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Could Cannabidiol Be a Treatment for Coronavirus Disease-19-Related Anxiety Disorders?

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Abstract

Coronavirus disease-19 (COVID-19)-related anxiety and post-traumatic stress symptoms (PTSS) or post-traumatic stress disorder (PTSD) are likely to be a significant long-term issue emerging from the current pandemic. We hypothesize that cannabidiol (CBD), a chemical isolated from *Cannabis sativa* with reported anxiolytic properties, could be a therapeutic option for the treatment of COVID-19-related anxiety disorders. In the global over-the-counter CBD market, anxiety, stress, depression, and sleep disorders are consistently the top reasons people use CBD. In small randomized controlled clinical trials, CBD (300–800 mg) reduces anxiety in healthy volunteers, patients with social anxiety disorder, those at clinical high risk of psychosis, in patients with Parkinson's disease, and in individuals with heroin use disorder. Observational studies and case reports support these findings, extending to patients with anxiety and sleep disorders, Crohn's disease, depression, and in PTSD. Larger ongoing trials in this area continue to add to this evidence base with relevant patient cohorts, sample sizes, and clinical end-points. Pre-clinical studies reveal the molecular targets of CBD in these indications as the cannabinoid receptor type 1 and cannabinoid receptor type 2 (mainly in fear memory processing), serotonin 1A receptor (mainly in anxiolysis) and peroxisome proliferator-activated receptor gamma (mainly in the underpinning anti-inflammatory/antioxidant effects). Observational and pre-clinical data also support CBD's therapeutic value in improving sleep (increased sleep duration/quality and reduction in nightmares) and depression, which are often comorbid with anxiety. Together these features of CBD make it an attractive novel therapeutic option in COVID-related PTSS that merits investigation and testing through appropriately designed randomized controlled trials.

Keywords: cannabidiol; anxiety; PTSD; sleep; COVID-19

Introduction

The phytochemical cannabidiol (CBD) is produced in the *Cannabis sativa* plant as its acidic precursor, cannabidiolic acid, which is converted to CBD with light, heat, and time. Unlike Δ^9-tetrahydrocannabinol (THC), CBD does not have psychotropic effects because it does not directly activate the cannabinoid receptor type 1 (CB_1).[1] Based on multiple clinical trials, purified CBD is now available as a licensed medicine in the drug Sativex (1:1 ratio of THC:CBD, licensed for spasticity in multiple sclerosis) and as Epidiolex (pure CBD, licensed for seizure reduction in rare forms of epilepsy).[2]

From a pharmacological point of view, CBD is an interesting chemical because it interacts with many protein receptors, transporters, ion channels, and enzymes (including key metabolic liver enzymes) (Table 1), which bring about the many beneficial effects of CBD.[3–6] However, CBD is not very potent at any of these molecular targets, partly explaining why there are limited adverse effects (AEs) and serious adverse effects (SAEs) with CBD medications. Recent systematic reviews of the clinical use of CBD found that AEs related to CBD include decreased appetite, diarrhea, sedation, and somnolence.[7] SAEs related to CBD in

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Table 1. The Polypharmacology of Cannabidiol

CBD's rich pharmacology
Receptors
Low CB_1/CB_2 affinity/possible antagonism
Some (indirect?) CB_1-/CB_2-mediated effects
$5HT_{1A}$ agonist
Peroxisome proliferator-activated receptor gamma activator
GPR55 antagonist
GPR18 agonist
Inverse agonist for GPR3, GPR6, and GPR12
Dopamine D2 partial agonist
Predicted dopamine D3 agonist
Adenosine receptor agonist
Glycine receptor agonist
Delta-type opioid receptor agonist
Ion
Activation of TRPV1, TRPV2, TRPV3, and TRPM8
Channels
Calcium channel inhibition
Enzymes
FAAH inhibitor
Inhibits CYP1A1, 2B6, 2C19, 3A4, and 3A5
Cyclooxygenase inhibitor/activator
Other
Binds to FABPs (competitive inhibition)
Adenosine uptake inhibitor

$5HT_{1A}$, serotonin1A; CB_1, cannabinoid receptor type 1; CB_2, cannabinoid receptor type 2; CBD, cannabidiol; CYP, cytochrome P450; FAAH, fatty acid amide hydrolase; FABP, fatty acid binding protein; GPR, g-protein coupled receptor; TRPM, melastatin-related transient receptor potential cation channels; TRPV1, transient receptor potential cation channel subfamily V member.

randomized controlled trials (RCTs) were rare and included elevated transaminases (related to concomitant valproate use), and sedation, lethargy, and upper respiratory tract infections (all related to concomitant clobazam use).[8] After excluding studies in childhood epilepsy (and, therefore, concomitant antiepileptic medications), the only adverse outcome associated with CBD treatment was diarrhea.[7] Thus, available data from clinical trials suggest CBD is well tolerated and has relatively few SAEs; however, interactions with other medications should be closely monitored.

The therapeutic potential of CBD is being explored in a wide range of disorders. There are currently nearly 100 registered trials investigating CBD, of which 21 are phase 3 (relevant patients in large numbers), covering chronic back pain, postsurgical pain, anxiety disorders, infantile spasms, Rett Syndrome, Tuberous Sclerosis Complex, bipolar depression, degenerative hallux disorders, and Fragile X syndrome. Recently, some researchers have speculated that CBD might be useful as an antiviral[9] or anti-inflammatory[10,11] agent in the current coronavirus disease-19 (COVID-19)/coronavirus pandemic, as well as being capable of downregulating the expression of key receptors (ACE2 and TMPRSS2) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in human epithelial cells.[12] It has also been postulated that CBD might inhibit the development of pulmonary fibrosis in COVID-19 patients.[13] Because of the growing evidence of the anxiolytic effects of CBD, we suggest CBD could also be a therapeutic option to treat long-lasting COVID-19-related anxiety and post-traumatic stress disorder (PTSD), which will be a significant issue of this pandemic.

COVID-Related Anxiety Disorders

PTSD is a common consequence of major disasters, including epidemics. Epidemiological projections made by the World Health Organization (WHO) show that postdisaster mental health problems range from mild to very severe distress, affecting between 20% and 50% of the population. A minority develops new and debilitating mental disorders, and those with pre-existing mental disorders need even more help than before. In the current pandemic, the WHO suggests that levels of loneliness, depression, harmful alcohol and drug use, and self-harm or suicidal behavior are also expected to rise. Considering the breadth of the COVID-19 pandemic, and the widespread impact of quarantine, social isolation, loss of loved ones (and the inability to grieve socially), loss of income and financial worries, potentially extreme and chronic illnesses (which themselves impact mental health), and frontline working, the current crisis is likely to trigger large numbers of people with long-lasting anxiety and PTSD or post-traumatic stress symptoms (PTSS). In fact, a recent article suggested "PTSD as the second tsunami of the SARS-CoV-2 pandemic."[14]

A systematic review of the evidence on the psychosocial impact of quarantine measures during previous coronavirus outbreaks showed that quarantine measures were consistently associated with negative psychosocial outcomes, including depressive symptoms, anxiety, anger, stress, post-traumatic stress, social isolation, loneliness, and stigmatisation.[15] For example, the rates of mental health symptoms after the SARS outbreak were between 4% and 17%, and were worst for health care workers. Survey respondents who had been isolated, worked in high-risk workplaces, or had friends or close relatives who contracted SARS were two to three times more likely to develop high levels of PTSS.[16]

In the current COVID-19 outbreak, an early study of residents in Wuhan and surrounding cities asked about

PTSS and sleep qualities. One month after the outbreak (data were collected in January 2020), the prevalence of PTSS was about 7%.[17] A subsequent study (1210 respondents from 194 Chinese cities) found 54% of respondents rated the psychological impact of the outbreak as moderate or severe, 17% reported moderate to severe depressive symptoms, 29% reported moderate to severe anxiety symptoms, and 8% reported moderate to severe stress levels.[18] Looking at the mental health effects of COVID-19 in younger people, a cross-sectional survey suggests that nearly 15% of respondents had PTSD symptoms and 40% had a tendency to have psychological problems.[19] In patients who contracted COVID-19, the degree of psychological distress may be related to the level of systemic inflammation.[20]

A multinational multicenter study on the psychological outcomes among health care workers during COVID-19 surveyed 906 health care workers.[21] Using the depression, anxiety, and stress scale (DASS-21) scoring system, the authors found anxiety in 16%, depression in 11%, and stress in 5% of the study participants. Seven percent of the study cohort screened positive for clinical concern of PTSD. Another cross-sectional survey of 1257 health care workers treating COVID-19 patients in China found significant reported symptoms of depression (50%), anxiety (45%), insomnia (34%), and distress (72%).[22]

Overall, a systematic review (published August 2020) of the effects of COVID-19 on psychological outcomes found high rates of anxiety (6%–51%), depression (15%–48%), PTSD (7%–54%), psychological distress (34%–38%), and stress (8%–82%) in the general population in China, Spain, Italy, Iran, the United States, Turkey, Nepal, and Denmark.[23] Their conclusion was that "mitigating the hazardous effects of COVID-19 on mental health is an international public health priority."

Pharmacological treatment strategies are likely to involve selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (SNRIs), serotonin 1A ($5HT_{1A}$) agonists, and benzodiazepines, all of which have side effect profiles that are not always tolerable to patients, including significant adverse events (e.g., insomnia, agitation, central nervous system depressive effects, and sexual dysfunction), symptom relapse, drug dependence, and withdrawal syndromes. Moreover, these treatments can show limited or short-lived efficacy in a significant number of patients, and their therapeutic effects can have a delayed onset of action of several weeks (in the case of SSRIs and SNRIs) (see Papagianni and Stevenson[24] for a previous review on this topic). Psychological treatments (e.g., exposure therapy) are also available, but again they can have limited or temporary therapeutic effects.[25] Thus, novel agents are required to manage these symptoms.

Clinical Studies with CBD in Anxiety and Related Disorders

Over-the-counter (OTC) CBD products have become very popular in the health and wellness markets globally. One of the features most often proclaimed for CBD is its ability to reduce stress and anxiety. A cross-sectional study of OTC CBD users found that the top 3 medical conditions for which CBD is used were pain, anxiety, and depression.[26] A more recent study found that the top reasons OTC CBD was used were stress relief, relaxation, and sleep improvement.[27] A 2020 analysis of social media content revealed that CBD is most discussed as a therapeutic option for anxiety disorders and pain.[28] However, there are issues with OTC CBD, including unreliable quality, potential presence of controlled substances,[29] and lower dosing options, which limit the use of CBD in serious anxiety conditions.

Alongside the anecdotal use of CBD for stress and anxiety, there is a growing body of clinical studies demonstrating the anxiolytic effects of CBD across various patient cohorts and various pathological situations. Several small proof-of-concept randomized controlled clinical trials and case series report on the ability of CBD to have positive effects on anxiety in healthy volunteers or patients with various diagnoses, and these studies are summarized in Table 2. It should be noted that the evidence base in this area is still of low quality. Although there are RCTs showing efficacy of CBD, seven of these were carried out in healthy volunteers, and only five were in relevant patient cohorts (Table 2). All of the trials were also in very small patient numbers. Thus, larger trials in relevant patients are required to confirm these findings.

In healthy volunteers in randomized controlled studies, acute doses of 300 or 600 mg given orally reduced the anxiety caused by public speaking,[30–32] and reduced the blood pressure and cardiovascular response to physical and mental stress (600 mg).[33] A dose-ascending placebo-controlled study in healthy volunteers found that a single 300 mg, but not 100 or 900 mg, dose of CBD was effective at reducing anxiety in a public speaking test.[34] Such anxiolytic effects of acute CBD treatment are associated with altered brain

Table 2. Published Clinical Evidence of Cannabidiol Efficacy in Anxiety Disorders Through Randomized Controlled Trials and Observational Studies

	Study type	Patient cohort	Dose	Findings
Randomized controlled trials				
Zuardi et al. (1993)[32]	Double-blind design and placebo-controlled	Four groups of 10 subjects	CBD (300 mg), diazepam (10 mg) or ipsapirone (5 mg) or placebo	CBD decreased anxiety after the simulated public speaking test (evaluated through the visual analog mood scale and state trait anxiety inventory) and was as effective as other pharmacological agents. Only diazepam was sedative.
Fusar-Poli et al. (2009)[30]	Double-blind and placebo-controlled	Fifteen healthy and right-handed men	Ten milligrams THC, 600 mg CBD or placebo	There was a trend for a reduction in anxiety after administration of CBD. CBD attenuated the blood oxygenation level-dependent signal in the amygdala and the anterior and posterior cingulate cortex, while subjects were processing intensely fearful faces, and its suppression of the amygdala and anterior cingulate responses was correlated with the concurrent reduction in skin conductance response fluctuations.
Bergamaschi et al. (2011)[37]	Double-blind	Twelve healthy volunteers and 24 patients with generalized SAD	CBD 600 mg	Pretreatment with CBD significantly reduced anxiety, cognitive impairment and discomfort in their speech performance.
Zuardi et al. (2017)[34]	Parallel-group, double-blind, and placebo-controlled	Sixty healthy subjects of both genders	Placebo, clonazepam (1 mg), and CBD (100, 300, and 900 mg)	Subjective anxiety measures in volunteers were reduced with CBD 300 mg, but not with CBD 100 and 900 mg, in the postspeech phase after a test of public speaking in a real situation.
Jadoon et al. (2017)[33]	Placebo-controlled, double-blind, and crossover	Nine healthy males	CBD 600 mg or placebo	CBD lowered BP (especially before and after stress), increased HR, decreased stroke volume, and caused a blunted forearm skin blood flow response to isometric exercise. In response to cold stress, subjects who had taken CBD had blunted BP and increased HR, with lower total peripheral resistance.
Bhattacharyya et al. (2018)[40]	Parallel-group, double-blind, and placebo-controlled	Thirty-three medication-naive participants at CHR-P and 19 HC	CBD 600 mg	Participants receiving placebo had reduced activation relative to controls in the right caudate during encoding and in the parahippocampal gyrus and midbrain. Within these three regions, activation in the CBD group was greater than in the placebo group but lower than in the control group.
Masataka (2019)[38]	Placebo-controlled	Thirty-seven Japanese teenagers with SAD and avoidant personality disorder	Cannabis oil containing 300 mg CBD or placebo	CBD significantly decreased anxiety during a simulated public speaking test.
Linares et al. (2019)[31]	Double-blind and parallel group	Fifty-seven healthy male subjects	CBD 150, 300, and 600 mg or placebo	CBD significantly reduced anxiety during a simulated public speaking test.
Hurd et al. (2019)[43]	Double-blind and placebo-controlled	Drug-abstinent individuals with heroin use disorder	CBD 400 or 800 mg, once daily for 3 consecutive days	Both doses of CBD significantly reduced both craving and anxiety induced by the presentation of salient drug cues, which persisted 7 days after the final CBD exposure. CBD reduced the drug cue-induced changes in HR and salivary cortisol levels.
Sultan et al. (2020)[36]	Placebo-controlled and double-blind	Healthy males ($n = 13$ per group)	CBD 600 mg or placebo orally for 1 week	In response to stress, volunteers who had taken CBD had lower systolic BP after acute and repeated dosing.
Appiah-Kusi et al. (2020)[41]	Placebo-controlled and double-blind	Thirty-two CHR-P patients and 26 HC	CBD 600 mg or placebo for 1 week	The change in cortisol associated with experimental stress exposure was greatest in HC and least in CHR-P patients, with CHR-CBD patients exhibiting an intermediate response. Changes in anxiety and experience of public speaking stress were greatest in the CHR-P and least in the HC, with CHR-CBD participants demonstrating an intermediate level of change.
de Faria et al. (2020)[42]	Double-blinded, placebo-controlled, and crossover	Twenty-four patients with Parkinson's disease	CBD 300 mg or a placebo	Acute CBD administration decreased anxiety in patients with Parkinson's disease, and there was also decreased tremor amplitude in an anxiogenic situation.

(*continued*)

Table 2. (Continued)

	Study type	Patient cohort	Dose	Findings
Uncontrolled trials/case reports and series				
Shannon and Opila-Lehman (2016)[48]	Case report	A 10-year-old girl with PTSD secondary to sexual abuse	CBD (25 mg) at bedtime, and 6–12 mg of CBD sublingual spray during the day as needed for anxiety	A gradual increase in sleep quality and quantity and a decrease in her anxiety were noted. After 5 months, the patient was sleeping in her own room most nights and handling the new school year with no difficulties.
Shannon et al. (2019)[44]	Case series	Seventy-two adults with concerns of anxiety ($n=47$) or poor sleep ($n=25$)	25-175 mg in the morning (anxiety) or evening (sleep)	Anxiety and sleep improved for most patients, and these improvements were sustained over time.
Elms et al. (2019)[47]	Case series	Eleven adult patients with DSM-5-diagnosed PTSD	Mean starting dose 33 mg and the mean total dose at the 8-week follow-up was 49 mg (range: 2–100)	Ten of 11 patients experienced a decrease in PTSD symptom severity. Four patients continued CBD for 36 weeks or more. They had an initial mean PCL-5 score of 57.75 with a mean score at 36 weeks of 29.25. CBD also offered relief in a subset of patients who reported frequent nightmares.
Laczkovics et al. (2020)[45]	Case report	Teenager with multiple substance use disorder, severe depression, social phobia, and narcissistic personality disorder	CBD with an initial dosage of 50 mg twice daily, gradually to 300 mg twice daily	By their request, the patient discontinued sertraline after 3 weeks of CBD treatment. There were no side effects regarding HR, BP, and weight. The patient improved regarding depressive as well as anxiety symptoms, including simple phobias and symptoms of paranoia and dissociation.
Klier et al. (2020)[46]	Case report	Fourteen-year-old patient with Crohn's disease with social phobia	CBD with an initial dosage of 100 mg per day, gradually to 600 mg per day for 19 weeks	CBD reduced the Clinical Global Impression Severity Scale from 5 to 3, and reduced the severity of symptoms of needle phobia, fear of medical intervention, and social phobia.
Gulbransen et al. (2020)[49]	Audit	Two hundred fifty-three patients presenting to Cannabis Care, New Zealand	CBD oil	Four hundred patients were assessed for CBD and 397 received a prescription. Follow-up was completed on 253 patients. Patients with noncancer pain and mental health symptoms achieved improvements to patient-reported pain, depression and anxiety symptoms.

Studies are presented in chronological order in each section.

BP, blood pressure; CHR-P, clinical high risk for psychosis; HC, healthy controls; HR, heart rate; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; SAD, social anxiety disorder; THC, tetrahydrocannabinol.

activity in corticolimbic regions (e.g., cingulate cortex and amygdala) that mediate cognition and emotional regulation.[30,35] In healthy volunteers, 7 days of treatment with CBD (600 mg/day) also reduced the hemodynamic response to acute physical stress.[36]

In medication-naive patients with generalized social anxiety disorder, acute oral doses of 300 or 600 mg reduced anxiety caused by public speaking in a randomized controlled study.[37] Similarly, in teenagers with social anxiety disorder, an RCT showed that 4 weeks CBD (300 mg/day) treatment decreased anxiety measures using the Fear of Negative Evaluation Questionnaire and the Liebowitz Social Anxiety Scale.[38] As with healthy volunteers, the anxiolytic effects of CBD in anxiety disorders are also linked to alterations in corticolimbic activity.[39] Moreover, in medication-naive participants at clinical high risk of psychosis, CBD (600 mg) partially normalized the alterations in limbic, striatal, and midbrain function in an RCT.[40] A follow-up study by the same group showed 7 days of treatment with CBD (600 mg/day) in patients at clinical high risk of psychosis partially restored the cortisol response elicited during the Trier Social Stress Test to that observed in the control group.[41] In this study, the experience of anxiety in response to the stress test was greatest in the high-risk patients and lowest in the healthy controls, with those at high risk who were treated with CBD for 7 days exhibiting an intermediate response.

Anxiety is often comorbid with other presentations, and the anxiolytic effects of CBD in other pathologies has also been tested in randomized controlled studies. In patients with Parkinson's disease, a single dose of CBD (300 mg) attenuated the anxiety experimentally induced by a Simulated Public Speaking Test in a randomized double-blinded placebo-controlled crossover trial.[42] In drug-abstinent individuals with heroin use

disorder, CBD (either 400 or 800 mg for 3 days) also reduced the anxiety and cortisol responses to the presentation of a drug cue in a double-blind randomized placebo-controlled trial.[43]

Several case reports also document the anxiolytic effects of CBD. In adults with concerns of anxiety or poor sleep, CBD treatment (25–175 mg per day) improved anxiety and sleep improved for most patients in a recent case series.[44] For a 16-year-old patient with multiple substance use disorder, severe depression, social phobia, and narcissistic personality disorder, treatment with CBD (100–600 mg/day for 8 weeks) improved depressive and anxiety symptoms.[45] CBD treatment (up to 600 mg per day for 19 weeks) in a 14-year-old patient with Crohn's disease and anxiety disorder (social phobia) reduced the severity of anxiety symptoms.[46] A case report and case series in PTSD patients treated with CBD (2–100 mg/day for 8 weeks) reported improvements in anxiety and sleep quality.[47,48] A recently published study of an audit of CBD-prescribed patients was completed on 253 patients.[49] Patients with noncancer pain and mental health symptoms achieved significant improvements to patient-reported pain, depression, and anxiety symptoms.

CBD's Mechanism of Action in Anxiety

Many pre-clinical studies have investigated the anxiolytic and mnemonic effects of CBD in animal models of anxiety and learned fear when CBD is administered systemically or directly into the brain, revealing potential mechanisms of action for CBD in these models.[50] Several receptors have been implicated to be molecular sites of action of CBD. The $5HT_{1A}$ receptor and transient receptor potential vanilloid 1 channel have been implicated in the anxiolytic effects of CBD.[51,52] Peroxisome proliferator-activated receptor gamma activation is also thought to be involved in the underpinning anti-inflammatory/antioxidant effects that help resolve the pathological effects that can lead to anxiety.[53] Activation of the CB_1 receptor has been implicated in the facilitatory effect of CBD on fear extinction, possibly as an indirect consequence of enhancing endocannabinoids within the brain.[54–56] Fear extinction is a form of inhibitory learning that suppresses learned fear and forms the theoretical basis for exposure therapy in the treatment of certain anxiety disorders.[25] Interestingly, a study in humans showed that CBD also enhanced fear extinction in healthy volunteers,[57] raising the possibility that CBD might enhance the therapeutic effects of psychological treatments.

In pre-clinical studies, CBD has also been shown to decrease dopamine (DA) transmission,[58] 5HT transmission[59] and to modulate synaptic plasticity in the amygdala and hippocampus.[60] CBD can also block the formation of associative, fear-related memories in specific neural regions, including the nucleus accumbens (NAc) and ventral hippocampus (vHIPP). Thus, Norris et al. reported that direct infusions of CBD into the rodent NAc potently blocked the formation of associative fear memories through a $5HT_{1A}$-receptor dependent mechanism.[58] These effects of CBD on fear-memory formation were also dependent on its ability to dampen the activity of DA neurons directly in the ventral tegmental area,[58] an effect that is similarly thought to underlie the putative antipsychotic properties of CBD.[61] CBD has also been reported to mitigate the anxiogenic effects of THC.[62] For example, coadministration of CBD with THC in the rodent vHIPP was shown to block the ability of THC alone to induce potentiation of fear-related memory formation. This effect was dependent on CBD's ability to block hyperstimulation of extracellular-signal-related kinase 1-2 phosphorylation states induced by THC.[63] Thus, the therapeutic ability of CBD in anxiety and stress management is not reliant on a single molecular target and involves many biological processes. This might also explain why CBD is anxiolytic in many different types of anxiety disorders. Accordingly, there is an urgent need to map and validate these pre-clinical molecular biomarkers associated with CBD's anxiolytic properties onto translational studies in human populations.

CBD and Sleep Disorders

As alluded to earlier, sleep disturbances are often reported in those suffering with anxiety, PTSS and PTSD,[64] and case series data suggest sleep disturbances are improved by CBD in patients with PTSD,[47,48] particularly in the reduction of nightmares (see Table 3 for a summary of studies that report improvements in sleep with CBD in humans). One placebo-controlled dose-ranging clinical study found that a dose of 160 mg CBD was effective at improving sleep duration in insomniac volunteers.[65] In pre-clinical studies, CBD has been shown to block anxiety-related rapid eye movement sleep alterations.[66] Observational uncontrolled clinical studies investigating the effects on sleep found CBD (25–300 mg/day) to have positive effects on sleep quality and to decrease sleep disturbances in patients with autism spectrum disorder,[67,68] Parkinson's disease,[69] chronic

Table 3. Published Clinical Evidence of Cannabidiol Efficacy in Sleep Disorders Through Randomized Controlled Trials and Observational Studies

	Study type	Patient cohort	Dose and length of treatment	Findings
RCTs				
Carlini and Cunha (1981)[65]	Double-blind and randomized	Fifteen insomniac volunteers	40, 80, and 160 mg CBD compared with placebo and 5 mg nitrazepam	Subjects receiving 160 mg CBD reported having slept significantly more than those receiving placebo; the volunteers also reported significantly less dream recall with the three doses of CBD than with placebo.
Linares et al. (2019)[31]	Crossover and double-blind design	Twenty-seven healthy subjects	CBD (300 mg) or placebo	Unlike other anxiolytic and antidepressant drugs, acute administration of an anxiolytic dose of CBD did not seem to interfere with the sleep cycle of healthy volunteers.
Uncontrolled trials/case reports and series				
Chagas et al. (2014)[69]	Case series	Four Parkinson's disease patients	CBD (75 mg/day (3 patients) or 300 mg/day (1 patient) for 6 weeks	Four patients treated with CBD had a substantial reduction in the frequency of rapid eye movement sleep behaviour disorder-related events.
Vigil et al. (2018)[71]	Mobile software application	Four hundred nine people with insomnia	Mean THC level was 20% and the mean CBD level was 5.7%	Releaf App™ users showed an average symptom severity reduction of −4.5 points on a 0–10 point visual analog scale. CBD was associated with greater, statistically significant, symptom relief than THC.
Barchel et al. (2019)[68]	Prospective and uncontrolled	Fifty-three children with autism spectrum disorder	CBD median daily dose was 90 (45–143) mg. Median duration of 66 (30–588) days	Reports on 21 patients with sleep problems were recorded. Of 21 reports, 71% improved, 24% had no change, and worsening of symptoms was reported in one patient.
Fleury-Teixeira et al. (2019)[67]	Observational study	Eighteen autistic patients	Pure CBD and CBD-enriched extract	The strongest improvements with CBD were reported for seizures, attention deficit/hyperactivity disorder, sleep disorders, and communication and social interaction deficits. Sleep disorders were improved by ∼40%.
Shannon et al. (2019)[44]	Case series	Seventy-two adults with concerns of anxiety ($n=47$) or poor sleep ($n=25$)	Twenty-five to 175 mg per day in the morning (for anxiety) or evening (for sleep)	On average, anxiety and sleep improved for most patients, and these improvements were sustained over time.
Capano et al. (2020)[70]	Prospective cohort study	One hundred thirty-one patients from a private pain management centre	Hemp extract CBD	More than half of chronic pain patients (53%) reduced or eliminated their opioids within 8 weeks with CBD-rich hemp extract. There was a significant relationship between CBD and Pittsburgh Sleep Quality Index ($p=0.003$), and Pain Intensity and Interference.

Studies are presented in chronological order in each section.

pain,[70] and in patients with insomnia.[44,71] Again, although the evidence base is of low quality, there is sufficient data to support the hypothesis that CBD would be beneficial in sleep disorders associated with anxiety, which merits testing.

Current and Future Approaches for Clinical Research with CBD in Anxiety-Related Disorders

Based on this positive background of pre-clinical data, anecdote and case reports, and small RCTs, numerous larger clinical trials are currently registered and ongoing (see clinicaltrials.gov) assessing the potential of CBD in anxiety-related disorders, which are summarized in Table 4. These trials cover relevant patient populations, including PTSD, anxiety (comorbid with breast cancer or Parkinson's disease), and generalized anxiety disorder, using clinically relevant primary endpoints. Interestingly, there is a recently registered trial specifically to assess the use of CBD (300 mg daily for 28 days) in the treatment of burnout and distress in

Table 4. Registered and Active Clinical Trials Examining the Potential of Cannabidiol in the Treatment of Anxiety Disorders

NCT no.	Title	Status	Conditions	Outcome measures	Sponsor/collaborators	Phase	*N*	Start date	Completion date
NCT03518801	Cannabidiol and Prolonged Exposure	Recruiting	PTSD	Clinician-administered PTSD scale DSM 5 (CAPS-5) | PTSD checklist (PCL-5)	University of California, San Diego	Phase 2	136	March 1, 2019	September 2023
NCT04197102	Use of CBD Oil in the Treatment of Posttraumatic Stress Disorder	Recruiting	PTSD	CAPS-5 | CGI | PCL-5 QIDS | SDS | WHOQOL-BSEF	University of Texas at Austin	Phase 2	120	January 15, 2020	January 5, 2023
NCT04504877	Burnout and Distress prevention with caNnabidiol in Front-line Health Care workerS deAling with COVID 19	Recruiting	COVID-19/Burn Out/PTSD	aMBI-HSS: Abbreviated Maslach Burnout Inventory—Human Services Survey | Post-traumatic stress disorder checklist for DSM-5 (PCL-5) | Brief measure for assessing generalized anxiety disorder: The GAD7 | PHQ-9: Patient's Health Questionnaire-9 | Change in proinflammatory cytokine concentration | No. of participants with treatment-related adverse events as assessed by CTCAE v5.0	University of Sao Paulo	Phase 2/Phase 3	102	June 16, 2020	September 2020
NCT04267679	Cannabidiol for Anxiety	Not yet recruiting	Anxiety	Generalized Anxiety Disorder 7-item scale | Perception of change | Protocol Compliance | Sleep quality	CB_2 Insights/Green Lotus Hemp	Phase 2	100	January 10, 2020	January 2, 2021
NCT04286594	A Clinical Trial of a Hemp-Derived Cannabidiol Product for Anxiety	Not yet recruiting	Anxiety	Change from Baseline in Self-Reported Anxiety as Assessed by the Beck Anxiety Inventory (BAI)	Mclean Hospital	Phase 2	75	April 1, 2020	March 2022
NCT03549819	Cannabidiol for the Treatment of Anxiety Disorders: An 8-Week Pilot Study	Not yet recruiting	Generalized Anxiety Disorder/Social Anxiety Disorder/Panic Disorder/Agoraphobia	Hamilton Anxiety Rating Scale (HAM-A) | Clinical Global Impression—Severity (CGI-S) | Clinical Global Impression—Improvement (CGI-I) | Generalized Anxiety Disorder-7 (GAD-7) | Liebowitz Social Anxiety Scale Self-Report (LSAS SR) | Panic and Agoraphobia Scale (PAS) | Quick Inventory of Depressive Symptomology (QIDS) | Sheehan Disability Scale (SDS) | World Health Organization Disability Assessment Scale (WHODAS 2.0) | Insomnia Severity Index (ISI)	McMaster University/Tilray	Phase 3	50	January 7, 2019	January 8, 2020

(*continued*)

Table 4. (Continued)

NCT no.	Title	Status	Conditions	Outcome measures	Sponsor/collaborators	Phase	*N*	Start date	Completion date
NCT04482244	RCT of CBD for Anxiety in Advanced Breast Cancer	Not yet recruiting	Advanced Breast Cancer/Anxiety CBD	Change in Anxiety Score-Visual Analog Mood Scale (VAMs) anxiety subscale | No. of Participants with Treatment-Related Adverse Events (PRO-CTCAEâ„¢) 5. | Mood Changes | Nausea Rate | Pain Rate | Pain intensity scale (PINS)	Dana-Farber Cancer Institute/Hans and Mavis Lopater Foundation	Phase 2	50	September 18, 2020	February 2023
NCT03248167	Cannabidiol as a Treatment for AUD Comorbid With PTSD	Recruiting	Alcohol Use Disorder/PTSD	No. of drinks per day | Weekly percentage of heavy drinking days | Weekly percentage of very heavy drinking days | Weekly percentage of subjects that are present and clean | Weekly percentage of days abstinent | Weekly average severity of alcohol craving | PTSD symptoms | Psychophysiological arousal-related heart rate | Psychophysiological arousal-related skin conductance | Trauma induced craving | Trauma-induced negative emotion	NYU Langone Health/National Institutes of Health (NIH)	Phase 1/Phase 2	48	September 16, 2019	August 2020
NCT02548559	Sublingual Cannabidiol for Anxiety	Recruiting	Anxiety	Change from Baseline in Self-Reported Anxiety as Assessed by the Beck Anxiety Inventory (BAI) | Change from Baseline in Anxiety Assessed by the Hamilton Anxiety Scale (HAM-A) | Change from Baseline in Self-Reported Anxiety Assessed by the State-Trait Anxiety Inventory (STAI)	Staci Gruber, PhD/Mclean Hospital	Phase 2	16	August 14, 2018	January 8, 2021
NCT04075435	Cannabidiol Solution for the Treatment of Behavioral Symptoms in Older Adults With Alzheimer's Dementia	Recruiting	Alzheimer Disease/Anxiety/ Agitation, Psychomotor	Anxiety Domain on the Neuropsychiatric Inventory-Clinician scale | Total score on the Generalized Anxiety Disorder 7 scale | Safety defined by absence of serious adverse events | Safety as defined by lack of treatment emergent cognitive impairment as measured by the Mini Mental Status Examination (MMSE) Safety defined as absence of treatment emergent delirium as measured by the Confusion Assessment Method (CAM)	Mclean Hospital/Spier Family Foundation	Early Phase 1	12	March 1, 2020	November 2021

frontline health care professionals who participate in the care of patients with COVID-19 (NCT04504877). Emerging data from these studies will establish whether there is potential for a licensed CBD product in this space.

Summary and Conclusion

Symptoms of anxiety and post-traumatic stress are going to be prevalent as a consequence of the COVID-19 pandemic, particularly in those most closely affected by the disease, and in those with pre-existing anxiety conditions. Unlike CBD, current antianxiety medications possess significant unwanted side effects, and delayed onset of action, limited efficacy in some patients, strong drug dependence, and withdrawal syndromes. Unlike THC, studies have shown that CBD lacks any rewarding effects of its own given that it fails to induce conditioned place preference or enhance the reinforcing effects of electrical brain self-stimulation.[72–74] CBD is already being evaluated as a potential treatment during the active coronavirus disease phase, and we suggest that the pre-clinical and clinical evidence base supports the hypothesis that CBD could be a novel pharmacological option for treating COVID-related anxiety disorders that merits testing through well-designed clinical trials. CBD could be more preferable compared with some of the medicines currently available with respect to its safety and side effect profile, although prescribers need to be aware of potential drug interactions with concomitant medication because of the effect of CBD on liver enzymes.

Authors' Contribution

The article was written, reviewed, and approved by S.E.O., C.W.S., and S.R.L.

Author Disclosure Statement

S.E.O. is a paid scientific advisor for Artelo Biosciences. C.W.S. and S.R.L. receive research funding from Artelo Biosciences, who have developed a CBD cocrystal for solid-state delivery. Cocrystals are defined as crystalline materials composed of two or more molecules within the same crystal lattice (FDA Guidance for Industry, 2016). The Artelo CBD cocrystal uses the coformer tetramethylpyrazine (TMP), which itself has evidence of activity in anxiety-related disorders or PTSD.[75,76]

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Abbreviations Used

$5HT_{1A}$ = serotonin 1A
AEs = adverse effects
BP = blood pressure
CB_1 = cannabinoid receptor type 1
CB_2 = cannabinoid receptor type 2
CBD = cannabidiol
CHR-P = clinical high risk for psychosis
COVID-19 = coronavirus disease-19
CYP = cytochrome P450
DA = decrease dopamine
FAAH = fatty acid amide hydrolase
FABP = fatty acid binding protein
GPR = g-protein coupled
HC = healthy controls
HR = heart rate
NAc = nucleus accumbens
OTC = over-the-counter
PCL-5 = PTSD Checklist for DSM-5
PTSD = post-traumatic stress disorder
PTSS = post-traumatic stress symptoms
RCTs = randomized controlled trials
SAEs = serious adverse effects
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SNRIs = selective noradrenaline reuptake inhibitors
SSRIs = selective serotonin reuptake inhibitors
THC = tetrahydrocannabinol
TRPM = melastatin-related transient receptor potential cation channels
TRPV1 = transient receptor potential cation channel subfamily V member
vHIPP = ventral hippocampus
WHO = World Health Organization