	CFC	Anxiogenic	NA
Campos et al. [81]	C57BL/6 mice	i.p.	**30**mg/kg 2 h after CUS, chronic daily/14 d	EPM NSF	Anxiolytic Anxiolytic	Both effects ↓ by AM251
Do Monte et al. [82]	L-E HR	IL	1 μg or **0.4** μg/0.2 μl 5 min before extinction daily/4 d	Extinction of CFC	Anxiolytic	Effect ↓ by IP rimonabant
Campos et al. [83]	Rat	i.p.	**5**mg/kg, chronic, daily/21 d	ETM	Anxiolytic Panicolytic	Panicolytic effect ↓ by intra-dlPAG WAY100635
Almeida et al. [84]	Rat	i.p.	**1**, 5, 15 mg/kg, acute	SI	Anxiolytic	NA
Gomes et al. [85]	WR	BNST	**30** and 60 nmol, acute	RS	Anxiogenic ↑ Tachydardia	Effect ↓ by WAY100635
Twardowschy et al. [86]	SM	i.p.	**3**mg/kg, acute	PS	Panicolytic	Effects ↓ by IP WAY100635
Focaga et al. [87]	WR	PL	15, **30**, 60 nmol, acute	EPM EPM after RS CFC	Anxiogenic Anxiolytic Anxiolytic	All effects ↓ by intra PL WAY100635 Anxiolytic EPM effect post-RS ↓ by IP metyrapone
Nardo et al. [88]	SM	i.p.	**30** mg/kg, acute	MBT	Anticompulsive	NA
da Silva et al. [89]	WR	SNpr	**5** μg/**0.2** μl	$GABA_A$ blockade in dlSC	Panicolytic	Both effects ↓ by AM251

Effective doses are in bold

Receptor specific agents: AM251 = cannabinoid receptor type 1 (CB_1R) inverse agonist; WAY100635 = 5-hydroxytryptamine 1A antagonist; SR141716A = CB_1R antagonist; rimonabant = CB_1R antagonist; capsazepine = transient receptor potential vanilloid type 1 antagonist; naloxone = opioid antagonist; flumazenil = $GABA_A$ receptor antagonist

Anxiolytic effects in models used: CER = reduced fear response; CFC = reduced conditioned freezing; CFC extinction = reduced freezing following extinction training; EPM = reduced % time in open arm; ETM = decreased inhibitory avoidance; L-DT = increased % time in light; VCT = increased licks indicating reduced conflict; NSF = reduced latency to feed; OF = increased % time in center; SI = increased social interaction

Anticomplusive effects: MBT = reduced burying

Panicolytic effects: ETM = decreased escape; $GABA_A$ blockade in dlSC = defensive immobility, and explosive escape; PAG-E-Stim = increased threshold for escape; PS = reduced explosive escape

WR = Wistar rats; SM = Swiss mice; L-E HR = Long–Evans hooded rats; i.p. = intraperitoneal; dlPAG = dorsolateral periaqueductal gray; i.c.v. = intracerebroventricular; PL = prelimbic; IL = infralimbic; BNST = bed nucleus of the stria terminalis; CeA = amygdala central nucleus; SNpr = substantia nigra pars reticularis; CUS = chronic unpredictable stress; GSCT = Geller–Seifter conflict test; CER = conditioned emotional response; EPM = elevated plus maze; VCT = Vogel conflict test; CFC = contextual fear conditioning; RS = restraint stress; ETM = elevated T maze; PAG E-stim = electrical stimulation of the dlPAG; L-DT = light–dark test; SI = social interaction; OF = open field; MBT = marble-burying test; PS = predator stress; NSF = novelty suppressed feeding test; $GABA_A$ = γ-aminobutyric acid receptor A; dlSC = deep layers superior colliculus; REM = rapid eye movement; NA = not applicable

activation [79], and also upon microinjection into the central nucleus of the amygdala [78]. In the prelimbic cortex, which drives expression of fear responses via connections with the amygdala [94], CBD had more complex effects: in unstressed rats, CBD was anxiogenic in the EPM, partially via 5-HT_{1A}R receptor activation; however, following acute restraint stress, CBD was anxiolytic [87]. Finally, the anxiolytic effects of systemic CBD partially depended on $GABA_A$ receptor activation in the EPM model but not in the VCT model [61, 62].

As noted, CBD has been found to have a bell-shaped response curve, with higher doses being ineffective. This may reflect activation of TRPV1 receptors at higher dose, as blockade of TRPV1 receptors in the DPAG rendered a previously ineffective high dose of CBD as anxiolytic in the EPM [66]. Given TRPV1 receptors have anxiogenic effects, this may indicate that at higher doses, CBD's interaction with TRPV1 receptors to some extent impedes anxiolytic actions, although was notably not sufficient to produce anxiogenic effects.

Stress-induced Anxiety Models

Stress is an important contributor to anxiety disorders, and traumatic stress exposure is essential to the development of PTSD. Systemically administered CBD reduced acute increases in heart rate and blood pressure induced by restraint stress, as well as the delayed (24 h) anxiogenic effects of stress in the EPM, partially by 5-HT_{1A}R activation [67, 73]. However intra-BNST microinjection of CBD *augmented* stress-induced heart rate increase, also partially via 5-HT_{1A}R activation [85]. In a subchronic study, CBD administered daily 1 h after predator stress (a proposed model of PTSD) reduced the long-lasting anxiogenic effects of chronic predator stress, partially via 5-HT_{1A}R activation [77]. In a chronic study, systemic CBD prevented increased anxiety produced by chronic unpredictable stress, in addition to increasing hippocampal AEA; these anxiolytic effects depended upon CB_1R activation and hippocampal neurogenesis, as demonstrated by genetic ablation techniques [81]. Prior stress also appears to *modulate* CBD's anxiogenic effects: microinjection of CBD into the prelimbic cortex of unstressed animals was anxiogenic in the EPM but following restraint stress was found to be anxiolytic [87]. Likewise, systemic CBD was anxiolytic in the EPM following but not prior to stress [65].

PD and Compulsive Behavior Models

CBD inhibited escape responses in the ETM and increased DPAG escape electrical threshold [68], both proposed models of panic attacks [95]. These effects partially depended on 5-HT_{1A}R activation but were not affected by CB_1R blockade. CBD was also panicolytic in the predator–prey model, which assesses explosive escape and defensive immobility in response to a boa constrictor snake, also partially via 5-HT_{1A}R activation; however, more consistent with an anxiogenic effect, CBD was also noted to decrease time spent outside the burrow and increase defensive attention (not shown in Table 1) [75, 86] . Finally, CBD, partially via CB_1Rs, decreased defensive immobility and explosive escape caused by bicuculline-induced neuronal activation in the superior colliculus [89]. Anticompulsive effects of CBD were investigated in marble-burying behavior, conceptualized to model OCD [96]. Acute systemic CBD reduced marble-burying behavior for up to 7 days, with no attenuation in effect up to high (120 mg/kg) doses, and effect shown to depend on CB_1Rs but not 5-HT_{1A}Rs [71, 74, 88].

Contextual Fear Conditioning, Fear Extinction, and Reconsolidation Blockade

Several studies assessed CBD using contextual fear conditioning. Briefly, this paradigm involves pairing a neutral context, the conditioned stimulus (CS), with an aversive unconditioned stimulus (US), a mild foot shock. After repeated pairings, the subject learns that the CS predicts the US, and subsequent CS presentation elicits freezing and other physiological responses. Systemic administration of CBD prior to CS re-exposure reduced conditioned cardiovascular responses [63], an effect reproduced by microinjection of CBD into the BNST, and partially mediated by 5-HT_{1A}R activation [79]. Similarly, CBD in the prelimbic cortex reduced conditioned freezing [70], an effect prevented by 5-HT_{1A}R blockade [87]. By contrast, CBD microinjection in the infralimbic cortex *enhanced* conditioned freezing [70]. Finally, El Batsh et al. [80] reported that repeated CBD doses over 21 days, that is chronic as opposed to acute treatment, *facilitated* conditioned freezing. In this study, CBD was administered prior to conditioning rather than prior to re-exposure as in acute studies, thus further directly comparable studies are required.

CBD has also been shown to enhance extinction of contextually conditioned fear responses. Extinction training involves repeated CS exposure in the absence of the US, leading to the formation of a new memory that inhibits fear responses and a decline in freezing over subsequent training sessions. Systemic CBD administration immediately before training markedly enhanced extinction, and this effect depended on CB_1R activation, without involvement of TRPV1 receptors [65]. Further studies showed CB_1Rs in the infralimbic cortex may be involved in this effect [82].

CBD also blocked reconsolidation of aversive memories in rat [76]. Briefly, fear memories, when reactivated by re-exposure (retrieval), enter into a labile state in

which the memory trace may either be reconsolidated or extinguished [97], and this process may be pharmacologically modulated to achieve reconsolidation blockade or extinction. When administered immediately following retrieval, CBD prevented freezing to the conditioned context upon further re-exposure, and no reinstatement or spontaneous recovery was observed over 3 weeks, consistent with reconsolidation blockade rather than extinction [76]. This effect depended on CB_1R activation but not 5-$HT_{1A}R$ activation [76].

Summary and Clinical Relevance

Overall, existing preclinical evidence strongly supports the potential of CBD as a treatment for anxiety disorders. CBD exhibits a broad range of actions, relevant to multiple symptom domains, including anxiolytic, panicolytic, and anticompulsive actions, as well as a decrease in autonomic arousal, a decrease in conditioned fear expression, enhancement of fear extinction, reconsolidation blockade, and prevention of the long-term anxiogenic effects of stress. Activation of 5-$HT_{1A}Rs$ appears to mediate anxiolytic and panicolytic effects, in addition to reducing conditioned fear expression, although CB_1R activation may play a limited role. By contrast, CB_1R activation appears to mediate CBD's anticompulsive effects, enhancement of fear extinction, reconsolidation blockade, and capacity to prevent the long-term anxiogenic consequences of stress, with involvement of hippocampal neurogenesis.

While CBD predominantly has acute anxiolytic effects, some species discrepancies are apparent. In addition, effects may be contingent on prior stress and vary according to brain region. A notable contrast between CBD and other agents that target the eCB system, including THC, direct CB_1R agonists and FAAH inhibitors, is a lack of anxiogenic effects at a higher dose. Further receptor-specific studies may elucidate the receptor specific basis of this distinct dose response profile. Further studies are also required to establish the efficacy of CBD when administered in chronic dosing, as relatively few relevant studies exist, with mixed results, including both anxiolytic and anxiogenic outcomes.

Overall, preclinical evidence supports systemic CBD as an acute treatment of GAD, SAD, PD, OCD, and PTSD, and suggests that CBD has the advantage of not producing anxiogenic effects at higher dose, as distinct from other agents that enhance CB_1R activation. In particular, results show potential for the treatment of multiple PTSD symptom domains, including reducing arousal and avoidance, preventing the long-term adverse effects of stress, as well as enhancing the extinction and blocking the reconsolidation of persistent fear memories.

Human Experimental and Clinical Studies

Evidence from Acute Psychological Studies

Relevant studies are summarized in Table 2. The anxiolytic effects of CBD in humans were first demonstrated in the context of reversing the anxiogenic effects of THC. CBD reduced THC-induced anxiety when administered simultaneously with this agent, but had no effect on baseline anxiety when administered alone [99, 100]. Further studies using higher doses supported a lack of anxiolytic effects at baseline [101, 107]. By contrast, CBD potently reduces experimentally induced anxiety or fear. CBD reduced anxiety associated with a simulated public speaking test in healthy subjects, and in subjects with SAD, showing a comparable efficacy to ipsapirone (a 5-$HT_{1A}R$ agonist) or diazepam [98, 105]. CBD also reduced the presumed anticipatory anxiety associated with undergoing a single-photon emission computed tomography (SPECT) imaging procedure, in both healthy and SAD subjects [102, 104]. Finally, CBD enhanced extinction of fear memories in healthy volunteers: specifically, inhaled CBD administered prior to or after extinction training in a contextual fear conditioning paradigm led to a trend-level enhancement in the reduction of skin conductance response during reinstatement, and a significant reduction in expectancy (of shock) ratings during reinstatement [106].

Evidence from Neuroimaging Studies

Relevant studies are summarized in Table 3. In a SPECT study of resting cerebral blood flow (rCBF) in normal subjects, CBD reduced rCBF in left medial temporal areas, including the amygdala and hippocampus, as well as the hypothalamus and left posterior cingulate gyrus, but increased rCBF in the left parahippocampal gyrus. These rCBF changes were not correlated with anxiolytic effects [102]. In a SPECT study, by the same authors, in patients with SAD, CBD reduced rCBF in overlapping, but distinct, limbic and paralimbic areas; again, with no correlations to anxiolytic effects [104].

In a series of placebo-controlled studies involving 15 healthy volunteers, Fusar-Poli et al. investigated the effects of CBD and THC on task-related blood-oxygen-level dependent functional magnetic resonance imaging activation, specifically the go/no-go and fearful faces tasks [109, 110]. The go/no-go task measures response inhibition, and is associated with activation of medial prefrontal, dorsolateral prefrontal, and parietal areas [111]. Response activation is diminished in PTSD and other anxiety disorders, and increased activation predicts response to treatment [112]. CBD produced no changes in predicted areas (relative to placebo) but reduced activation in the left insula, superior temporal gyrus, and transverse temporal gyrus. The fearful faces task activates the amygdala, and other medial temporal areas involved in

Table 2 Human psychological studies

Study	Subjects, design	CBD route, dose	Measure	Effect
Karniol et al. [99]	HV, DBP	Oral, 15, 30, 60 mg, alone or with THC, acute, at 55, 95, 155, and 185 min	Anxiety and pulse rate after THC and at baseline	↓ THC-induced increases in subjective anxiety and pulse rate No effect at baseline
Zuardi et al., [100]	HV, DBP	Oral 1 mg/kg alone or with THC, acute, 80 min	STAI score after THC	↓ THC-induced increases in STAI scores
Zuardi et al. [98]	HV, DBP	Oral 300 mg, acute, 80 min	VAMS, STAI and BP following SPST	↓ STAI scores ↓ VAMS scores ↓ BP
Martin-Santos et al. [101]	HV, DBP	Oral 600 mg, acute, 1, 2, 3 h	Baseline anxiety and pulse rate	No effect
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	VAMS before SPECT SPECT	↓ VAMS scores
Bhattacharyya et al. [103]	15 HV DBP	Oral 600 mg, acute, 1, 2, 3 h	STAI scores VAMS scores	↓ STAI scores ↓ VAMS scores
Crippa et al. [104]	SAD and HC DBP	Oral 400 mg, acute, 75 and 140 min	VAMS before SPECT SPECT	↓ VAMS scores
Bergamaschi et al. [105]	SAD and HC DBP	Oral 600 mg, acute, 1, 2, 3 h	VAMS, SSPS-N, cognitive impairment, SCR, HR after SPST	↓ VAMS, SSPS-N and cognitive impairment, no effect on SCR or HR
Das et al. [106]	HV DBP	Inhaled, 32 mg, acute, immediately following, before, after extinction	SCR and shock expectancy following extinction	CBD after extinction training produced trend level reduction in SCR and decreased shock expectancy
Hindocha et al. [107]	Varying in schizotypy and cannabis use, DBP	Inhaled, 16 mg, acute	Baseline VAS anxiety	No significant effect of CBD

HV = healthy volunteers; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; THC = $^{\Delta}$9-tetrahydrocannabinol; STAI = Spielberger's state trait anxiety inventory; VAMS = visual analog mood scale; BP = blood pressure; SPST = simulated public speaking test; SCR = skin conductance response; SPECT = single-photon emission computed tomography; SSPS-N = negative self-evaluation subscale; HR = heart rate; VAS = visual analog scale, CBD = cannabidiol

Table 3 Neuroimaging studies

Study	Subjects, design	CBD route, dose, timing	Measure	Effect of CBD
Crippa et al. [102]	10 HV, DBP	Oral 400 mg, acute, 60 and 75 min	SPECT, resting (rCBF)	↓ rCBF in left medial temporal cluster, including amygdala and HPC, also ↓ rCBF in the HYP and posterior cingulate gyrus ↑ rCBF in left PHG
Borgwardt et al. [108]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI during oddball and go/no-go task	↓ Activation in left insula, STG and MTG
Fusar-Poli et al. [109]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI activation during fearful faces task	↓ Activation in left medial temporal region, including amygdala and anterior PHG, and in right ACC and PCC
Fusar-Poli et al. [110]	15 HV, DBP	Oral 600 mg, acute, 1–2 h	fMRI functional connectivity during fearful faces task	↓ Functional connectivity between L) AMY and ACC
Crippa et al. [104]	SAD and HC DBP	Oral 400 mg, acute, 75 and 140 min	SPECT, resting (rCBF)	↓ rCBF in the left PHG, HPC and ITG. ↑ rCBF in the right posterior cingulate gyrus

CBD = cannabidiol; HV = healthy controls; DBP = double-blind placebo; SAD = social anxiety disorder; HC = healthy controls; SPECT = single-photo emission computed tomography; rCBF = regional cerebral blood flow; fMRI = functional magnetic resonance imaging; HPC = hippocampus; HYP = hypothalamus; PHG = parahippocampal gyrus; STG = superior temporal gyrus; MTG = medial temporal gyrus; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex

emotion processing, and heightened amygdala response activation has been reported in anxiety disorders, including GAD and PTSD [113, 114]. CBD attenuated blood-oxygen-level dependent activation in the left amygdala, and the anterior and posterior cingulate cortex in response to intensely fearful faces, and also reduced amplitude in skin conductance fluctuation, which was highly correlated with amygdala activation [109]. Dynamic causal modeling analysis in this data set further showed CBD reduced forward functional connectivity between the amygdala and anterior cingulate cortex [110].

Evidence from Epidemiological and Chronic Studies

Epidemiological studies of various neuropsychiatric disorders indicate that a higher CBD content in chronically consumed cannabis may protect against adverse effects of THC, including psychotic symptoms, drug cravings, memory loss, and hippocampal gray matter loss [115–118] (reviewed in [119]). As THC acutely induces anxiety, this pattern may also be evident for chronic anxiety symptoms. Two studies were identified, including an uncontrolled retrospective study in civilian patients with PTSD patients [120], and a case study in a patient with severe sexual abuse-related PTSD [121], which showed that chronic cannabis use significantly reduces PTSD symptoms; however, these studies did not include data on the THC:CBD ratio. Thus, overall, no outcome data are currently available regarding the chronic effects of CBD in the treatment of anxiety symptoms, nor do any data exist regarding the potential protective effects of CBD on anxiety potentially induced by chronic THC use.

Summary and Clinical Relevance

Evidence from human studies strongly supports the potential for CBD as a treatment for anxiety disorders: at oral doses ranging from 300 to 600 mg, CBD reduces experimentally induced anxiety in healthy controls, without affecting baseline anxiety levels, and reduces anxiety in patients with SAD. Limited results in healthy subjects also support the efficacy of CBD in acutely enhancing fear extinction, suggesting potential for the treatment of PTSD, or for enhancing cognitive behavioral therapy. Neuroimaging findings provide evidence of neurobiological targets that may underlie CBD's anxiolytic effects, including reduced amygdala activation and altered medial prefrontal amygdala connectivity, although current findings are limited by small sample sizes, and a lack of independent replication. Further studies are also required to establish whether chronic, in addition to acute CBD dosing is anxiolytic in human. Also, clinical findings are currently limited to SAD, whereas preclinical evidence suggests CBD's potential to treat multiple symptom domains relevant to GAD, PD, and, particularly, PTSD.

Conclusions

Preclinical evidence conclusively demonstrates CBD's efficacy in reducing anxiety behaviors relevant to multiple disorders, including PTSD, GAD, PD, OCD, and SAD, with a notable lack of anxiogenic effects. CBD's anxiolytic actions appear to depend upon CB_1Rs and 5-HT_{1A}Rs in several brain regions; however, investigation of additional receptor actions may reveal further mechanisms. Human experimental findings support preclinical findings, and also suggest a lack of anxiogenic effects, minimal sedative effects, and an excellent safety profile. Current preclinical and human findings mostly involve acute CBD dosing in healthy subjects, so further studies are required to establish whether chronic dosing of CBD has similar effects in relevant clinical populations. Overall, this review emphasizes the potential value and need for further study of CBD in the treatment of anxiety disorders.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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