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Review Article

The Therapeutic Potential of Major Cannabinoids in the Management of Anxiety Disorders: Rediscovering Psychopharmacology

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Abstract

Anxiety disorders represent the most prevalent and arguably challenging form of mental illness, with many patients experiencing insufficient relief despite advances in pharmacological treatments and psychotherapy. The constellation of anxiety disorders overlaps phenomenologically and etiologically with other disorders, including depression, post-traumatic stress disorder (PTSD), and obsessive compulsive disorder (OCD). Moreover, anxiety is a significant symptom or comorbidity in various other psychiatric, neurodevelopmental, and neurodegenerative conditions. Despite this, no truly novel class of drugs specifically for anxiety disorders has been successfully developed or widely approved in the past 30 years. The endocannabinoid system, noteworthy for its role in regulating synaptic plasticity within anxiety-associated brain regions, has propelled cannabinoids into the spotlight of anti-anxiety research. The present commentary explores nonclinical and clinical psychological evidence regarding the anxiety-modulating properties of phytocannabinoids. It reviews emerging clinical findings on cannabis-based products, such as cannabidiol, for addressing both primary and secondary forms of social and situational anxiety.

Keywords: Cannabis; Cannabidiol; Anxiety; Anxiety disorder; Psychopharmacology

Abbreviations: AEA: anandamide; ASD: autism spectrum disorder; CACOS: CA Clinical Observational Study; CB1R: cannabinoid receptor 1; CB2R: cannabinoid receptor 2; CBD: cannabidiol; CBT: cognitive behavioral therapy; eCB: endocannabinoid; ESAS-r: Edmonton Symptom Assessment System; FNE: Fear of Negative Evaluation scale; GAD: generalized anxiety disorder; GAD-7: Generalized Anxiety Disorder-7 scale; HADS-A: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; MCID: minimally clinically important difference; PD: Parkinson's disease; PROMIS-9: Patient-Reported Outcomes

Measurement Information System-29; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; RWE: real-world evidence; SAD: social anxiety disorder; SPST: simulated public speaking test; SSRI: selective serotonin reuptake inhibitor; THC: Δ9-tetrahydrocannabinol

Introduction

Although fear and anxiety are natural adaptive responses to threatening stimuli, pathological anxiety is marked by heightened vigilance and persistent and excessive worry, which disrupts an individual's daily life [1]. Anxiety disorders are the most common category of mental illness, with a worldwide prevalence of over 4% [2] and as high as 27% for psychiatric populations, and are differentiated from each other by the situations that induce anxiety and the cognitive states with which they are associated. The most common anxiety disorders include generalized anxiety disorder (GAD), panic disorder, social anxiety disorder (SAD), and specific phobias. Together, anxiety disorders contribute to an increased risk of unemployment, relationship breakdown, diminished sense of well-being, and suicide [3-5]. Additionally, the global burden of anxiety is increasing – disability-adjusted life years (DALYs) lost to anxiety disorders rose by 53.7% between 1990 and 2019 [6]. Anxiety is also a central symptom of other psychiatric, neurodevelopmental, and neurodegenerative disorders, including post-traumatic stress disorder (PTSD), autism spectrum disorders (ASD), and Parkinson's disease (PD) [1,7-9].

Distinct from the extreme or pathological end of the anxiety spectrum, anxiety is a normal, if pervasive, affective experience. Everyone experiences transient episodes of anxiety in the course of daily living. When anxiety interferes with the performance of tasks that have professional or personal significance, some response is strongly indicated. The need for effective and safe anxiety management is clear – oral antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs), alongside psychotherapy, are currently recognized as the standard of care for first- and second-line treatments [10,11].

Unfortunately, these treatments have high failure rates, with up to 50% of patients with GAD failing to respond to at least one antidepressant medication, and cognitive behavior therapy (CBT) being effective in only 49.5% of people with anxiety disorders [12,13]. Even among patients who have experienced some success with mainstream management, up to one-third report having partially met or unmet needs in their care [14]. For example, SSRIs and SNRIs have a slow onset of effect of up to 8 weeks before symptoms begin to subside [10,11]. Additionally, many of these medications have undesirable side effects, including sexual dysfunction, weight gain, and fatigue, which can significantly impact quality of life [10].

Alternative and adjunctive treatment options are needed, and medical cannabis products may serve as an option for some patients. In Canada, where medical cannabis has been available since 2001, 63.6% of people who use medical cannabis report it to be highly effective in treating their anxiety symptoms [15]. Accordingly, a range of studies have begun to examine the pharmacological, neurobiological, and clinical evidence for the use of cannabis-based products or individual cannabinoids to treat anxiety. While nonclinical, clinical, and psychological studies have been reviewed in detail elsewhere [16,17], this commentary seeks to synthesize key perspectives and hot-button topics and contextualize them within the ongoing scientific and clinical discourse.

Methods

This commentary was developed through a selective review of literature deemed most relevant by the authors to address the topic. The selection process prioritized systematic and topical reviews, primary research published in reputable peer-reviewed scientific journals, and authoritative reports from recognized institutions. Sources were identified using academic databases such as PubMed, Scopus, and Google Scholar, with search terms tailored to the subject matter. Most studies reviewed were no older than 2019; the oldest was published in 2011. Only English language publications were included. No generative artificial intelligence (AI) tools were used in the development of this work.

The inclusion of sources was guided by their contribution to the discussion's objectives rather than by a priority on achieving exhaustive review. Priority was given to works that provided novel/recent clinical reports and emerging experimental data or highlighted gaps in current understanding.

The Endocannabinoid System and Anxiety

The endocannabinoid system is a complex regulatory network comprised of signaling lipids (endocannabinoids, eCBs), G-protein-coupled receptors (GPCRs), and downstream signaling and degradation pathways found throughout the central nervous system (CNS) and peripheral tissues [18]. In the central nervous system, the two most well-studied endocannabinoids (eCBs) are 2-arachidonoyl glycerol (2-AG) and anandamide (AEA), which are synthesized in response to neuronal activation by the cleavage of membrane phospholipids. eCBs activate multiple G-protein coupled receptors, ion channels, and metabolic and gene transcription pathways in both neuronal and glial cells [19,20]. Among their best-characterized targets are the cannabinoid receptors 1 (CB1R) and 2 (CB2R), which are coupled to inhibitory G proteins to modulate a host of downstream signaling pathways, including adenylyl cyclase and mitogen-activated protein kinase pathways, depending on their ligand profiles [21]. Notably, high densities of CB1R have been found in anxiety-relevant brain regions, including the hippocampus, amygdala, limbic and frontal

cortices in humans [22]. Moreover, both CB1R and CB2R have been found to couple with other GPCRs, including D2 dopamine receptors, orexin A receptors, adenosine 2A receptors, and delta opioid receptors. Additionally, eCBs can modulate the activity of other ion channels, such as 5HT3, TRPV1, GABA-A, and glycine receptors [18]. This pleiotropic breadth of impact enables the endocannabinoid system to act as a crucial modulator of synaptic plasticity at a diverse range of synapses.

In contrast to traditional neurotransmitter systems, endocannabinoid signaling generally occurs through retrograde transmission; eCBs are typically synthesized and released from postsynaptic terminals, where they bind to CB1R on pre- and postsynaptic axon terminals or CB2R on glial cells (Figure 1) [23]. Once released, 2-AG and AEA are rapidly internalized and degraded by monoglyceride lipase (MGL) and fatty acid amide hydrolase (FAAH), respectively [24]. Research in rats has shown that intravenous administration of low-dose AEA alone can reduce anxiety-like behaviors in the light/dark box task [25]. Conversely, higher doses appear anxiogenic, reflecting differential activation of eCB receptors. The dose-response pattern is reliably seen in acute or short-term administration but may be difficult to generalize about with chronic cannabinoid use in light of the development of tolerance.

The activation of both CB1R and CB2R has been implicated in anxiety-like behaviors in animals, in complex cell-type, dose-, and sex-specific patterns [26,27]. For example, CB1R activity in the hippocampus dampens the activation of the hypothalamic-pituitary-adrenal axis in response to acute stress, and the anxiolytic effects of eCBs in the midbrain, hypothalamus, and amygdala are dependent on CB1R and/or CB2R activity [26,28-31]. Genetic knockout studies have demonstrated that CB1R activation in prefrontal glutamatergic neurons is necessary for anxiolysis, whereas CB1R on GABAergic terminals appears to be required for the anxiogenic effects observed in some studies [32,33]. As noted earlier, the degree of CBR activation adds yet an additional level of complexity to this system, where CB1R is activated by low doses of agonists, which seem to be anxiolytic [34] while higher doses produce the opposite effect [35,36]. Interestingly, the anxiogenic effects of high doses of phytocannabinoids may be mediated by the activation of the TRPV1 receptor [27]. Recent evidence also suggested that the CB1R in the intestine is involved in the regulation of anxiety [37]. Conditional knockout of the *Cb1r* gene in the intestinal epithelium of male mice lead to reduced anxiety-like behaviors. CB2R is also thought to be involved in the regulation of anxiety-related behaviors, with genetic manipulation in animals revealing that overexpression in the brain, including the CA1 pyramidal neurons of the hippocampus, leads to anxiolytic behaviors [38,39].

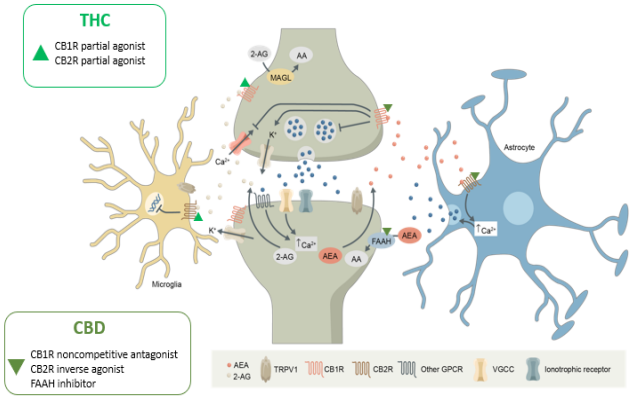

Figure 1: Endogenous and phytocannabinoids at an example synapse.

2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; AEA, anandamide; CB1R, cannabinoid receptor 1; CB2R, cannabinoid receptor 2; CBD, cannabidiol; Ca2+, calcium ion; FAAH, fatty-acid amide hydrolase; GPCR, G-protein coupled receptor; MAGL, monoacylglycerol lipase; THC, Δ9-tetrahydrocannabinol; TRPV1, transient receptor potential cation channel subfamily V member 1; VGCC, voltage-gated calcium channel.

Phytocannabinoids and nonclinical models of anxiety

Although the species within the *Cannabis* genus contain over 120 cannabinoids with the potential to interact with the endocannabinoid system (phytocannabinoids), the most abundant and well-characterized are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Figure 1) [40,41]. THC is widely regarded as the main psychotropic component of cannabis and is a partial agonist for both CB1R and CB2R [40]. Although high THC strains of cannabis are generally preferred for recreational use, this molecule also has therapeutic benefits, especially with respect to analgesia, increasing appetite, and aiding in sleep [42]. CBD, on the other hand, has more diffuse interactions with the endocannabinoid system, acting as a noncompetitive CB1R antagonist, an inverse agonist of CB2R, and an inhibitor of AEA uptake and degradation [42]. CBD also directly interacts with elements of the adenosine, glutamate, serotonin, and dopamine neurotransmitter systems, and with various other ion channels, among others, making it an interesting candidate for psychiatric therapy [17,42-45].

As such, both THC and CBD continue to be examined for their potential to ameliorate anxiety-like behaviors in nonclinical models [16,17,46]. For example, intraperitoneal injections of 2.5 mg/kg of THC or 200 mg/kg of CBD in mice reduced immobility in the forced swim test – a behavioral measure of despair which

also responds to SSRIs [47]. In fact, repeated THC injections were found to have anti-depressant-like effects in mice through the interaction between CB1R and serotonergic neurocircuitry [48]. Conversely, various doses of THC alone can be anxiogenic, but CBD may attenuate this effect through CB1R in animals as well as humans [49-53].

The evidence for CBD alone is based on a myriad of animal studies and psychological research in healthy participants, which has been extensively reviewed elsewhere [16,17,54]. Briefly, CBD reduces anxiety-like behaviors in dose- and paradigm-specific manners [53,55,56]. For example, acute doses of CBD increased the time that rodents spent in the open arms of an elevated plus maze in a manner similar to benzodiazepines, but higher doses did not seem to have an effect [53,56]. Similarly, in the open field and light/dark tests, acute injections of 1mg/kg CBD produced significant anxiolytic effects, while doses of 5, 10, or 50 mg/kg did not [55]. CBD injections directly into anxiety-relevant brain structures, such as the periaqueductal gray (PAG), have also been shown to have anxiolytic effects after more chronic exposure paradigms; [57] the PAG is involved in emotional responses and has been associated with feelings of dread in humans [52,58]. Interestingly, these studies indicated that the anxiolytic effects of CBD are achieved, at least partially, through its interaction with the serotonergic system [57,59]. Additionally, CBD may be particularly effective in reducing panic and anxiety behaviors in animals that were previously exposed to stress [59,60]. For example, CBD injections into the prelimbic prefrontal cortex of rats reduced anxious behaviors in the elevated plus maze, but only in animals who experienced a restraint stress 24 hours prior [59]. Similarly, CBD injections facilitated the extinction of conditioned fear responses in rodents [60].

There is evidence that the anxiolytic effect of CBD on fear and anxiety carries over to human research as well. Indeed, 'real-world evidence' suggests that at least 40% of individuals who use CBD do so to relieve self-perceived anxiety, and laboratory studies and trials in healthy individuals largely substantiate these results [17,61]. In healthy volunteers who underwent fear conditioning, inhaling 32 mg of vaporized CBD helped to consolidate extinction training, as evidenced by reduced physiological fear responses upon fear reinstatement [62]. Oral CBD in healthy individuals has been shown to reduce anxiety in a variety of stress-inducing laboratory settings, including simulated public speaking tests (SPST) and neuroimaging experiments, and correlated with altered activity in limbic, paralimbic, and prefrontal cortices [17,63,64]. Recently, 300 mg of oral CBD (but not 150 or 600 mg) was shown to reduce subjective anxiety during the SPST [65]. The same dose of CBD also reduced anxiety immediately after a real public speaking task, as did 1 mg of the anti-anxiety medication clonazepam [66]. Furthermore, in healthy individuals with elevated trait worry, repeated administration of 300 mg CBD over 2 weeks significantly reduced general anxiety scores compared to placebo [67].

Recent clinical evidence for cannabinoids to treat anxiety

Studies in clinically relevant populations have used a range of methodologies to evaluate the effect of cannabis and cannabinoids on anxiety and have faced unique challenges posed by variable regulatory statuses of medical cannabis products and discrepancies in product composition and dosing among studies [68,69]. Nonetheless, a combination of case reports, real-world evidence (RWE) collection, and small randomized controlled trials (RCTs) has suggested that some patients with clinical anxiety may benefit from medical cannabis products (Table 1).

In a 2019 meta-analysis, Black et al. found 31 studies, including 17 RCTs investigating the use of cannabinoids to treat anxiety, either as a primary diagnosis or as a symptom of other conditions [70]. Their analysis found that the use of pharmaceutical-grade cannabinoids led to greater reductions in anxiety symptoms than placebo (SMD -0.25 [95% CI -0.49—0.01]). Notably, most of the studies included in this analysis were performed in participants with a primary diagnosis of chronic non-cancer pain or multiple sclerosis rather than anxiety disorders, per se. This analysis also showed, however, that cannabis use did not increase the number or severity of treatment-emergent adverse events, compared to placebo or active comparators, which indicated that it is well tolerated in these populations.

Cannabis has also been shown to reduce anxiety in other disorders where it is a central symptom. For patients with PTSD, oral or inhaled cannabis decreased anxiety symptoms after as little as 1 month of use, and continued to have an effect after 6 months [71]. Naturalistic use of cannabis during the 8-week observational outpatient phase of an RCT on opioid detoxification and withdrawal was associated with lower anxiety scores ($F[1,151]=4.43$; $p=0.037$) for the 32% of patients who reported use [72]. Additionally, in a three-month observational study, medical cannabis significantly reduced anxiety for both males (-1.1 points; $p < 0.05$) and females (-1.2 points; $p < 0.001$) with cancer, as measured by the Edmonton Symptom Assessment System questionnaire (ESAS-r). The ESAS-r is a validated measure of cancer symptom change, with a minimal clinically important difference of≥ 1 point [73,74].

Individuals with PD are another important population to consider, as neurodegeneration can be, at least partially, associated with the presence of anxiety in up to 67% of patients [75]. Moreover, traditional anti-anxiety medications may worsen symptoms, including tremor, cognitive deficits, and falls [76]. In PD, a cross-sectional survey in the United States found that 58.3% of patients who used cannabis, whether authorized by a medical provider or not, reported that it improved their anxiety symptoms [77].

Although limited, research in populations with diagnosed anxiety disorders also points toward an anxiolytic effect of cannabinoid-based products. A large prospective observational study, which followed over 2000 participants with various chronic health conditions, found that use of cannabis oil for 3 months resulted in statistically and clinically significant reductions in anxiety (7.17-point reduction; p<0.001) [78]. Importantly, in the subset of participants with diagnosed anxiety disorders (n=748), the effect of cannabis oil remained, with participants seeing a 5.77-point reduction in the DASS-21 Anxiety subscale. This reduction corresponded to a shift from "moderate to severe" to "mild" anxiety symptoms.

Study	Type	Sample size	Sample Characteristics	Primary Diagnosis	Dose	CBD:THC Ratio	Route of Administration	Treatment Duration	Anxiety Measure	Results	Adverse Events
Stack et al., 2023* [79]	Interim analysis of retrospective, observational study	96	Median age = 48 years 53% male; 47% female	Unspecified anxiety disorder	20 mg CBD and 20 mg THC (median)	1:1	Oral liquid or capsules	Median = 154.4 days	Anxiety subscale of PROMIS-29	4.9-point reduction in score from baseline (MCID=4; p<0.001)	Common AEs included dry mouth, fatigue, and dizziness. Positive relationship between THC concentration and dry mouth and nausea.
Stack et al., 2023* [79]	Interim analysis of retrospective, observational study	18	Median age = 48 years 53% male; 47% female	Unspecified anxiety disorder	6 mg CBD and 33.8 mg THC (median)	1:1.5	Oral liquid or capsules	Median = 154.4 days	Anxiety subscale of PROMIS-29	4.9-point reduction in score from baseline (MCID=4; p=011)	Common AEs included dry mouth, fatigue, and dizziness. Positive relationship between THC concentration and dry mouth and nausea.
Tait et al., 2023 [78]	Interim analysis of prospective observational study	748	In overall sample (n=2762): Age 18 - 97 (mean = 51 years) 37.2% male; 62.8% female 22.4% had used cannabis recreationally	Generalized anxiety or mixed depression and anxiety	Median daily doses: 1:0 = 1.0 ml (50mg CBD) 20:1 = 1.0ml (20mg CBD and 1mg THC) 10:10 = 0.75 ml (7.5 mg CBD and 7.5 mg THC) 5:20 = 0.57 ml (2.85 mg CBD and 11.4 mg THC)	Variable: 1:0 20:1 10:10 5:20	Oral oil	3 months	Anxiety subscale of DASS-21	5.77-point reduction after 3 months; average scores shifted from moderate/severe to mild anxiety	Not reported
Pillai et al., 2022 [71]	Prospective case series from patient registry	162	Mean age = 37.62 years 59.88% male 66.67% had comorbid anxiety/ depression	PTSD	Oils: Median daily dose of CBD = 45 mg Median daily dose of THC = 14 mg Flower: Median daily dose of CBD = 2.0 mg Median daily dose of THC = 137.50 mg	Variable	Oral/sublingual (11.73%), inhaled flower (49.38%), or both (29.63%)	6 months	Generalized Anxiety Disorder-7 (GAD-7)	7.0-point reduction at 1 months (p<0.001) 8.0 point reduction at 3 months (p<0.001) 6.5 point reduction at 6 months (p<0.001)	AEs reported by 20.37% of patients, with the majority graded mild or moderate. The most common AEs were insomnia and fatigue.
Bisaga et al., 2015 [72]	Observational outpatient phase of a placebo-controlled trial	60	Mean age = 37.9 years 83.3% male 58.75% White, 28.75% Hispanic, 8.75% Black	Opioid use disorder	Not reported	Not reported	Inhaled flower	8 weeks	HAM-D	Cannabis use during outpatient clinic follow-up for opioid withdrawal was associated with lower HAM-D scores (F[1,151]=4.43; p=0.037)	Related to cannabis use, not reported
Holden et al., 2022 [77]	Cross-sectional observational	1881	Mean age = 66.5 years 58.5% male 97.9% White	Parkinson's disease	CBD: 0 mg (12.9%) <5 mg/day (21.7%) 6-50 mg/day (24.7%) 51-200 mg/day (5.3%) 201-600 mg/day (2.0%) >600 mg (2.3%) THC: 0 mg (18.1%) < 5 mg/day (23%) 6-50 mg (20.1%) > 50mg/day (3.8%)	High CBD:low THC (30.4%) Similar THC:CBD (13.1%) High THC:low CBD (26.2%)	Inhaled flower (17%) Edible oil (30.4%) Food (29.3%) Sublingual tincture (24.5%) Skin cream (15.6%)	≤ 6 months (52.5%) > 1 year (33.0%)	Self-report	58.3% of users report mildly or markedly better anxiety	Most common adverse effects on pre-existing PD symptoms were dry mouth, dizziness, thinking/memory problems, increased appetite/weight, daytime sleepiness, balance problems
Peball et al., 2020 [80]	Double-blind randomized, placebo-controlled, phase II trial	47	Mean age = 65.05 years 60% male, 40% female	Parkinson's disease	0.25 mg once daily titrated to 1 mg twice daily	Nabilone	Synthetic THC analog	4 weeks	HADS-A MDS-UPDRS Item 1.4	No significant change in HADS-A score from baseline Treatment group showed in anxiety item of MDS-UPDRS compared to placebo (mean difference = 0.37; p=0.044)	AEs were mild or moderate severity. The most common TAEs during the open-label phase were fatigue, dizziness, dry mouth, and sleepiness. The one possible TAE during the randomization phase was panic attack.
Kasvis et al., 2022 [73]	Prospective observational	358	Mean age = 57.6 years 47.8% male; 52.2% female	Cancer	Not reported	31.1% THC dominant 48% Balanced 20.9% CBD dominant	58.9% oral 13.8% inhalation 25.6% combination	3 months	ESAS-r	Statistically significant and clinically meaningful improvements in anxiety for males (-1.1; p<0.05) and females (-1.2; p<0.001). THC:CBD balanced formulations significantly reduced anxiety in the total cohort (-1.48; p<0.01)	3.6% of participants reported AEs, including 2 serious AEs (cerebrovascular event and pneumonia). The most common moderate AEs were drowsiness/ tiredness

* subanalyses of the same study; AE, adverse event; CBD, cannabidiol; DASS-21, Depression Anxiety Stress Scale-21; ESAS-r, Edmonton Symptom Assessment System; GAD, generalized anxiety disorder; GAD-7, Generalized Anxiety Disorder 7-item scale; HADS-A, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Depression Rating Scale; MCID, minimum clinically important difference; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PROMIS-9, Patient-Reported Outcomes Measurement Information System-29; PTSD, post-traumatic stress disorder; THC, Δ9-tetrahydrocannabinol.

Table 1: Cannabis for anxiety and anxiety disorders.

THC-containing products

Analyses of RWE datasets have shown that the cannabinoid composition of cannabis products impacts clinical outcomes for patients with anxiety. In an interim analysis of the CA Clinics Observational Study (CACOS), a retrospective registry dataset of medical cannabis prescriptions in Australia, participants using balanced (n=96; median daily dose of 20 mg CBD and 20 mg THC), or THC-dominant (n=18; median daily dose of 6 mg CBD and 33.8 mg THC) formulations of oral cannabis saw a 4.9-point reduction in anxiety scores on the Patient-Reported Outcomes Measurement Information System-29 (PROMIS-9; p<0.001 and p=0.011, respectively) [79]. Both THC-dominant and balanced formulations also lead to significant reductions in depression (4.0 and 4.6 points; p<0.001 and p=0.018, respectively) and fatigue (5.6 and 6.8 points; p<0.001 and p=0.033, respectively) scores in participants with diagnosed anxiety disorders. Interestingly, participants who used THC-only products (n=10; median daily dose of 38 mg THC) had no significant change in their anxiety or depression scores after treatment. Furthermore, this analysis determined that there were no significant differences in negative health outcomes when factoring in cannabis formulation types or different classifications of anxiety disorders.

In a combined analysis of an observational study of male and female cancer patients, balanced THC:CBD products were associated with anxiety reduction on the ESAS-r (-1.48; p<0.01), whereas THC- or CBD-dominant products did not have an effect [73]. These findings may be related to the interplay between pain and anxiety in these participants. However, further research is needed to illuminate these mechanisms more fully. In PD, a large cross-sectional observational study found that patients who use products with higher THC concentrations are more likely to report improvement in anxiety than those who used balanced or CBD-dominant products (p < 0.05) [77]. Conversely, nabilone, a synthetic THC analog, showed mixed effects on anxiety in a placebo-controlled trial with PD participants [80]. While nabilone treatment for 4 weeks showed no benefit for anxiety in the Hospital Anxiety and Depression Scale (mean change = 0.26; p=0.793), treatment led to greater improvement in scores on the anxiety item of the Movement Disorder Society-sponsored version of the Unified Parkinson's Disease Rating Scale (MDS-UPRDS), compared to placebo (mean difference = 0.37; p=0.044). Whether this discrepancy is due to differences in the outcomes measured by each scale or unknown neurobiological differences in the response to synthetic versus phytocannabinoids remains to be understood.

CBD-only products

Based on nonclinical evidence and studies in healthy volunteers, CBD alone has garnered increasing interest as a therapeutic target for anxiety, both in cases of primary anxiety and in populations experiencing anxiety as a symptom of other diagnoses [16,17,81-83]. Notably, although more than 20 clinical trials on the effect of CBD on anxiety disorders are underway, few appear to be designed to yield robust evidence for treatment efficacy [84]. On the other hand, multi-armed, placebo-controlled randomized control trials, though small, have been bolstered by observational and open-label studies that suggested that CBD products can reduce self-reported and clinician-rated anxiety symptoms for up to one year (Table 2).

Multiple studies have focused on adolescent and adult populations with SAD. For example, a double blind, placebo-controlled trial in Japan found that CBD oil improved anxiety symptoms in young adults with SAD [85]. After 4 weeks of treatment, scores on the Fear of Negative Evaluation (FNE) scale in the CBD group were 5.3 points lower than their pre-intervention scores. In contrast, the placebo group saw a 0.2 point reduction (p=0.02 vs p=0.29 for CBD and placebo groups, respectively). Additionally, the post-intervention scores of the CBD group were significantly lower than the post-intervention scores of the placebo group (19.1 vs 23.3; p=0.0002). These findings were replicated on a separate anxiety scale in this cohort; scores on the Liebowitz Social Anxiety Scale (LSAS) decreased by 12.1 points in the CBD group (p=0.03) compared to 3.1 points in the placebo group (p=0.42), which suggested a robust effect of treatment. In another study, a preliminary report in adults with SAD found that a single oral dose of 400 mg CBD significantly decreased subjective anxiety before and after neuroimaging [86]. This approach to exploring convergent validity provided confirmatory evidence that CBD also heralded changes in cerebral blood flow to anxiety-related cortical and limbic brain regions compared to placebo. Similarly, a single dose of 600 mg CBD before SPST significantly reduced anxiety, discomfort, and cognitive impairment in a study of 12 participants with SAD [87]. The effect of this acute administration, given 1.5 hours prior to the anxiety-inducing task, was in stark contrast to conventional anxiety treatments, which required repeated administrations, had long latency periods, and/or unwanted side effects. Finally, in a recent open-label, phase II trial in 31 young adults, Berger et al. found that oral doses of up to 800 mg/day of CBD lead to a 42.6% reduction in self-reported anxiety scores after 8 weeks of treatment [88]. Notably, the participants in this study had at least one DSM-5 diagnosed anxiety disorder and were not responsive to traditional cognitive-behavioral therapy (CBT) or antidepressant treatments. Together, these findings suggested that acute and chronic CBD treatments can provide diverse anxiety-reducing effects, at least for a subgroup of patients with SAD.

Recent RCTs have also provided support for the use of CBD in a range of anxiety disorders other than SAD. A study of 178 individuals with mild to moderate anxiety disorders found that a novel formulation of an oral CBD product gradually reduced anxiety symptoms over 12 weeks [89]. At the end of the trial, the CBD group scored 7.02 points lower than the placebo group on the GAD-7 scale, after normalizing to baseline values (p<0.001). Similar results were observed with HAM-A scores, where the CBD group saw an

11.54-point reduction in anxiety scores compared to a 0.7-point increase in the placebo group at the end of treatment ($p<0.0001$). Interestingly, no significant increase in anxiety was observed when the treatment was tapered at the end of the study, which suggested that the neuroplastic effects of CBD treatment may persist even after treatment discontinuation. Conversely, an RCT in patients with treatment-refractory panic disorder with agoraphobia or social anxiety disorder found that 300 mg of CBD was no better than placebo in reducing avoidance behavior or anxiety during extinction therapy sessions [90]. These results may be due to the severity of symptoms in this patient population or their need for more consistent or well-timed CBD dosing.

In a large retrospective chart review of psychiatric patients, relatively low doses of CBD lead to improvements in anxiety after 1 month of treatment, which were generally maintained for up to 3 months [91]. In fact, 79.2% of participants experienced improvements in anxiety within the first month, and an additional 78.1% saw further decreases in anxiety symptoms between months 1 and 2. In the CACOS dataset, oral CBD alone produced similar anxiolytic results to THC-dominant and balanced formulations and significantly improved anxiety symptoms in adults with anxiety disorders [79]. On average, participants achieved a 4.4-point reduction in anxiety symptoms, where the minimally clinically important difference (MCID) was determined to be 4. Furthermore, 50% of participants' anxiety scores improved, based on t-score calculations, while 16.1% of scores worsened, and 33.9% remained unchanged. Notably, CBD-only products also significantly improved depression and fatigue symptoms and increased these participants' ability to participate in social roles and activities.

CBD products have also been shown to reduce anxiety as a symptom of other psychiatric, neurodevelopmental, and neurodegenerative disorders. For example, in a subset of the CACOS dataset, 100 mg/day oral CBD significantly reduced anxiety in patients with post-traumatic stress disorder (PTSD; $p<0.001$) [79]. In addition, CBD may have improved PTSD symptoms overall, and anxiety specifically, in a subgroup of patients who experienced specific types of traumatic events [92-94]. In a Brazilian RCT, participants with PTSD were asked to recall the traumatic events after taking 300 mg of CBD or a placebo [94]. Participants in the CBD group whose trauma was non-sexual in nature reported less anxiety than those with sexually-based trauma (mean difference=11.42, $p=0.035$). Similarly, CBD treatment was associated with less anxiety than placebo in the same group of participants (mean difference = -9.82; $p=0.033$).

In a randomized control trial investigating the role of CBD in reducing drug-cravings in abstinent participants with heroin use disorder, those in the 400 or 800 mg of CBD groups reported significantly less anxiety in response to a drug cue than the placebo group ($p=0.0079$) [95]. Importantly, a similar reduction in anxiety was observed 1 hour and 24 hours after a single dose of CBD, as well as 7 days after three daily doses, which suggested that CBD may have acute and long-lasting anxiolytic effects in this population. For elderly participants with PD, 300 mg of CBD taken immediately before a Simulated Public Speaking Task lead to decreased anxiety compared to placebo [96].

Anxiety is also a common feature of neurodevelopmental disorders, including ASD, and may not respond well to standard treatments alone [7,97]. In a retrospective observational study of children with ASD who were treated with sublingual, CBD-dominant preparations of cannabis, daily treatment lead to "much improved" or "very much improved" changes in anxiety over several months [98]. Interestingly, 61% of children showed considerable improvements in behavior problems, and 33% took fewer medications after treatment, with 24% stopping other psychiatric medications altogether. Similarly, in a prospective observational study, 47.1% (8/17) of parents of participants with ASD reported improvement in their child's anxiety symptoms after treatment with CBD-dominant cannabis oil [99]. Anxiety in fragile X syndrome, a genetic neurodevelopmental disorder with symptomology that overlaps with ASD, may also be sensitive to CBD treatment; a 12-week trial of a CBD transdermal gel lead to a 52.3% reduction in anxiety symptoms as rated by parents and a 38.2% reduction as rated by clinicians ($p<0.001$) [100].

Importantly, the above studies have concluded that CBD treatment is generally safe and tolerable across clinical samples, with no studies reporting serious adverse events (AEs; see Tables 1 and 2). The most commonly reported AEs likely related to treatment included somnolence, digestive issues, and changes in appetite. This finding aligned with the literature, which indicated that CBD is well tolerated, even at high doses (up to 1500 mg/day) [101].

Study	Type	Sample size	Sample Characteristics	Primary Diagnosis	Dose	CBD:THC Ratio	Route of Administration	Treatment Duration	Anxiety Measure	Results	Adverse Events
Gunduzgurti et al., 2024 [89]	Double-blind, phase III, RCT	178	Age 18-64 years Mean age = 37.4 years 63.45% male; 36.55% female	Mild to moderate anxiety disorder	Starting at 150 mg/mL, twice per day, titrated up to 300 mg/mL, twice per day, if needed	>99.9% CBD	Nanodispersible oral solution	15 weeks	GAD-7 HAM-A	CBD group had greater improvements in anxiety on the GAD-7 than placebo group (difference in mean change from baseline = -7.02; p<0.001). CBD group had greater improvements in anxiety on the HAM-A than placebo group (difference in mean change from baseline = -11.9; p<0.001).	32.3% of participants reported AEs; all were mild to moderate in severity. The most common AEs were gastrointestinal disorders (19.1%) including abdominal pain, diarrhea, and nausea, along with headache (4.5%) and dizziness (2.2%)
Shannon et al., 2019 [91]	Retrospective case series	72	Age 18 - 70 years Mean age = 34 years 59.6% male among participants with anxiety disorders	65.3% anxiety disorder 34.7% sleep disorder	25, 50, 75, or 175 mg/day per clinician's preference	>99.9% CBD	Oral capsules	3 months	HAM-A	79.2% of participants experienced improvements in anxiety after 1 month, and 78.1% experienced further improvements between months 1 and 2. 15.3% and 19.5% of participants experienced worsening anxiety within the same time frames.	Few patients reported side effects; three noted mild sedation which resolved within a few weeks of treatment; one patient noted dry eyes
Berger et al., 2022 [88]	Open-label, single-arm Phase II	31	age 12-15 years lack of response to standard CBT and/ or antidepressant medication	DSM-5 anxiety disorders: GAD (n=3) SAD (n=14) Specific phobia (n=1) GAD +SAD (n=6) panic disorder + SAD (n=4) GAD + SAD + panic disorder (n=2)	fixed-flexible schedule starting at 200 mg/day: increasing by 200 mg/day without clinical improvement. Maximum of 400mg/day in week 1, 600 mg/ day at week 4, and 800 mg/day at week 8.	>99.9% CBD	Oral capsules	12 weeks	OASIS	42.6% reduction from baseline	Possibly drug-related AEs occurred in 19/31 (61.3%) participants Mild to moderate fatigue, low mood, changes in appetite, drowsiness, nausea, dry mouth, insomnia, and hot flashes or cold chills. All resolved spontaneously.
Stack et al., 2023† [79]	Interim analysis of retrospective, observational study	112	53% male; 47% female Median age = 48 years	Unspecified anxiety disorder	100 mg/day (median)	>99.9% CBD	Oral liquid or capsules	Variable, median = 154.4 days	PROMIS-29	4.4-point reduction in score from baseline (MCID=4; p<0.001)	Somnolence reported by 29.9% and dry mouth reported by 29.3%of participants
Kwee et al., 2022 [90]	Double-blind, placebo-controlled, randomized trial	80	Mean age = 36.7 years 60% male; 40% female	Panic disorder with agorophobia or social anxiety disorder	300 mg/session	>99.9% CBD	Oral capsules	Once per weekly 90-min exposure therapy session, for 8 weeks	FQ BAI	No significant difference between CBD and placebo on avoidance behavior or overall anxiety during single therapy sessions, or across 8-week regimen.	AEs were mild or moderate in severity. TEAEs were dizziness, drowsiness, tiredness, and feeling of a strong blood flow (1 occurrence each)
Masataka et al., 2019 [85]	Double blind, placebo-controlled trial	37	70.3% male; 29.7% female 18-19 years of age Cannabis-naïve No comorbid anxiety or mood disorders	SAD	300 mg/day	>99.9% CBD	Oil	4 weeks	FNE LSAS	Post-intervention reduction of 5.3 points in FNE (p=0.02 vs 0.2-point reduction; p=0.29 for placebo)	None reported, although 3 participants in the CBD group withdrew due to the taste/smell of the oil
Crippa et al., 2011 [86]	Placebo-controlled trial	10	Aged 20-33 years Mean age = 24.2 years 100% male	SAD	400 mg once	>99.9% CBD	Oral capsules	Test duration	VAMS	Acute CBD was associated with significantly lower anxiety during cannula insertion (p=0.02), pre-test resting (p=0.006), and post-test imaging (p=0.003).	Not reported
Bergamaschi et al., 2011 [87]	Double blind, placebo-controlled trial	24	Treatment naïve with no concomitant psychiatric disorders. 50% male; 50% female Mean age =23.8 years	SAD	600 mg once	>99.9% CBD	Oil in gelatin capsules	Test duration	VAMS SSPS-N	Significantly lower anxiety during the speaking task for participants on CBD compared to placebo (p=0.007). Significantly lower SSPS-N scores at anticipatory (p=0.043) and speech (p=0.001) phases in CBD vs Placebo group.	Not reported
Stack et al., 2023† [79]	Interim analysis of retrospective, observational study	35	53% male; 47% female Median age = 48 years	PTSD	100 mg/day (median)	>99.9% CBD	Oral liquid or capsules	Variable, median = 154.4 days	PROMIS-29	Significant decreases in anxiety (p<0.001)	Somnolence reported by 29.9% and dry mouth reported by 29.3%of participants
Bolsoni et al., 2022a* [93]	Double-blind, randomized, placebo-controlled trial	33	Age 18 - 60 years Mean age = 33.22 years 24.2% male, 75.8% female	PTSD	300 mg	99.6% CBD	Oral capsules	90 minutes	STAI-E VAMS	No significant effect of CBD on either measure of anxiety, compared to placebo.	Not reported
Bolsoni et al., 2022b* [94]	Double-blind, randomized, placebo-controlled trial	33	Age 18 - 60 years Mean age = 33.22 years 24.2% male, 75.8% female	PTSD	300 mg	99.6% CBD	Oral capsules	90 minutes	VAMS	Significantly lower anxiety scores after non-sexual trauma recall in the CBD group compared to placebo (mean difference = -9.82; p=0.033). CBD was associated with greater reductions in post-recall anxiety for participants with non-sexual compared to sexual trauma (mean difference=11.42, p=0.035).	Not reported
Hurd et al., 2019 [95]	Double-blind randomized, placebo-controlled trial	42	Mean age = 49.8 years 83.3% male; 16.7% female 69% Black; 16.7% Hispanic; 11.9% White	Heroin use disorder	400mg/day or 800mg/day	>99.9% CBD	Oral solution	7 days	VAS-A	Across all session, baseline-adjusted anxiety after drug-cues was 0.97 for placebo, 0.48 for 400mg CBD, and 0.24 for 800mg CBD (main effect of drug, p=0.0079)	No serious AEs: Mild diarrhea, headache, and tiredness were reported in 3, 3, and 2 participants, respectively,
de Faria et al., 2020 [96]	Randomized, double-blind, crossover trial	24	Mean age = 64.13 years 92% male	Parkinson's disease	300 mg	99.9% CBD	Oral capsules	15 days	VAMS; SSPS	Acute CBD decreased anxiety across all phases of the SPST, compared to placebo (F[1,21]=6.27; p<0.021)	Not reported
Aran et al., 2019 [98]	Retrospective observational	60	Age 5-18 years (mean=11.8 years) 83% male 82% treated with medications and cannabis concomitantly	Autism spectrum disorder	1 mg/kg/day titrated to max. 10 mg/kg/day	20:1	Sublingual oil	7-13 months	CGIC	39% of caregivers reported considerable improvement in anxiety	51% of patients reported AEs. The most common AEs (>5%) were sleep disturbances, restlessness, nervousness, loss of appetite, gastrointestinal symptoms, unexplained laugh.
Barchel et al., 2019 [99]	Prospective observational	17	Age 4-22 years (mean = 11 years) 85% male; 15% female	Autism spectrum disorder	Recommended daily dose of 16 mg/kg/day up to 600mg maximum	20:1	Sublingual oil	Median duration of follow-up = 66 days	Parent report	47.1% had improvement of anxiety symptoms, 29.4% had no change, and 23.5% had worsened symptoms	Most frequent AEs were somnolence and decreased appetite
Heussler et al., 2019 [100]	Open-label trial	20	Age 6-17 years (mean = 10.4 years) 75% male; 25% female 90% White; 10% Middle Eastern 50% with co-morbid anxiety	Fragile X syndrome	50 mg to a maximum daily dose of 250 mg	Not reported	Transdermal gel	12 weeks	ADAMS PARS-R	52.3% reduction in general anxiety sub scores of ADAMS after 12 weeks (p<0.001). 38.2% reduction in PARS-R scores (p<0.001)	30% reported possible or probably TEAEs, and 70% wee mild and resolved by end of trial. Most common AEs (>10%) were gastroenteritis, vomiting, and upper respiratory tract infection.

* studies in the same cohort; † subanalyses of the same study; ADAMS, Anxiety Depression and Mood Scales; AE, adverse event; BAI, Beck Anxiety Inventory; CBD, cannabidiol; CBT, cognitive-behavioral therapy; CGIC, Caregiver Global Impression of Change; FNE, Fear of Negative Evaluation Scale; FQ, Fear Questionnaire; GAD, generalized anxiety disorder; GAD-7, Generalized Anxiety Disorder 7-item scale; HADS-A, Hospital Anxiety and Depression Scale; HAM-A; Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; LSAS, Liebowitz Social Anxiety Scale; OASIS, Overall Anxiety and Impairment Scale; MCID, minimum clinically important difference; PARS-R, Pediatric Anxiety Rating Scale; PD, Parkinson's disease; PROMIS-9, Patient-Reported Outcomes Measurement Information System-29; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; SSPS, Self-Statements during Public Speaking Scale; SSPS-N, Self-Statements during Public Speaking Scale – Negative self-evaluation subscale; SPST, Simulated Public Speaking Task; STAI-E, State-Trait Anxiety Inventory; TEAE, treatment-emergent adverse events; THC, Δ9-tetrahydrocannabinol; VAMS, Visual Analog Mood Scale; VAS-A, Visual Analog Scale for Anxiety.

Table 2: CBD for anxiety and anxiety disorders.

Conclusions and Future Directions

Despite the scarcity of large, robustly designed, sufficiently powered multicenter RCTs in this field, there is converging evidence from nonclinical, clinical, and RCT studies to suggest that cannabinoid-based medicines in general, and CBD in particular, may help to alleviate anxiety symptoms in diverse populations with unmet treatment needs. Although multiple clinical trials are currently underway [84,102], it is important to consider the limitations that may be inherent to these studies. RCTs with cannabinoid-based medicines are hindered by the variable regulatory status of medical cannabis between and within regions. This limits potential access for clinically relevant populations and results in potentially biased sampling. Additionally, and unlike traditional pharmaceutical products, cannabinoid-based medicines vary greatly in their cannabinoid composition and purity among studies, and potentially between batches within the same study. This variability complicates data analysis and makes comparing results between and among studies, even within similar clinical populations difficult [103]. For example, cannabinoids in general, and THC specifically, may have a biphasic effect on anxiety symptoms [104,105]. Future research should include carefully calibrated dose-response studies to optimize the efficacy and safety of cannabinoid-based products. Finally, some studies have identified an expectancy bias, where simply expecting to receive a dose of CBD is enough to produce anxiolytic effects [106-108]. This effect should be measured and controlled for in ongoing and future research. While both evidence and opinion with regard to abuse and dependence issues in the medical cannabis realm seem increasingly supportive of the safety of these agents, there remains much to test in future investigations.

Most research has focused on participants with SAD; yet, more research is needed to explore the effect of different cannabinoid formulations in individuals with other anxiety disorders. For example, although GAD is the most common anxiety disorder [109], it is underrepresented in this body of research, especially in females [110]. Moreover, most individuals with anxiety disorders are not sufficiently treated with current first- or second-line therapies, which highlights their need for additional treatment options [111]. Additionally, most RCTs use oral or inhaled cannabinoid-based products, and the route of administration has the potential to impact the onset and duration of clinical effects as well as the risk of adverse events [112,113]. For example, smoked cannabis flower is associated with an increased risk of cancer, periodontal disease, and oral lesions [114]. In addition, although some studies have pointed toward an increased risk of cancer with smoked cannabis flower, the link is controversial as these effects are often confounded with the co-use of tobacco [115-117]. Nonetheless, novel safe delivery methods for cannabinoid-based products are warranted. One option might include cannabinoid-containing chewing gums, which have begun to be investigated in other therapeutic areas and may allow cannabinoids to be added to the anti-anxiety effects of gum-chewing, in general [118-121].

Furthermore, minor cannabinoids present a largely unexplored avenue of research as potential treatments for anxiety [122,123]. For example, both acute and subchronic dosing of oral cannabigerol (CBG) appears to be anxiolytic for mice in the elevated plus maze [123]. A recent review found eight nonclinical studies exploring the effect of cannabinoids other than THC and CBD in anxiety models. Despite their limitations and mixed results, compounds like cannabidiolic acid methyl ester (CBDA-ME) emerged as promising candidates for follow up [122].

Cannabinoid-based medicinal products may represent an important emerging therapy option for individuals with anxiety and anxiety disorders, but more research is needed to identify specific product compositions, formulations, routes of administration, and treatment paradigms that are effective for distinct patient populations. In 2023, the US Senate passed a bill allowing Veterans Administration (VA) physicians to recommend (not prescribe) medical cannabis to veterans in states where it is legal. The US Department of Veterans Affairs has openly encouraged patients and providers to discuss cannabis use to support safe and effective treatment plans. The implications for combat-related post-traumatic stress disorder (PTSD) are self-evident but require meaningful, rigorous trials. While RCTs will continue to be important, RWE studies in this field can help fill in the gaps by addressing the abovementioned limitations [124,125]. For example, well-controlled, prospective observational studies using data from patient registries can achieve the larger sample sizes and extended treatment timelines needed to observe nuances in cannabinoid composition and dosing. Similarly, open-label studies will allow for the recruitment of clinically relevant participants, including those with comorbid diagnoses and complex treatment histories, which may be excluded from traditional RCTs [126]. Although more data are needed, from a combination of RCTs and RWE studies, to understand the clinical potential of cannabinoid-based medicines to treat anxiety, it seems fair to assert that these products show promising potential to alleviate unmet treatment needs for patients.

It has been said that to reflexively assume medicines are “simplistic and lazy responses to psychiatric illness” is destructive [127]. A more accurate view of medicines involves fully understanding the spectrum of risks and benefits, then using them skillfully to best address symptoms that may otherwise be refractory to management. Discouraging individuals with anxiety disorders from utilizing effective medications, when indicated, is irresponsible. Morehead emphasizes that the obsolete view that those disabled by anxiety are too weak characterologically to face their difficulties without a pill is “downright cruel” [127]. Additionally, extensive research

shows that medications and psychotherapy are complementary and even synergistic approaches to managing anxiety disorders [128].

A wealth of contemporary research underscores the truism that psychopharmacology, far from being a "lazy" fix, is a nuanced tool in the clinician's arsenal—one whose judicious application can be as artful as it is scientific. Understanding the appropriate use of novel medications means weighing the well-documented efficacy in reducing core anxiety symptoms against their side-effect profiles and the need for ongoing monitoring. For example, SSRIs have been shown in meta-analysis to achieve response rates up to 60% in generalized anxiety disorder populations, with an acceptably low incidence of serious adverse events [129]. When initiated and titrated thoughtfully—taking into account comorbidities, patient history, health status, historical tendencies, preference, and pharmacokinetic interactions—these agents offer relief that, for many, would otherwise be refractory to purely psychotherapeutic approaches [130]. We would assert that the same is likely true for cannabinoid agents.

Moreover, the interplay between medication and psychotherapy is often synergistic rather than competitive. A landmark series of randomized controlled trials demonstrated that combining SSRIs with CBT not only accelerates symptomatic remission but also reduces relapse rates at follow-up compared to either modality alone [131]. This empirical synergy exemplifies the biopsychosocial model first articulated by Engel, in which biological interventions (medication), psychological strategies (therapy), and social/contextual factors (support networks, stressors) are all seen as integral—and mutually reinforcing—elements of high-quality care [132]. In the quest for more effective care, the concepts of precision or personalized medicine, which incorporate individual biological and social variables, are beginning to become embedded in the biopsychosocial framework.

Importantly, dismissing pharmacotherapy on the grounds that it reflects characterological weakness misconstrues both the pathophysiology of anxiety disorders and the goals of compassionate medicine. As we have seen, anxiety disorders involve dysregulation of neural circuits (e.g., amygdala-prefrontal pathways) and neurotransmitter systems (serotonin, GABA), processes that are not amenable to "willpower" alone [133]. As Morehead poignantly argues, implying that sufferers simply lack fortitude is "downright cruel" [127]. Let us not forget that the American Psychiatric Association guidelines advocate for a stepped-care approach—beginning with evidence-based psychotherapy, adding or switching to pharmacotherapy when indicated, and always engaging patients collaboratively in shared decision-making [134]. To withhold or stigmatize effective and fundamentally low risk medications is not only unscientific but undermines the ethical imperative to alleviate suffering wherever it lies.

In sum, high-quality, evolving anxiety care embraces the full continuum of interventions. It respects the profound relief that creative drug research & development wedded to evidence-based pharmacotherapy can achieve, i.e., support of the coping and resilience-building power of psychotherapy, situated both within a biopsychosocial framework that is responsive to the complexity of the human being.

Statements and Declarations

Ethical Considerations/Consent to Participate/Consent for Publication: N/A: This review and commentary did not involve the development or collection of new or original data involving human participants or animals. All analyses and opinions were created using previously published or publicly available information. As such, Institutional Review Board (IRB) approval and informed consent were not required.

Conflicting Interest: PP, AWH, and WKS are paid consultants to Aspeya, Switzerland; KV, KB, and AZ were contracted employees of Aspeya, Switzerland, at the time of manuscript preparation; JH is a full-time employee of Aspeya. The review opinions and commentary expressed in the present manuscript are solely those of the authors and do not necessarily represent those held by Aspeya.

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