

## Review

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# Targeting the endocannabinoid system to treat anxiety-related disorders

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**Abstract:** The endocannabinoid system plays an important role in the control of emotions, and its dysregulation has been implicated in several psychiatric disorders. The most common self-reported reason for using cannabis is rooted in its ability to reduce feelings of stress, tension, and anxiety. Nevertheless, there are only few studies in controlled clinical settings that confirm that administration of cannabinoids can benefit patients with a post-traumatic stress disorder (PTSD). There are considerable encouraging pre-clinical data to suggest that endocannabinoid-targeted therapeutics for anxiety disorders should continue. In this review, we will describe data supporting a role for the endocannabinoid system in preventing and treating anxiety-like behavior in animal models and PTSD patients. Cannabinoids have shown beneficial outcomes in rat and mouse models of anxiety and PTSD, but they also may have untoward effects that discourage their chronic usage, including anxiogenic effects. Hence, clinical and pre-clinical research on the endocannabinoid system should further study the effects of cannabinoids on anxiety and help determine whether the benefits of using exogenous cannabinoids outweigh the risks. In general, this review suggests that targeting the endocannabinoid system represents an attractive and novel approach to the treatment of anxiety-related disorders and, in particular, PTSD.

**Keywords:** anxiety-related disorders; cannabinoids; endocannabinoid system; post-traumatic stress disorder (PTSD).

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## Introduction

Cannabis is widely used for medicinal and social purposes and is legal in some countries. The most common self-reported reason for using cannabis is rooted in its ability to reduce feelings of stress, tension, and anxiety.

Studies of the endocannabinoid system support its importance for multiple aspects of brain function including modulation of the hypothalamic-pituitary-adrenal (HPA) axis; regulation of mood, anxiety, and reward; and extinction of fear learning [1–8]. Hence, the involvement of the endocannabinoid system in mood and anxiety provides new targets for the development of novel therapeutic agents for a wide range of psychiatric disorders [1, 4, 8, 9].

Anxiety disorders are chronic, disabling conditions that impose enormous costs both on individuals and on society [10]. Post-traumatic stress disorder (PTSD) is defined under the trauma- and stressor-related disorders and might develop following exposure to an extreme traumatic event [11]. There are four diagnostic clusters of behavioral symptoms: (i) re-experiencing symptoms involve spontaneous, uncontrollable intrusions of the traumatic memory that manifest themselves as nightmares or memory flashbacks. (ii) Avoidance symptoms are best described as an individual's efforts to distance himself/herself from trauma-related stimuli and can also include emotional and social withdrawal behaviors. (iii) Patients also demonstrate negative alterations in cognitions and mood. (iv) Finally, hyperarousal symptoms include robust physiological reactions such as irritability, hypervigilance, and exaggerated startle [12].

Not all patients respond to the currently available pharmacotherapeutic treatment options [13], and although a number of available drugs (e.g. benzodiazepines, antidepressants, adrenergic antagonists) have been used in clinical settings to explore the possible therapeutic avenues for treating PTSD, they still fall short owing to limited response, high remission rates, and tolerability issues [14].

## The endocannabinoid system

$\Delta^9$ -Tetrahydrocannabinol (THC), the psychoactive constituent of marijuana, was identified in 1964 [15]. This discovery encouraged the identification of the endogenous endocannabinoid system, which includes the cannabinoid receptors (CB1 and CB2), endocannabinoids [anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG)], enzymes involved in their synthesis and metabolism [fatty acid amide hydrolase (FAAH) for anandamide and the monoacylglycerol lipase (MAGL) for 2-AG], and an endocannabinoid transporter [16–18]. Endocannabinoids act as retrograde messengers and are synthesized on demand post-synaptically from lipid precursors. Anandamide and 2-AG levels in the synapse are regulated by their enzymes (FAAH and MAGL) and the endocannabinoid transporter [17, 19]. Anandamide, 2-AG, FAAH, and the CB1 receptor are expressed in brain areas involved in stress, fear, emotions, and reward including the amygdala, nucleus accumbens, hippocampus, and prefrontal cortex (PFC) [17, 20–23].

## Endocannabinoids and conditioned fear

CB1 receptor agonists are reported to induce biphasic effects on anxiety that have been demonstrated in animal models (for reviews, see Refs. [8, 24, 25]). In general, an anxiolytic-like effect tends to appear after using low doses of cannabinoid agonists, whereas higher doses produce an anxiogenic response [26, 27]. Haller et al. [28] found that the FAAH inhibitor URB597 (0.1–0.3 mg/kg) did not produce anxiolytic effects when the aversiveness of the testing procedures was minimized (e.g. by handling rats daily or by employing low illumination during testing). In contrast, URB597 had robust anxiolytic effects when the aversiveness of the testing environment was increased.

It has been recently shown [29] that the highly selective CB1 receptor agonist ACEA increased anxiety-like behavior in the elevated plus maze and open field test. Furthermore, although both the low (0.1 mg/kg) and the high (0.5 mg/kg) dose of ACEA facilitated fear extinction, the low dose attenuated, and the high dose potentiated, fear-induced corticosterone release, suggesting that the extent to which cannabinoids are anxiogenic or anxiolytic not only is dose dependent, but also depends on the differences in sensitivities of CB1 receptors in different neuronal systems.

The formation of a fear memory following a traumatic event is an important mechanism for the subsequent

development of PTSD. Animal models are powerful tools for elucidating the molecular mechanisms and the pathophysiology of mental disorders and for developing novel pharmacological treatments. A number of animal models have been developed to mimic the traumatic events that induce the symptoms of intense and recurrent fear characteristic of patients with PTSD. One approach has used Pavlovian fear conditioning, in which rodents are trained to associate shock delivery with either a cue or a context, and memory for the association is later tested by measuring freezing behavior upon re-exposure to the conditioned cue in the absence of shock [30].

Considerable data exist on the effects of enhancing endocannabinoid signaling on conditioned fear in animals. For example, the CB1/CB2 receptor agonist WIN55,212-2 (2.5 and 5.0 mg/kg), given systemically 30 min before the conditioning phase, impaired the acquisition of contextual fear conditioning [31]. When WIN55,212-2 (10 or 30 ng) was infused into the hippocampus 1 h before the retention test, it impaired the retrieval of contextual fear memory [32]. Similarly, systemic injections of THC impaired retrieval [6 mg/kg, intraperitoneally (ip)] as well as acquisition (10 mg/kg, ip) in the passive avoidance test in rats [33] and post-training intra-CA1 administration of WIN55,212-2 (0.25, 0.5, and 1  $\mu$ g) dose dependently decreased memory retrieval in mice [34]. We have shown that intra-basolateral amygdala (BLA) or intra-CA1 WIN55,212-2 (5  $\mu$ g) had no effect on the acquisition of inhibitory avoidance conditioning in rats [3, 35].

Several studies found that cannabinoid agonists may enhance memory consolidation. Intra-BLA WIN55,212-2 (5–50 ng per side), infused immediately after inhibitory avoidance training, induced dose-dependent enhancement of 48-h retention performance [36], and propofol, which inhibits FAAH, administered intraperitoneally after training, also significantly increased memory consolidation [37]. A similar enhancing effect was found with the administration of URB507 (3, 10, or 30 ng) into the BLA, hippocampus, or medial PFC shortly after inhibitory avoidance training [38].

Recently, Llorente-Berzal et al. [39] compared the contribution of AEA and 2-AG to fear expression. The CB2 agonist JWH133 (3 mg/kg) failed to affect the acute freezing response, whereas the CB1 agonist CP55,940 (50  $\mu$ g/kg) augmented it. The endocannabinoid uptake inhibitor AM404 (3 mg/kg) reduced the acute freezing response. AEA degradation inhibition by URB597 (1 mg/kg) decreased, whereas 2-AG degradation inhibition by JZL184 (4 and 8 mg/kg) increased the freezing response.

Lemos et al. [40] showed that systemic and intra-prelimbic injection of cannabidiol, a major non-psychotomimetic

cannabinoid present in the *Cannabis sativa* plant, impaired contextual fear retrieval. Fogaça et al. [41] showed that intra-infra limbic (IL) cannabidiol enhanced contextual fear retrieval.

See Table 1 for a general summary of the pharmacological studies examining the effects of exogenous cannabinoids on conditioned fear.

## Endocannabinoids and extinction

One of the hallmark symptoms in PTSD is avoiding activities, places, thoughts, or feelings that remind you of the trauma. Impaired extinction of fear memories is thought to contribute to the development and persistence of the persistent memories of the trauma and avoidance [42, 43].

It has been argued that, in PTSD, conditioned fear fails to extinguish, and reminders of traumatic events can cause pathological conditioned fear responses for decades after danger has passed. Hence, considerable efforts have been aimed at pharmacologically enhancing extinction (reviewed in Ref. [44]).

Enhancing endocannabinoid signaling has been shown to facilitate extinction in various studies [35, 45–48]. The facilitating effect on extinction was demonstrated when drugs were aimed at the fear circuit (i.e. BLA, CA1, and PFC). Intra-CA1 WIN55,212-2, AM404, or AEA facilitated the extinction of inhibitory avoidance [35, 49]. A similar effect was observed in the IL; intra-IL WIN55,212-2, AM404, URB597, or cannabidiol also facilitated extinction [50, 51]. A recent study demonstrated that enhanced

inhibitory input via activation of CB1 receptor-expressing cholecystokinin-positive interneurons selectively reduced the firing of BLA fear neurons and promoted extinction [52]. Other studies have also stressed the importance of the endocannabinoid system in the BLA in fear extinction (e.g. Refs. [3, 5]).

See Table 2 for a general summary of the pharmacological studies examining the effects of exogenous cannabinoids administered into the brain's fear circuit on extinction.

Targeting the endocannabinoid system could ameliorate stress-related symptoms by treating the cognitive and emotional features of PTSD. The first “cognitive” approach is to enhance extinction learning. There are many compounds that have been suggested as possible enhancers of extinction (for a review, see Ref. [44]). The rationale for using extinction enhancers is that, in exposure-based treatment approaches, patients are asked to repeatedly confront or revisit details of their trauma memory and associated aversive emotions and thoughts in the absence of negative consequences (e.g. actual life threat), with the goal of extinction and new learning. However, because PTSD and trauma-related memories are resistant to extinction, it is to be expected that extinction effects would be variable at best [53]. Hence, cannabinoids may enhance extinction memories. A second approach is to use cannabinoids to treat the “emotional” features of PTSD. Because of the anxiety-relieving effects of cannabinoids, endocannabinoid signaling has a prominent role in the regulation of fear, anxiety, and stress responses (reviewed in Refs. [54–57]).

**Table 1:** The effects of exogenous cannabinoids on conditioned fear.

Memory phase/paradigm	Drug and dose	Effect on memory	References
Contextual fear acquisition	WIN55,212-2 (2.5 and 5 mg/kg, i.p.)	Impaired	[31]
Contextual fear retrieval	WIN55,212-2 (10 or 30 ng, intra-hippocampal)	Impaired	[32]
	Cannabidiol (30 nmol, intra-PL)		[40]
	Cannabidiol (10 mg/kg, i.p.)		[40]
	Cannabidiol (15 and 30 nmol, intra-IL)	Enhanced	[41]
Inhibitory avoidance acquisition	WIN55,212-2 (5 µg, intra-amygdala; 5 µg, intra-hippocampal)	No effect	[3, 35]
	Δ9-THC (10 mg/kg, i.p.)	Impaired	[33]
Inhibitory avoidance retrieval	Δ9-THC (6 mg/kg, i.p.)	Impaired	[33]
	WIN55,212-2 (0.25, 0.5, or 1 µg, intra-hippocampal)		[34]
Inhibitory avoidance consolidation	WIN55,212-2 (5–50 ng, intra-BLA)	Enhanced	[36]
	Propofol (300 or 350 mg/kg, i.p.)		[37]
	URB597 (3, 10, or 30 ng, intra-BLA, hippocampus, PFC)		[38]
Cued fear-conditioning retrieval	JWH133 (3 mg/kg, i.p.)	No effect	[39]
	CP55,940 (50 µg/kg, i.p.)	Enhanced	
	JZL184 (4 and 8 mg/kg, i.p.)	Enhanced	
	AM404 (3 mg/kg, i.p.)	Impaired	
	URB597 (1 mg/kg, i.p.)	Impaired	

PL, prelimbic; IL, infralimbic; BLA, basolateral amygdala; PFC, prefrontal cortex.

**Table 2:** The effects of exogenous cannabinoids administered into the brain's fear circuit on extinction.

Brain area	Drug	Paradigm	Effect on extinction	References
CA1	WIN55,212-2 (5 µg), AM404 (200 ng) AEA (0.17 ng)	Inhibitory avoidance Contextual fear	Facilitated	[31] [44]
IL	WIN55,212-2 (0.05 µg), AM404 (0.2 µg), URB597 (0.3 µg) Cannabidiol (0.4 µg)	Potentiated startle Contextual fear	Facilitated	[45] [46]
BLA	WIN55,212-2 (5 µg) WIN55,212-2 (5 µg)	Inhibitory avoidance Fear-potentiated startle	No effect	[3] [48]

CA1, CA1 area of the hippocampus; IL, infralimbic; BLA, basolateral amygdala; AEA, anandamide.

## Endocannabinoids and animal PTSD models

Preclinical animal models do not replicate the human condition in its entirety, but seek to mimic symptoms or endophenotypes associated with PTSD. Here we describe several PTSD models in mice and rats that were studied in the context of enhancing endocannabinoid signaling: the model of single-prolonged stress (SPS), the model of exposure to trauma and situational reminders, and the model of exposure to predator stress.

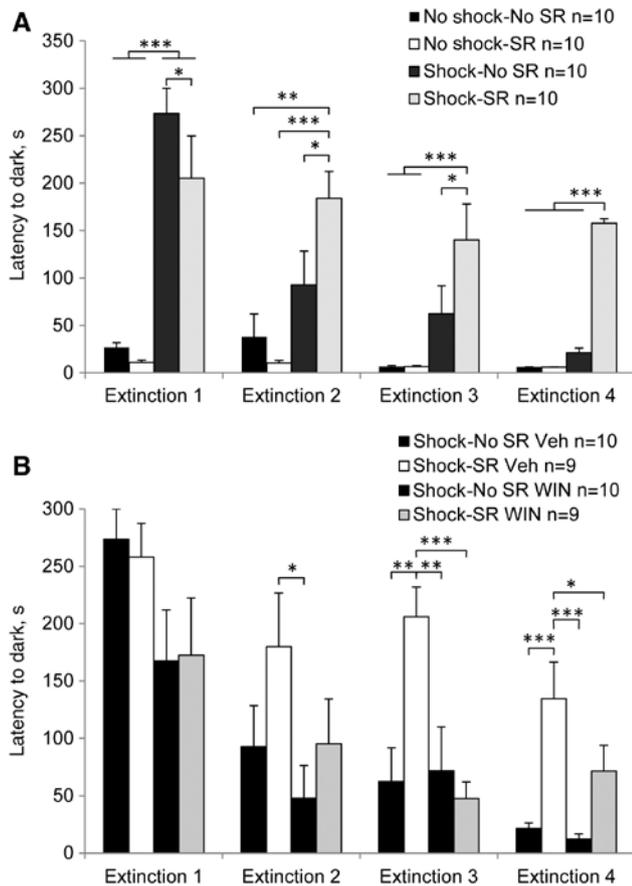
Exposure to SPS involves three different stress paradigms that are not related to conditioned fear: restraint, forced swim, and sedation; after an undisturbed period of 7 days, the rats showed enhanced negative feedback on the HPA axis and an exaggerated acoustic startle response (ASR) [58, 59]. We also found that exposure to SPS enhanced conditioned avoidance and impaired extinction while enhancing ASR, negative feedback on the HPA axis, and anxiety [4]. The cannabinoid CB1/2 receptor agonist WIN55,212-2 (0.5 mg/kg) administered intraperitoneally 2 or 24 h (but not 48 h) after SPS prevented the trauma-induced alterations in inhibitory avoidance conditioning and extinction, ASR potentiation, and HPA axis inhibition. Our findings are of considerable interest since they indicate a relatively broad therapeutic time window in the aftermath of trauma exposure for preventive treatment with cannabinoids. The preventive effects of WIN55,212-2 on extinction were found to be mediated by CB1 and glucocorticoid receptors in the amygdala and hippocampus [60].

However, it has become increasingly clear that the consequences of exposure to trauma are affected not only by the aspects of the event itself, but also by the frequency and severity of trauma reminders. Places and situations are the most frequent trauma reminder; hence, specific environments can be particularly distressing

[61] and the frequency of exposure to trauma reminders is one of the most potent post-trauma mediators of PTSD symptoms [62].

Pynoos et al. [63] developed a model of PTSD in which mice were exposed to a single footshock followed by contextual reminders of the shock. In this paradigm, the animal is re-exposed to situational reminders without any apparent external reinforcement. The contextual reminder was chosen for two reasons: first, to prevent desensitization, which might occur if the mouse entered the shock compartment and did not receive a shock, and, second, to develop an analogue that resembles a common posttraumatic human phenomenon in which traumatized individuals are often confronted with reminders of a traumatic event, but not, except for repeated trauma, with a replication of the traumatic moment. Accordingly, rats reintroduced to the environment where they were initially shocked exhibited increased anxiety-like behaviors in both an elevated plus maze and an open field, as well as heightened startle reflexes, learned helplessness, and impaired social behavior [64, 65].

We have recently [66] exposed rats to a footshock (1.5 mA, 10 s) on day 1 followed by exposure to situational reminders of the shock on days 3 and 5, and tested them 1 week later. Exposure to reminders exacerbated the effects of the shock as rats exposed to shock and reminders, but not to shock alone, showed impaired extinction of the traumatic event, impaired plasticity in the pathway projecting from the hippocampus to the nucleus accumbens, and enhanced latency to startle. WIN55,212-2 administered 2 h after the shock prevented the effects of the shock and reminders on extinction, plasticity, and startle response. WIN55,212-2 also prevented the shock/reminders-induced alterations in CB1 receptors in the PFC and CA1. See Figure 1 for the effects of exposure to shock and reminders on the extinction of the traumatic event itself and for the preventive effects of the cannabinoid agonist WIN55,212-2 on extinction [66].



**Figure 1:** WIN55,212-2 prevents the effects of shock and situational reminders (SR) on extinction.

(A) On Extinction 1, the shock groups (shock-no SR, shock-SR) demonstrated increased latency compared with the no-shock groups. On Extinctions 2–4, the shock-SR group demonstrated increased latency compared with all groups (\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ). This suggests that exposure to SRs exacerbated the effects of the shock on extinction kinetics. (B) When WIN55,212-2 (WIN) was injected 2 h after the shock, the shock-SR vehicle (Veh) group showed increased latency compared with the shock-no SR WIN group on Extinction 2. On Extinctions 3 and 4, the shock-SR Veh group showed increased latency compared with all groups (\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ). Hence, WIN55,212-2 prevented the shock/SR-induced impairment in extinction kinetics (data published by Korem and Akirav [66] in *Neuropsychopharmacology*).

Using the model of exposure to a predator (cat), Campos et al. [67] showed that cannabidiol treatment (5 mg/kg per day for 7 days) starting 1 h after exposure to a predator prevented the anxiogenic effects in rats. The authors suggested that repeated cannabidiol administration prevented the long-lasting anxiogenic effects observed after predator exposure, probably by facilitating 5HT<sub>1A</sub> receptor-mediated neurotransmission. The results suggest that cannabidiol has a beneficial potential for PTSD treatment and that 5HT<sub>1A</sub> receptors could

be a therapeutic target in this disorder. The authors also found that, 7 days after the predator threat, the CB<sub>1</sub> mRNA expression was down-regulated in the frontal cortex and amygdaloid complex [67]. Mayer et al. [68] used a similar model and failed to find a long-term anxiolytic effect of THC (1, 5, and 10 mg/kg) administered 1 h after predator scent stress.

Hsiao et al. [69] employed repeated combination tests (RCT) as a model for progressive anxiety. RCT induced an anxiogenic effect in the elevated plus maze and the open field tests. RCT also resulted in PTSD-like sleep symptoms by decreasing non-REM (rapid eye movement) sleep during the first hour after RCT and suppressing REM sleep during hours 4–10 after the RCT. Cannabidiol microinjected into the central nucleus of the amygdala had an anxiolytic effect in the elevated plus maze and the open field tests, and efficiently blocked anxiety-induced REM sleep suppression.

Taken together, these preclinical results strongly suggest that exogenous cannabinoids administered in proximity to trauma exposure could prevent the development of PTSD-like symptoms [4, 60, 66, 67, 69].

## Human studies

Accumulating data from both clinical and preclinical studies suggest that targeting the endocannabinoid system may benefit PTSD. Given the similarities between extinction procedures and exposure-based psychotherapy used for the treatment of fear disorders in humans [70], the endocannabinoid system represents a novel pharmacological target for anxiety disorders related to inappropriate retention of aversive memories [45, 46, 71]. Accordingly, human studies suggest that cannabinoids may be used as an adjunct to extinction-based therapies for anxiety disorders. In support, Rabinak et al. [71] found that healthy subjects who received THC showed enhanced extinction memory and ventromedial PFC and hippocampal activation to a previously extinguished conditioned stimulus during extinction memory recall. Hence, pre-extinction administration of THC modulates prefrontal-limbic circuits during fear extinction in humans and prompts future investigation to test whether cannabinoid agonists can rescue or correct the impaired behavioral and neural function during extinction recall in patients with PTSD. Das et al. [72] employed a Pavlovian fear-conditioning paradigm in order to assess the effects of cannabidiol on extinction and consolidation. Participants received cannabidiol (32 mg) following, before,

or after extinction, and were tested 48 h later for recall and after reinstatement. Cannabidiol given post-extinction enhanced the consolidation of extinction learning, suggesting that cannabidiol can enhance extinction and may have potential as an adjunct to extinction-based therapies for anxiety disorders.

Klumpers et al. [73] administered THC (10 mg) to healthy subjects prior to the extinction session of a 3-day conditioning protocol. During the extinction training, THC reduced conditioned skin conductance responses, but not fear-potentiated startle. This effect was not retained at the retention test 2 days later, suggesting that it was dependent on the acute effects of the drug. The authors argued that it could be that CB1 facilitation does not affect conditioned fear extinction lastingly in healthy humans and discussed the lack of specificity of THC as a CB1 agonist.

Gorka et al. [74] examined the effects of THC on functional connectivity between amygdala subregions and the PFC during socio-emotional threat in healthy adults. They found that THC enhanced basolateral and superficial amygdala connectivity to the rostral anterior cingulate/medial PFC, suggesting that THC can potentially reduce threat perception or enhance socio-emotional regulation.

Studies in humans also suggested alterations in the endocannabinoid system in PTSD. Hauer et al. [75] indicated that individuals with PTSD show significant differences in plasma concentrations of endocannabinoids and related *N*-acyl-ethanolamides when compared to healthy controls and to subjects who did not develop PTSD after trauma exposure. Neumeister et al. [6] reported that PTSD patients demonstrated elevated brain cannabinoid CB1 receptor availability and suggested that abnormal CB1 receptor-mediated anandamide signaling is implicated in the etiology of PTSD.

Two open-label clinical trials demonstrated the potential benefits of cannabis in patients with PTSD. Fraser [76] found that the majority (72%) of patients receiving the synthetic cannabinoid nabilone experienced either a cessation of nightmares or a significant reduction in nightmare intensity. Subjective improvement in sleep time and sleep quality, and a reduction of daytime flashbacks and night sweats were also noted by some patients. Hence, the study supports the potential benefits of nabilone for the management of treatment-resistant nightmares in PTSD. There is also a previous report on the anxiolytic effects of nabilone in 25 outpatients suffering from anxiety [77].

Roitman et al. [78] examined 10 outpatients with chronic PTSD, on stable medication, who received THC

twice a day for 3 weeks (5 mg/kg) as an add-on treatment. They found that THC significantly improved global symptom severity, sleep quality, frequency of nightmares, and PTSD hyperarousal symptoms.

The comorbidity between cannabis abuse and PTSD is usually described in the literature as a negative aspect, with the increase in substance abuse after a disaster as a cause for public long-term health consequences. However, another side of the coin needs to be addressed. It is possible that PTSD patients use cannabis as a self-medication. In support of this hypothesis, one study among Vietnam veterans indicated that cannabis use was helpful in managing PTSD symptoms, with particular respect to the hyperarousal state [79]. Furthermore, it has been shown that there is a correlation between post-traumatic stress symptom severity and motivation to use marijuana in order to cope with emotional distress [80].

Although plant-derived cannabinoids provide relief from different PTSD symptoms, self-medication with cannabis may cause significant harm. It has been argued that direct activation of CB1 receptors with plant-derived cannabinoids may lead to a rapid down-regulation of the endocannabinoid signaling system, thus worsening the illness and which can result in tolerance and addiction [81–83]. There is substantial evidence that cannabis use can expose people to varying complications (e.g. risk of addiction, cognitive impairment). Thus, it is important to determine the benefit/risk of cannabis with precision and to implement policy measures based on evidence to maximize the benefits and minimize the harm [84].

## Future directions

The data reviewed in this paper support the notion that agents that facilitate endocannabinoid signaling may offer therapeutic benefits for PTSD. Cannabinoid receptor agonists and FAAH-selective inhibitors that enhance anandamide or CB1 signaling provide anti-anxiety effects in rodents [25]. There are also data to suggest that enhancing endocannabinoid signaling prevents behavioral and synaptic adaptations to intense stress that underlies the development and worsening of anxiety disorders and PTSD in particular [4, 60, 66, 67]. In contrast, dysregulation of the endocannabinoid system is associated with various pathophysiological states, including psychiatric disorders (for a review, see Ref. [85]).

Nevertheless, there are some inconsistencies regarding the effects of exogenous cannabinoids on anxiety. It has been suggested that many of the psychological

effects of cannabis are biphasic, depending principally on the dose level and, to a certain extent, on the personality of the user [86]. Some of the reasons for these dose-dependent patterns are that different receptors are sensitive to the action of cannabinoids, with different activities on anxiety responses, and that activation of CB1 receptors in different brain areas results in different behaviors [87].

Another reason involves the use of different agents to enhance endocannabinoid signaling. It has been suggested that using indirect pathways to enhance the endocannabinoid system (e.g. by blocking its enzymatic hydrolysis) will produce a more circumscribed and beneficial spectrum of biological effects than those caused by direct CB1 receptor activation (using THC for example) [6]. In support, clinical and preclinical studies indicate that cannabidiol has anxiolytic properties [69, 88–90] and studies blocking FAAH by the specific inhibitor URB597 demonstrate anxiolytic behaviors in a variety of species using different anxiety paradigms [91–94].

## Conclusions

The endocannabinoid system is a potential target for preventing and treating anxiety-related disorders, particularly PTSD. Preclinical and clinical data strongly suggest that anxiety is associated with decreased endocannabinoid tone [6, 95] and that CB1 receptors in the fear circuit in the brain are crucially involved in the anxiolytic effects of cannabinoids [6, 48, 60, 66, 86, 96, 97].

Cannabis is legal in several states and is prescribed for PTSD patients in others. This calls for extensive clinical research on the effects of cannabinoids in PTSD patients and in determining whether the benefits of using exogenous cannabinoids outweigh the risks.

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