Curr Treat Options Psych (2022) 9:163–173
DOI 10.1007/s40501-022-00260-8

Novel Therapeutics in Mood Disorders (R Mansur, Section Editor)

Medicinal Cannabis for the Treatment of Anxiety Disorders: a Narrative Review

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Published online: 23 April 2022

This article is part of the Topical Collection on *Novel Therapeutics in Mood Disorders*.

Keywords Anxiety · Cannabis · Cannabidiol · Tetrahydrocannabinol · Terpene

Abstract

Purpose of review Anxiety is a prevalent mental health condition which manifests as a disproportionate response of fear to a perceived threat. Different types of anxiety disorders vary in their pathophysiology, symptoms and treatments. The causes of anxiety disorders are complex and largely unknown; however, it has been suggested that a number of brain mechanisms and neurotransmitters are involved in the development of these conditions. While there are non-pharmacological treatments for anxiety, many patients are prescribed medications such as selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors and/or benzodiazepines. Unfortunately, these medications have issues with efficacy and safety, and therefore, there is a continuing need for newer medicines. The cannabis constituents of tetrahydrocannabinol (THC), cannabidiol (CBD) and terpenes have been proposed as a potential treatment for anxiety conditions.

Recent findings Medicinal cannabis constituents act on the endocannabinoid system (ECS) and other targets. The ECS affects several physiological functions through modulation of the central nervous system and inflammatory pathways. In particular, CBD has been suggested to exhibit anxiolytic properties, whereas THC can either have an anxiogenic or anxiolytic effect, depending on the dose, route of administration and individual genetic

and environmental factors. There is also evidence that terpenes could be effective in anxiety management.
Summary Currently, there is a gap in the literature as to whether standardised CBD and/or THC preparations can be used for anxiety disorders. Further information is required to know the precise doses and CBD-THC ratios from human clinical trials and real-world patient use.

Introduction

Anxiety is a normal emotion that individuals experience in response to situations that they perceive as threatening [1, 2]. The Yerkes-Dodson law suggests that there is a relationship between anxiety and performance [3]. A moderate level of anxiety or arousal can improve an individual's execution of tasks, but a high level of anxiety can reduce this efficiency [3]. Associated physiological symptoms of anxiety include heart palpitations, high blood pressure and changes to breathing patterns. The physical effects are accompanied by psychological feelings of tension, concern and impending doom [4].
These reactions serve as a protection mechanism that allow an individual to respond quickly to threats, but can be detrimental when excessive [2]. Anxiety disorders occur when there is a persistently high level of anxiousness that is disproportionate to the perceived, or real, threat [1, 2]. This prolonged state of fear can impair an individual's functioning and result in avoidance behaviours in an attempt to minimise their symptoms, particularly when challenged with triggering situations [5].
With anxiety disorders underreported and underdiagnosed, it has been suggested that the prevalence is actually higher than the data shows [6]. As a disabling condition with high societal prevalence, anxiety disorders pose a disease burden that is associated with increased morbidity and mortality and therefore high social and economic costs [6, 7].

Anxiety pathophysiology

There are a range of brain mechanisms and neurotransmitters that have been implicated in anxiety; however, the exact pathophysiology is unknown [2, 8•, 9, 10]. There are common discrepancies in brain functionality that are observed in patients with anxiety disorders, particularly in the limbic system [2]. This system is responsible for emotional processing and associated responsive behaviour and is comprised of the hypothalamus, amygdala, thalamus and the hippocampus [11]. In particular, the amygdala has been identified as a key structure related to anxiety, as it is responsible for the initial response to, and emotional processing of, threatening stimuli [2, 12]. Studies using magnetic resonance imaging have suggested that the amygdala is overreactive in anxiety disorders, causing greater negative emotional processing [13]. This has been observed in generalised anxiety disorder (GAD), social anxiety and specific phobias [8•, 12]. The hippocampus plays a key role in memory and is believed to contribute to learned responses to fearful situations seen in anxiety, such as patterns of avoidance or panic [7, 12]. Abnormalities in the hippocampus can potentially be associated with an

increased risk of anxiety disorders, particularly post-traumatic stress disorder (PTSD) [9, 12].

The insular cortex within the brain is thought to be strongly related to the limbic system and has been observed as overreactive in anxiety disorders [12]. It is thought to play a role in fear regulation and is particularly relevant to the pathophysiology of specific phobias and PTSD [14]. The prefrontal cortex (PFC) has a range of functions, including social processing, and has also been implicated in anxiety [12]. Hyporegulation of the PFC has been suggested to contribute to disturbed emotional regulation [8•, 12]. The limbic system, particularly the amygdala, and the PFC are thought to be strongly associated with one another, and dysregulation between the two is a possible mechanism in the pathophysiology of anxiety [8•, 12].

An imbalance of neurotransmitters in the brain also may play a role in the development of anxiety [15]. The two major central nervous system neurotransmitters are gamma-aminobutyric acid (GABA) and glutamate, which have inhibitory and excitatory effects, respectively [16]. As a neurotransmission inhibitor, GABA acts on receptors in specific parts of the brain, such as the structures in the limbic pathway, and reduces the hyperactivity that is observed with anxiety [16]. Serotonin imbalances have also been suggested in consideration of the pathophysiology of anxiety, although the exact role of serotonin is unclear [10]. Other neurotransmitters that may have a role in a person's response to fear and development of anxiety include adenosine, hormones and cannabinoids, although their exact mechanisms are underresearched and unclear [15].

The endocannabinoid system

The endocannabinoid system (ECS) is widely distributed throughout the body, including within the central nervous system, immune system and gastrointestinal system [17]. Functions of the ECS include regulation of ion channels, neurotransmitter release and cellular physiology [18, 19]. The ECS refers to the endogenous neurotransmitters and their synthesis, transport and degradation processes, as well as the receptors with which they interact [17, 18, 20]. Two of the key endogenous cannabinoids are arachidonic acid derivatives: 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (AEA) [17]. Both 2-AG and AEA are neurotransmitters that act as retrograde messengers [19]. While these two primary endogenous cannabinoids are structurally similar, their synthetic processes are different. The synthesis of AEA begins with arachidonic acid which is converted by the enzyme N-acyltransferase into *N*-arachidonoyl-phosphatidylethanolamine, a precursor for the endogenous cannabinoid [17, 20]. This precursor is stored in lipid membranes and the subsequent release of AEA is catalysed by a specific phospholipase D [17]. Diacetylglycerise lipases catalyse the reaction between arachidonic acid and diacylglycerol to form 2-AG; its primary synthesis pathway [20, 21]. The synthesis and release of these cannabinoids occurs when signalled through

cell depolarisation, increased calcium concentration or metabotropic receptor stimulation [20].

Once released, endogenous cannabinoids interact with receptors, most importantly, cannabinoid type 1 receptor (CB1R) and cannabinoid type 2 receptor (CB2R). These are G-protein-coupled receptors primarily of the i/o subtypes with inhibitory actions [18]. Cannabinoid type 1 receptors are found on both central and peripheral neurons, cardiovascular and reproductive systems, and the gastrointestinal tract [22]. Cannabinoid type 2 receptors are found on immune cells, blood cells and post-synaptically in areas of the CNS [22]. Cannabinoid type 2 receptors have been found specifically in the microglia of the brain and are thought to be upregulated in tissue injury or inflammation [23]. Although both CB1R and CB2R are found in the brain, CB1R is more abundant and can produce a range of neuromodulatory effects through its distribution in the cortex, basal ganglia, hippocampus and cerebellum [23]. The areas in which they are found suggest CB1Rs should be considered in the pathophysiology and therapeutic treatment of neuropsychological disorders [24•].

Cannabis

Cannabis sativa (cannabis) is a plant that contains hundreds of chemical constituents, and its therapeutic use dates back thousands of years [25, 26]. The major and most extensively researched constituents of cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD) [27]. These compounds interact differently with cannabinoid receptors and have different targets outside the ECS, driving their unique therapeutic effects, even though their chemical structures are relatively similar [27]. Cannabis has long been listed as an illegal recreational drug and access to cannabis for medicinal purposes in Australia was only legalised in 2016 [28]. Since then, a number of pharmaceutical-grade products with different THC and CBD ratios have been made available; however, the heterogeneity in the market makes it difficult to compare them and determine optimal therapeutic preparations [29•].

Tetrahydrocannabinol (THC)

Tetrahydrocannabinol is the major psychoactive constituent of cannabis and produces a psychological response associated with feelings of relaxation and euphoria, also known as a 'high', which drives the recreational use of cannabis [25, 29•]. There are several naturally existing structural conformations of THC. Delta-9-tetrahydrocannabinol (Δ9-THC) is the most common form of THC and interacts with both CB1R and CB2R [25]. Delta-8-tetrahydrocannabinol (Δ8-THC), an isomer of Δ9-THC, is not as well researched and has been found to interact with CB1R, but it is unclear whether it interacts with CB2R [23]. The psychoactive properties of THC

are due to its partial agonism of CB1Rs in the brain; however, this can be dose dependent [25, 30, 31]. The presence of other cannabinoid agonists can change the effect that THC has on these receptors [25]. Tetrahydrocannabinol can behave as an inverse agonist, reportedly inhibiting G-protein activation of CB2Rs, and as an antagonist at CB1Rs when administered with more efficient agonists of these receptors [25].

Tetrahydrocannabinol has a narrow therapeutic window between its potential therapeutic benefits and unwanted psychological reactions associated with its use, which can make dosing challenging [32]. It is commonly reported that THC at lower doses can produce effects such as euphoria, relaxation and sociability, whereas higher doses can have adverse effects including dysphoria, panic and phobia [33]. This can also vary between individuals, as those who are predisposed to anxiety could be more likely to experience these reactions even with lower doses of THC [31, 34]. In addition, the variable effect of THC between people is also influenced by genetic and environmental factors, as well as by the route of administration, with the oral vs inhalation routes having different pharmacokinetic pathways and psychoactive properties [30, 32, 35]. The feelings of anxiousness and panic brought on by THC are thought to originate in the amygdala, a structure of the brain known to exert hyperactivity in anxiety [29•, 36].

As the ECS is widespread throughout the body and the brain, THC can have a range of beneficial effects and therefore therapeutic applications, particularly as an antiemetic or appetite stimulant [30, 32]. Dronabinol and nabilone are synthetic compounds of THC that have been developed and approved for these indications [32]. Dronabinol is used in the USA for appetite stimulation for acquired immunodeficiency syndrome patients and as an antiemetic for cancer patients undergoing chemotherapy [32]. Nabilone is also used as an antiemetic during chemotherapy, and it is more potent than dronabinol as it is used at a lower dose and, therefore, is favoured of the two drugs for this indication [29•].

Cannabidiol (CBD)

Cannabidiol is a non-psychoactive constituent of cannabis; however, it still exerts pharmacological activity that can have therapeutic applications [25]. Cannabidiol can be extracted from cannabis sativa plants or hemp, which is a cannabis species typically grown for industrial use [37]. There are several proposed pharmacological targets of CBD, such as G-protein-coupled receptors and ion channels, including the transient receptor potential cation channel and serotonin 5-HT1a receptor (5-HT1a). Cannabidiol is also a known inhibitor of cytochrome P450 enzymes [25]. In addition, it has been observed that while CBD has a low affinity for both CB1R and CB2R, even at low concentrations, it can still interact with these receptors [38]. The nature of these interactions varies; at low concentrations, it behaves as an inverse agonist and at high concentrations as an antagonist

[38]. Based on in vitro studies, it is also hypothesised that CBD may act as a low efficacy agonist at CB1R; however, this has not been demonstrated in vivo [25].

Cannabidiol has a range of pharmacological effects and therefore could be a viable treatment for a number of conditions [27]. Cannabidiol can interact with ion channels, neurotransmitter transporters and membrane receptors, and these are the proposed mechanism for CBD's anti-epileptic activity [39]. There is evidence that CBD can be an effective treatment for Lennox Gastaut syndrome and Dravet syndrome, reducing the frequency of seizures in treated patients [40]. It has been suggested that the role CBD plays in mood is due to its interactions with CB1Rs in the limbic and paralimbic systems [27]. As an antagonist at CB1Rs, CBD can also block THC from binding to these receptors and decrease its psychoactive properties [27]. Cannabidiol's antagonism in the brain is a proposed mechanism for the antipsychotic properties it exerts; however, more research is required in this area [38]. Inflammation is thought to be mediated by CB2R in the periphery, and as an inverse agonist, it is thought that CBD could affect this and, therefore, could have anti-inflammatory applications [23, 25]. The favourable side effect profile of CBD is due to its lacking psychoactive properties, which supports the development of CBD as a medicine [27].

Terpenes

Terpenes are a diverse group of naturally existing compounds, present in a number of herbs, flowers and fruits, as well as cannabis plants [41, 42]. Terpenes influence the fragrance and taste of these natural products and are utilised commercially in products such as perfumes, essential oils and food flavourings [41]. The number of isoprene units of a terpene molecule effects its pharmacological activity, as well as its classification as a monoterpene, sesquiterpene, diterpene, sesterpene or triterpene [41]. Cannabis contains a number of monoterpenes including limonene, β-myrcene, α-pinene, linalool and terpinolene, which are responsible for the distinct scent of cannabis [43]. Many terpenes can also be used therapeutically, for example paclitaxel is a natural terpene that has an established role in the treatment of specific cancers [43–45]. The properties of terpenes are strain specific, and cannabis terpenes have therapeutic potential in the treatment of epilepsy, anxiety and inflammation [43, 44].

Cannabis and anxiety

Cannabis can exert paradoxical effects when it comes to anxiety. Overall, the evidence surrounding cannabis and anxiety is conflicting, with some studies concluding cannabis can induce anxiety, while other studies suggest cannabis has anxiolytic properties [23]. Cannabis is reportedly used by individuals who

experience anxiousness to alleviate their symptoms [25, 46]. Chronic, heavy cannabis use, particularly by adolescents, is a risk factor for the development of anxiety in later life, potentially because of the downregulation of CB1Rs [36, 47]. A study of 11 cannabis users and 19 matched healthy control participants used high-resolution research tomography to examine CB1R function 2 and 28 days after abstinence from the drug. The results showed that dependence on cannabis was associated with the downregulation of CB1Rs, which rapidly reverses when a person stops using the drug [48].

The different constituents of cannabis (THC, CBD and terpenes) interact differently with receptors and neurotransmitters in the CNS and ECS [49•]. Consequently, each of these has different effects on anxiety, and therefore, their individual therapeutic potential needs to be considered [25].

Tetrahydrocannabinol is considered to be primarily responsible for the anxiogenic effects of cannabis [25]. Studies have demonstrated that high doses of THC, specifically Δ9-THC, can cause significant levels of anxiety and fear [36]. These can be so extreme that they induce panic attacks, even in those without an anxiety disorder [36]. Whilst THC is known to induce anxiety, some studies have also reported anxiolytic properties at low doses, thought to be due to binding at CB1Rs in the limbic regions of the brain [25, 36]. A recent study of 10 Canadian military personnel with PTSD found that nabilone titrated to a dose of up to 3.0 mg over 7 weeks was effective compared with placebo for PTSD, particularly for reducing nightmares [50]. Nabilone was not effective compared with placebo for the treatment of GAD, and a number of the studies that used THC for affective disorders found either no symptom improvement or increased anxiety [51•].

The specific dose of THC required to exert maximal anxiolytic effects without anxiogenic side effects is unclear and thought to be impacted by a number of patient factors such as external stressors, patient tolerance and whether they are prone to anxiousness [25]. Currently, the evidence is lacking as to whether THC is viable as a treatment in isolation for anxiety disorders [25, 51•].

Cannabidiol does not have psychoactive effects so it may be an effective treatment for anxiety [51•]. Human and animal studies have demonstrated the anxiolytic effects of CBD, but the exact mechanism by which this occurs is largely unknown [25]. Several studies have proposed that CBD interacts with 5-HT1a and this is a key mechanism behind its anxiolytic effects [25, 36, 51•]. Serotonin has been implicated as a key neurotransmitter involved in the pathophysiology of anxiety, and current treatments for anxiety address its imbalance. In rodents, CBD increases serotonin release in the prefrontal cortex, an area of the brain of significance when considering anxiety in humans [52]. Allosteric modulation of 5-HT1a receptors is also a proposed mechanism of CBD's anxiolytic activity [52]. Additionally, it has been suggested that CBD decreases the metabolism of AEA, increasing its interactions with CB1R, a potential mechanism behind the anxiolytic effects [53•].

Doses of 25–600 mg of CBD have been shown to alleviate the symptoms of anxiety [52, 53•]. An exact dose–response relationship is yet to be established, but a key difference to THC is that higher doses of CBD do not result in any anxiogenic side effects [51•]. It is thought that CBD counters the psychoactive side effects associated with THC when administered together and that it could be a viable treatment for anxiety due to its tolerability [51•,

53•]. At high doses, it has been found that CBD has a rapid onset of action, which is of clinical relevance for social anxiety, and so, studies have looked at the effects of one-off CBD doses before exposure to threatening situations associated with social anxiety, such as public speaking [54, 55]. In one study, a double-blind trial was undertaken with 24 participants with GAD. Half were given a single dose of 600 mg CBD and the other half placebo 1.5 h before a simulated public speaking test. The results showed that CBD reduced anxiety, cognitive impairment and discomfort [54]. In a second study, 10 participants were given 400 mg CBD or placebo, with the CBD group displaying significantly decreased subjective anxiety [55].

The efficacy of CBD has also been observed for GAD using daily doses of 25–125 mg to reduce anxiety levels in diagnosed patients [51•, 53•]. Animal studies have suggested that CBD could also be effective in PTSD, through memory suppression and extinction [56•].

Terpenes could also be a possible treatment for anxiety disorders; however, the evidence is conflicting. Linalool is one of the major terpene constituents in cannabis that has been suggested to interact with the CNS, and as such, it may exert anxiolytic activity [57]. Previous studies in mice concluded that linalool did not reduce anxiety responses, but could potentially be useful for depression [57]. In contrast, a recent study examined the efficacy of linalool in the treatment of GAD. From 539 participants with GAD who were given either 80 or 160 mg silexan (linalool containing oil), 20 mg paroxetine, or placebo once daily for 10 weeks, the study concluded that silexan was superior to placebo and its efficacy was similar to the paroxetine [58].

Conclusion

Anxiety is a prevalent condition with a high disease burden. Currently, the primary treatments for anxiety disorders are antidepressants and benzodiazepines; however, their use is limited because of issues relating to efficacy and safety. Medicinal cannabis has anxiolytic properties, particularly CBD, and is suspected to be an effective treatment for a number of anxiety disorders; however, rigorous evidence from controlled clinical trials is lacking. Further studies are needed to first examine the efficacy of standardised preparations of CBD, with or without THC, on different patient populations. These should aim to explore which anxiety disorders medicinal cannabis is effective at treating, at which doses, and examine any factors behind interpatient variability. Second, studies are needed to assess whether medicinal cannabis is more effective for intermittent symptoms of anxiousness and whether it should be used on a when-required basis or whether it can be used as maintenance therapy for anxiety disorders and taken on a daily basis. Finally, research should also look into formulation design factors in terms of CBD and THC ratios, and the route of the delivery (i.e. capsules, oils or inhalation). With demand and access to medicinal cannabis increasing, further research is crucial to ensure its safe and effective use.

Author contribution

Each author contributed substantially to this manuscript. S. K. S. was responsible for the acquisition, analysis and interpretation of findings and drafting of the manuscript; E. A. S. was responsible for conception and design, interpretation of findings, drafting and revision of the manuscript and N. J. W. was responsible for conception and design, drafting and substantial revision.

Funding

Open Access funding enabled and organized by CAUL and its Member Institutions

Declarations

Competing interests
S. K. S. has no competing financial interests. N. J. W. is a director of the Australian Medicinal Cannabis Association and Science Director of Canngea Pty Ltd. EAS is funded by scholarships from the University of Sydney and Canngea Pty Ltd and is affiliated to Applied Cannabis Research Pty Ltd. as a consultant.

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