

CASE REPORT

Cannabidiol as a personalized treatment for anxiety: clinical cases in Mexico

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Abstract

Anxiety-related disorders are one of the most common mental health issues worldwide. Mexico has reported an increase in the prevalence of these ailments secondary to the confinement derived from the COVID-19 pandemic. Given the limitations of commonly used treatments for these disorders, a need arises to develop new pharmacological treatments for these patients. This paper has the primary objective of evaluating the efficacy and safety of cannabidiol isolate in drug compounding used as a personalized treatment in patients with anxiety

disorders through the presentation of four clinical cases.

Keywords: anxiety, cannabidiol, CBD, delta-9-tetrahydrocannabinol, endocannabinoid system, insomnia, medical cannabis.

Citation

Ortiz Rios FC, Dávila Ruiz IG, Sacal Dumani E. Cannabidiol as a personalized treatment for anxiety: clinical cases in Mexico. *Drugs in Context*. 2022;11:2022-3-2. <https://doi.org/10.7573/dic.2022-3-2>

Introduction

According to data provided by the World Health Organization (WHO) in 2015, anxiety disorders were estimated to have a 3.6% worldwide prevalence, with an estimated 7.7% prevalence in the American continent.¹ This ranks anxiety-related disorders as one of the most common mental health issues worldwide.²⁻⁴ Furthermore, the COVID-19 pandemic has had a significant impact on global mental health, with varied effects. In March 2022, the WHO published a scientific report on this regard, reporting a 25.6% worldwide increase in anxiety disorders in 2020.⁵ However, one study⁶ indicated that increases in mental health symptoms were not significant for college students, teenagers, and children, but two meta-analyses^{7,8} evaluating children and teenagers reported an anxiety prevalence of one in every five individuals, with greater symptoms in older children and teenagers, but with greater long-term effects and greater incidence in female children than those reported in male children.⁵

In Mexico, an estimated 28.6% of the adult population will suffer from some sort of mental health disorder during their lifetime, with anxiety being one of the most

prevalent ailments.² Furthermore, a 23.4% increase has been reported in the prevalence of anxiety disorders in the Mexican population secondary to the confinement and other effects derived from the COVID-19 pandemic.⁹

Anxiety is defined as an emotional state characterized by a maladaptive and excessive emotional response when faced with potentially dangerous circumstances¹⁰ and is related to the anticipation of a future worry and associated with muscle tension and evasive behaviours. Anxiety disorders differ from normal feelings of nervousness or anxiety in that they involve excessive fear or anxiety before stimuli that should not trigger these intense feelings.¹¹ These disorders include generalized anxiety disorder, panic disorder, post-traumatic stress disorder (PTSD), social anxiety disorder (or social phobia), and obsessive-compulsive disorder (OCD). Both PTSD and OCD are no longer classified as anxiety disorders but excessive anxiety is a fundamental piece in the symptomatic development of both.¹²

There are currently no laboratory or imaging tests capable of typifying or orienting the diagnosis towards anxiety disorders. Nowadays, diagnoses are performed mainly through clinical evaluation; laboratory and

imaging tests should be requested only when clinical signs of specific non-psychiatric pathologies are found. Treatment availability for these disorders varies between countries;¹³ however, evidence-based treatments for anxiety disorders generally include cognitive-behavioural therapy and medications, which can help decrease automatic negative reactivity to threatening stimuli. The selection of initial treatment should be determined considering symptom severity and presence of comorbidities and by performing an individualized risk-benefit assessment of the possible side effects of the medications prescribed.¹⁴

Current pharmacological treatments include serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, benzodiazepines, monoamine oxidase inhibitors, tricyclic antidepressants, and 5-hydroxytryptamine receptor partial agonists. These medications are usually associated with limited response rates and residual symptoms, in addition to adverse effects that may limit tolerance and adherence to treatment.¹² Psychological approaches may also be used, such as cognitive-behavioural therapy, exposure therapy and cognitive processing therapy. However, these therapies tend to be expensive and limited in some therapeutic contexts.¹⁵ The incidence of anxiety-related disorders and the limitations regarding their treatment give a high priority to the development of new pharmacological treatments for these patients.¹²

More than 150 phytocannabinoids have been discovered thus far in the *Cannabis sativa* plant,¹⁶ with delta-9-tetrahydrocannabinol and cannabidiol (CBD) being the two most abundant and studied of them all. Particularly, CBD has shown anxiolytic effects in humans and animals.¹⁷ These effects result in part from their interaction with the endocannabinoid system (ECS), which is known to be present in all vertebrates and comprises cannabinoid receptors (type 1 (CB1R) and type 2 (CB2R)), endogenous ligands known as endocannabinoids (anandamide and 2-arachidonoylglycerol), transport proteins, and enzymes involved in their synthesis and degradation. The main function of the ECS is to maintain homeostasis in the organism.¹⁸

Some of the anxiolytic effects of CBD occur when it interacts with components of the ECS, which are intimately related to emotions because of their distribution in the 'emotional' or limbic system, where they regulate synaptic neurotransmission.¹⁹ However, its effects are not limited to the ECS: this cannabinoid has demonstrated that it is able to interact with a great variety of receptors in the human body (many of which are related to anxiety modulation) as well as with endogenous and exogenous molecules. For instance, it

is known that CBD interacts with receptors both in the central and peripheral nervous systems, some of which regulate fear and anxiety. These receptors include the 5-HT_{1A} serotonin receptor, CB1R and CB2R cannabinoid receptors, and the transient receptor potential vanilloid type 1 (TRPV1).^{15,20} It is believed that the acute anxiolytic effects of CBD at low and medium doses involve the activation of 5-HT_{1A}. Whilst TRPV1 antagonism allows for the anxiolytic effects of CBD doses, higher doses of this cannabinoid involve TRPV1 agonism and accompanying angiogenic effects. Activity over TRPV1 seems to be exclusive to CBD and some other minor cannabinoids.¹⁵ CBD provides anxiolytic effects through varied mechanisms of action, some of which are exemplified in Figure 1.²¹

According to the reports by WHO, CBD has not demonstrated any potential for abuse or dependence; it is considered well tolerated and has a good safety profile.²²⁻²⁴ Furthermore, its associated psychoactive effects include reduction of anxiety and stress, with increasing evidence of the anxiolytic effects that this cannabinoid may provide.²⁵

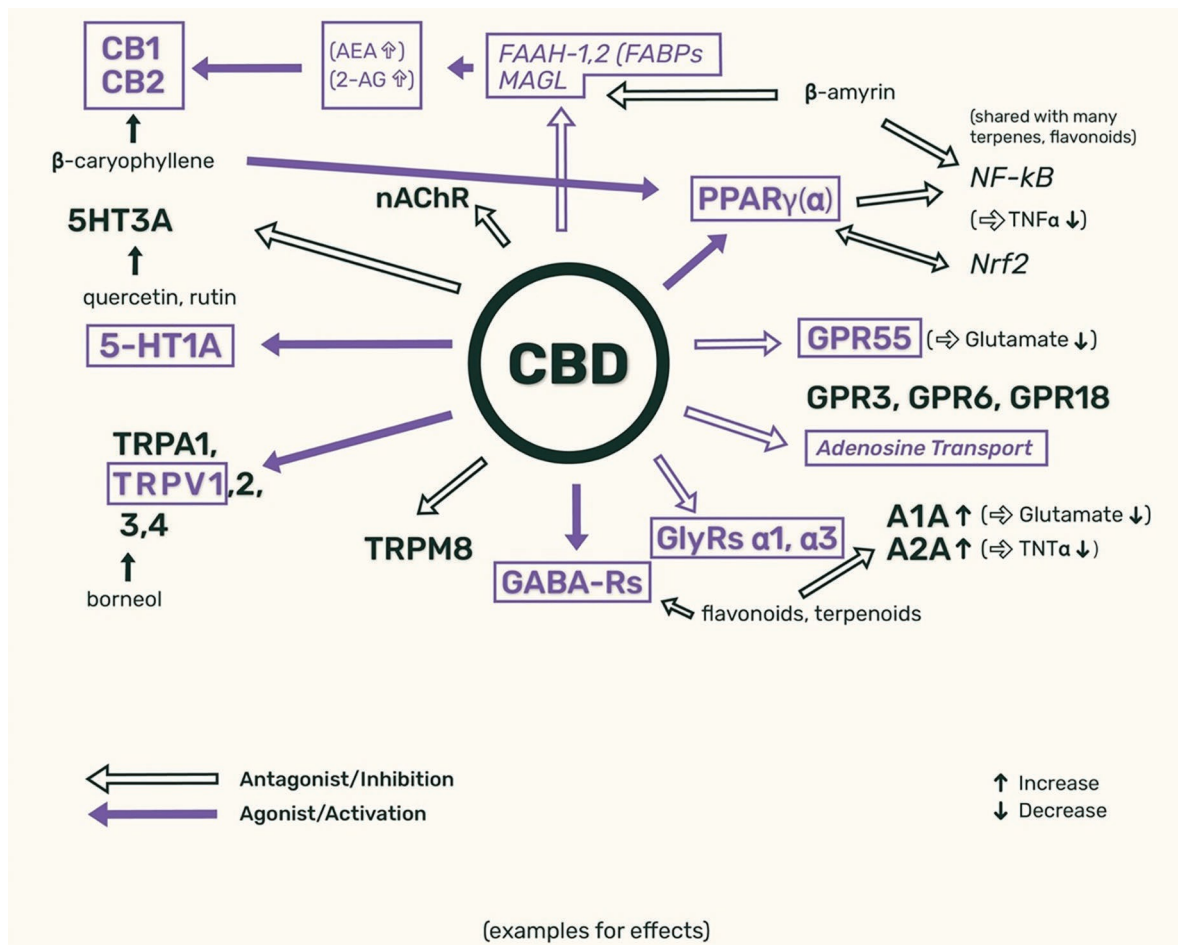
The following clinical cases are presented to provide more evidence towards this matter, with the primary objective of evaluating the efficacy and safety of CBD in drug compounding used as a personalized treatment in patients with anxiety disorders in Mexico, and with the secondary objective of showing that patients who suffer from anxiety-derived insomnia may obtain a better quality of sleep with this treatment, thus offering a new pharmacological treatment option for these patients with less reported adverse effects and little to no abuse potential.

Methods

Procedures and design

A retrospective revision of four clinical cases was performed, all of whom had previously been diagnosed with generalized anxiety disorders by psychiatrists and received conventional pharmacological treatment (as established by the Clinical Practice Guidelines²⁶). The medications prescribed provided partial relief of symptoms, but the results reported were neither optimal nor long lasting. The patients, seeking to reduce or avoid the use of psychiatric medications, decided to consult medical physicians practicing endocannabinology in order to obtain treatments with CBD-based personalized drug compounding. Personalized drug compounding means that prescription, dosing, follow-up, and results will depend on the physiological, genetic, pharmacological, and systemic characteristics of each

Figure 1. Examples of the interaction of cannabidiol (CBD) and non-cannabinoids in hemp with the endocannabinoid system. Highlighting in purple some of the interactions with anxiogenic pathways.



A1A, adenosine receptor 1A; AEA, anandamide; 2-AG, 2-arachidonoylglycerol; CB, cannabinoid receptor; FAAH, fatty acid amide hydrolase; FABP, fatty acid-binding protein; GABA-Rs, gamma aminobutyric acid receptors; GlyRs, glycine receptors; GPR, G protein-coupled receptor; GPR55, G protein-coupled receptor 55 (orphan receptor); 5-HT, 5-hydroxytryptamine receptor; MAGL, monoacylglycerol lipase; nAChR, nicotinic acetylcholine receptor; NF-kB, nuclear factor-kB; Nrf2, nuclear factor erythroid-derived 2; PPAR, peroxisome proliferator-activated receptor; TNF α , tumour necrosis factor- α ; TRP, transient receptor potential.
Adapted from ref.²¹

patient, including their individual ECS responses. These patients attended a private medical practice and were selected by medical professionals for inclusion in this article.

Four patients with psychiatric disorders were selected, all of whom were adults who had already been diagnosed with anxiety disorders causing sleep alterations. The selection process considered all current patients diagnosed with anxiety disorders, sleep disorders, or a combination of both. Diagnosis was confirmed through clinical evaluation and standardized research tools: the Hamilton Anxiety Rating Scale (HAM-A), the Pittsburgh Sleep Quality Index (PSQI), and ICD-10 diagnos-

tic guidelines for anxiety disorders, followed by initial psychological measures. These evaluations were performed monthly, during follow-up consultations. Comorbidities (psychiatric or not) were not a cause for exclusion. As a result, other medications could be administered depending on the routine follow-up for individual patients.

As this text is a brief retrospective revision of clinical cases, it does not require evaluation or approval by an Ethics Committee. Selection of these cases also depended on the patients' consent to receive CBD treatment as a supplemental therapy for at least one of these two disorders and having received at least 1 month of active

treatment with CBD. The patients were treated with CBD in addition to their regular pharmacological treatment for anxiety and received their usual medical attention. In order to protect patient data confidentiality, we have de-identified any personal patient information so that the patients' identities remain confidential and may not be ascertained in any way.

CBD dosage ranges for the treatment of anxiety disorders have been reported to be very ample and no standardized dosages currently exist.^{27,28} Dosing for this study was individually adapted to each patient based on prior research examining the safety of CBD, considering the limited evidence available on clinical trials in psychiatric populations,^{16,28-33} and following MacCallum and Russo's practical considerations;³⁴ therapy was started at a low dose between 5 and 20 mg per day, divided into two or three oral administrations per day. Afterwards, the dose was slowly increased until beneficial effects were observed in each patient without the appearance of side effects. The decision to increase CBD dosage depended on the absence of side effects and the treatment efficacy at the time of each follow-up consultation.

The active principle used was a CBD isolate with a purity of 99.7% from drug-compounding brand Botican* (Mexico), formulated into compounded drugs created individually for each patient.

Clinical cases

Case 1

Male patient, 54 years old, Mexican nationality, manager.

Background: Hereditary and familial: Diabetes mellitus type 2 and arterial hypertension.

Pathology: Psoriasis diagnosed 30 years ago under treatment with topical calcitriol. Gastroesophageal reflux disease diagnosed since May 2021 under treatment with pantoprazole 40 mg daily. The patient indicates smoking three cigarettes per week and an alcohol intake of one glass of wine daily. Colles' fracture in the right hand with no complications, currently under remission. Denies drug use and reports allergy to penicillin.

Reason for consultation: The patient reported that, starting on November 2020, he suffered periods of high stress, restlessness, difficulty concentrating, irritability, and fatigue, all of which were affecting his personal and work life.

Additionally, he had problems sleeping for the last 5 years, which was intermittently treated with bromazepam 6 mg three times a week and diphenhydramine 25 mg daily, causing oral dryness in recent months. He did not report any other symptoms and reported that he was not taking bromazepam or diphenhydramine at the time of consultation, and requested information regarding treatment with cannabinoid medicine as suggested by his treating physician.

The initial consultation focused on performing a full clinical history and follow-up as indicated in the Clinical Practice Guidelines. According to the HAM-A scores, the patient presented with moderate-to-severe anxiety and a poor sleep quality according to the PSQI. The generalized anxiety disorder diagnosis referred by the primary care physician was confirmed per diagnostic criteria of the ICD-10.

After the initial consultation, the physician focused on providing information regarding treatment, educating the patient on sleep hygiene and nutrition, and started treatment with a compounded drug: Botican* CBD isolate 1000 mg in 20 mL of olive oil (concentration 50 mg/mL, 30 drops per mL, 1.66 mg/drop), at a dose of 20 mg daily (10 mg BID) sublingually. One week later, the patient reported no change in his symptoms, and thus the dose was titrated upwards, with an increase of 1.66 mg (one drop) per day over 3 weeks reaching a dose of 60 mg/day (30 mg BID), providing weekly follow-ups as the dose was increased. One month later, during the follow-up consultation, the following laboratory tests were requested: complete blood count, 27-element metabolic panel, thyroid profile, liver profile, and urinalysis, and the results came back within normal ranges. Clinically, the patient reported improvement in falling asleep – only presenting difficulty sleeping twice in the prior 2 weeks which he attributed to an increase in his stress levels. The remaining symptoms also decreased, with the exception of a persisting lack in concentration and the inability to sleep the two aforementioned times. An increase in the concentration of his compounded drug was prescribed: CBD isolate 3000 mg in 30 mL olive oil (100 mg/mL, 30 drops per mL, 3.3 mg/drop), titrating up to a dose of 80 mg daily (26.66 mg TID). The patient was given instructions to keep daily records and send them to the physician weekly to monitor the appearance of any adverse effects. During the second month of treatment, the patient reported improvement in his quality of sleep,

*As compounded drugs are not patented, 'Botican' refers to the trademark brand under which these particular compounded drugs are sold in Mexico.

remission of the anxiety symptoms, and improvement in his daily life activities; therefore, the dose was maintained for the following 3 months. Most recently, the patient showed clinical improvement, with the HAM-A scale reporting mild anxiety and PSQI showing good sleep quality. The patient also reported improvement in his quality of sleep and life and no adverse effects whatsoever.

Case 2

Female patient, 45 years old, Mexican nationality, office worker.

Background: Hereditary and familial: Diabetes mellitus type 2 from both her maternal and paternal sides. Maternal and paternal grandmothers deceased with a history of breast cancer, father with colon cancer diagnosis, mother with hypertension controlled under treatment.

Pathology: Atopic dermatitis diagnosed in 2013, treatment with topical desonide only during worsening periods. In 2014, she started presenting symptoms of anxiety, reporting difficulty falling asleep, periods of 'depression', work and personal problems, anger, and sadness, for which she visited her primary care physician. She was diagnosed with generalized anxiety disorder and was prescribed citalopram 10 mg SID nightly and continued with that same treatment upon consultation. She reported a diagnosis of hypothyroidism since December 2020 under treatment with levothyroxine 50 µg on an empty stomach from Monday through Friday. She had a cholecystectomy in 2018 with no complications and a history of two C-sections with no complications 9 and 7 years ago. Sprained ankles on two occasions (second degree left and first degree right). Left ankle fracture in July 2021. Denied allergies, smoking, drinking alcohol, and drug use.

Reason for consultation: The patient reported that, starting on January 2021, her anxiety symptoms worsened, reported difficulty falling asleep, emotional instability, difficulty concentrating, and periods of anger, sadness, and guilt. Furthermore, she suffered from atopic dermatitis on the hands with signs of reddening, rash, and inflammation of the area. She continued taking her citalopram treatment at 10 mg daily, with no improvement. Therefore, she sought therapeutical alternatives with CBD-based drug compounding.

The initial consultation focused on performing a full clinical history and follow-up per Clinical Practice Guidelines. The HAM-A scale reported moderate-to-severe anxiety, PSQI reported poor quality of sleep, and ICD-10 diagnostic criteria confirmed a

generalized anxiety disorder diagnosis. Additionally, the patient was provided with information regarding treatment, educating her on lifestyle changes, recommending psychological treatment, and a prescription of a compounded drug: Botican* CBD isolate 1000 mg in 20 mL of olive oil (50 mg/mL, 1.66 mg/drop) at a dose of 10 mg daily (3.33 mg TID) sublingually. One month later, laboratory tests were requested (CBC, 27-element metabolic panel, thyroid profile, liver profile, and urinalysis), with results within normal ranges. Clinically, the patient reported an improvement in falling asleep, decreased dermatitis symptoms, and less emotional reactivity as well as having started cognitive-behavioural therapy. Her prescription was refilled with the same formula, and the 10 mg/day dose was maintained. During the second month, the patient reported feeling clinically stable but again having difficulty sleeping; therefore, a new prescription was issued for CBD isolate 2000 mg in 20 mL olive oil (100 mg/mL, 3.3 mg/drop) titrating an additional 3.3 mg per day up to a dose of 26.6 mg daily (13.3 mg BID). In the third month, the patient reported improvement, and the dose was maintained and only the carrier oil was changed (CBD isolate 2000 mg in 20 mL grapeseed oil) per the patient's request. A clinical follow-up evaluation was performed 3 months later, where the patient reported ongoing anxiety symptoms, and therefore the dosage was increased with a new prescription: CBD isolate 3000 mg in 30 mL olive oil (100 mg/mL), with a daily increase of 3.33 mg until a dose of 33.3 mg/day was reached, divided into 13.3 mg in the morning and 20 mg at night. The patient was still under treatment with citalopram 10 mg daily, CBD 33.3 mg daily, and cognitive-behavioural therapy at the time of writing this manuscript. The patient reported no symptoms; she was easily able to fall asleep and concentrate and showed no signs of emotional instability or dermatitis on the hands. The HAM-A scale reported absence or remission of the disorder, and PSQI showed good quality of sleep. She described herself to be in better health, with positive changes in her quality of sleep and life, and reported no adverse effects thus far.

Case 3

Male patient, 49 years old, Mexican nationality, attorney.

Background: Hereditary and familial: mother with obesity and cancer.

Pathology: Rosacea since childhood, which worsens with wine intake and with intense exercise; appendectomy in August 2020, reported a diagnosis of depression and anxiety provided by a mental health specialist 2 years prior after one panic attack, and has been under

treatment with vortioxetine at 10 mg daily, vitamin D 2000 UI daily, vitamin E 5000 UI daily, and vitamin C 500 mg daily ever since. The patient reported an alcohol intake of two glasses of wine twice per week. He denies allergies, smoking, and any other drug use.

Reason for consultation: He stated, "I am not a person who enjoys sleeping." Since 2018, he wakes up two to three times every night, taking up to an hour to fall back asleep, with too many thoughts in his head. He had difficulty concentrating and was easily distracted, in addition to feeling constantly stressed and anxious, and reported low libido. He reported that vortioxetine made him feel sleepy in the mornings but still woke up during the night, and therefore he requested help because he no longer wishes to take the medication (vortioxetine).

The reported diagnosis was confirmed using the HAM-A scale, indicating mild-to-moderate anxiety. The PSQI reported poor quality of sleep, and ICD-10 diagnostic criteria for generalized anxiety disorder and chronic insomnia also confirmed the diagnoses.

The initial consultation focused on sleep hygiene; as the patient reported wanting to suspend vortioxetine abruptly, a gradual weaning off the vortioxetine was suggested instead, to avoid secondary effects from sudden suspension. The proposed weaning plan was as follows:

- Week 1: Vortioxetine 7.5 mg
- Week 2: Vortioxetine 5 mg
- Week 3: Vortioxetine 2.5 mg
- Week 4: Vortioxetine 2.5 mg alternating one day with treatment and one day without.
- Week 5: Suspend vortioxetine

At the same consultation, treatment was started with a compounded drug formula, Botican* CBD isolate 1500 mg in 30 mL of olive oil (50 mg/mL) at a dose of 25 mg/day sublingually BID (8.3 mg in the morning and 16.6 mg at night), in addition to magnesium glycinate 400 mg at night. Requested laboratory tests: complete blood panel, metabolic panel, fasting insulin, 25 hydroxyvitamin D3 levels, and saliva cortisol.

One month later, after just having suspended the vortioxetine, he returned to consultation with his laboratory test results, with the following out of ranges: glucose (68 mg/dL), flattened saliva cortisol curve, and a low cortisol response upon waking. Clinically, the patient reported a significant improvement in his sleep quality but the anxiety symptoms continued; therefore, vortioxetine was suspended completely and the CBD dose was increased to 33.3 mg/day TID (6.6, 10, and 16.6 mg). The patient was

told to call his physician every other day during the first week of treatment. On his third consultation, after one month of treatment, he was no longer taking vortioxetine but was still taking CBD and reporting good quality of sleep, without waking up, with no significant manifestations of anxiety, with a balanced emotional state, and with no adverse effects. The HAM-A scale reported mild anxiety, whilst the PSQI reported good quality of sleep.

Case 4

Female patient, 35 years old, Mexican nationality, photographer.

Background: No significant hereditary or familial background.

Pathology: Septoplasty at age 20, appendectomy at age 28. The patient indicated an alcohol intake of two glasses of wine twice a week, denied other medical diagnoses, smoking, or drug use. She is allergic to benzocaine and paraphenylenediamine.

Reason for consultation: Anxiety during the nights, increasing after an earthquake. She reported thinking that "it will happen again at any time" and a series of catastrophic thoughts about her family's health. She also reported an occasional sensation of heat and breathlessness not associated with skin coloration or decreased oxygen saturation, sensation of sadness, low energy, lack of motivation, poor concentration, and difficulty paying attention. She took small naps during the day. She reported she has always been anxious and was under treatment with sertraline 50 mg before, which she restarted in July 2021 but suspended suddenly in October 2021 due to a lack of results. She suffered from recurring migraines starting 15 years ago and happening at least once a year, which worsened in May 2020: 'flashing lights' trigger the episodes. She was under treatment with sumatriptan 50 mg when she had a migraine episode. Additionally, she had low libido and problems falling asleep, for which she is taking melatonin 3 mg sublingually before bedtime, but reported not to be taking them at the time of consultation.

The patient was evaluated using the HAM-A and PSQI scales, showing mild-to-moderate anxiety and poor quality of sleep, respectively. Additionally, ICD-10 diagnostic guidelines for anxiety disorders confirmed a diagnosis of generalized anxiety disorder.

The initial consultation focused on providing the patient with general information regarding treatment. A compounded drug was prescribed: Botican* CBD isolate 1500 mg in 30 mL of olive oil (50 mg/mL), at a dose

of 20 mg daily, divided 6.6 mg in the morning and 13.3 mg at night with symptom reporting every other day for the first 2 weeks, and nutritional supplementation with two capsules before bedtime, consisting of a mixture of 5-hydroxytryptophan 100 mg, glycine 500 mg, tryptophan 400 mg, chamomile (*Matricaria chamomilla*) 200 mg, lemon balm (*Melissa officinalis* L.) 200 mg, vitamin B6 20 mg, and magnesium glycinate 400 mg at night. The following laboratory tests were requested: complete blood panel, 27-element metabolic panel, homocysteine, folic acid and B12 levels, morning cortisol, and DHEA-s. One month later, the patient returned with her laboratory tests, with the following results outside of normal ranges: cholesterol (226 mg/dL), LDL (137 mg/dL), cortisol (11.3 µg/dL). Clinically, the patient reported, "I have been feeling very well." She reported a slight energy deficiency but the treatment and dosage were maintained.

Three months later, a follow-up evaluation was performed, and the patient was found to be clinically stable, with a HAM-A scale reporting absence or remission of the disorder and a PSQI reporting good quality of sleep. The patient self-reported: feeling well and 'balanced', sleeping adequately (8 hours with no awakening), no new migraine episodes, with a significant decrease in her anxiety levels and not reporting any adverse effects from the CBD treatment.

Discussion

This case report describes the treatment of four patients aged between 24 and 54 years old diagnosed with anxiety disorders and insomnia, who had not previously responded well to conventional treatment with cognitive-behavioural therapy or antidepressant medications and whose symptoms related to these two disorders were mitigated by the use of CBD in addition to conventional treatment.

Diverse studies have repeatedly shown the prevalence of sleep alterations caused by anxiety after a traumatic experience,^{19,35} and even though the patients mentioned in these clinical cases did not experience a particular traumatic event, all of them were diagnosed with an anxiety disorder which in turn caused a sleep disorder. The main finding when evaluating these clinical cases is that the CBD isolate in a personalized formula (compounded drug) was an effective and safe pharmacological compound that reduced anxiety and its secondary insomnia in these patients. Despite dose adjustments, results continued to be consistent in all four cases presented.

CBD treatment duration and dosages for anxiety and psychotic symptoms are not currently clear.²⁸ In the cas-

es presented here, treatment was started at a minimal dosage and was gradually adjusted upwards as needed by each individual patient. The final doses used in these patients (20–80 mg/day) were much lower than those reported in published clinical case reports that treated patients with some anxiety-related disorders (25–800 mg/day),^{19,28–31} and despite these doses not being the lowest reported in all clinical trials published regarding anxiety, they were indeed lower than most doses reported in several clinical trials (15–900 mg).^{10,32,33,35–38} This could be due to several variables, such as the concomitant use of cognitive therapies (Case 2), routine psychiatric medication (Cases 2 and 3), the use of nutritional supplements (Cases 3 and 4), and the dosage adjustment performed in all four cases until the observation of beneficial effects in each individual patient (Table 1), whilst most clinical studies have previously used a single CBD dosage and did not include support from other therapies or medications. This could point towards the importance of an integrative approach to treatment so that these patients can observe better results.

The available experimental evidence has demonstrated that CBD is capable of antagonizing CB1/CB2 receptor agonists^{17,39–42} even despite its low affinity for these receptors and at reasonably low concentrations. Although this was originally proposed in some research, other studies have identified the pharmacological promiscuity of CBD, which makes it premature to draw solid conclusions regarding all the mechanisms of action of this cannabinoid.⁴³

The role that cannabinoids play in anxiety is highly debated. Exogenous cannabinoids show both anxiolytic and anxiogenic properties. One possible explanation for this bidirectional effect is its dependence on the dose administered (for instance, high doses of synthetic cannabinoids are anxiogenic, whilst low doses are anxiolytic).⁴⁴ The clinical cases presented in this review reported significant improvements both in their anxiety symptoms and their sleep problems once CBD treatment was started when compared to prior psychiatric treatments alone, which could be partly related to the low doses used (a maximum of 80 mg/day), agreeing with Luchicchi and Pistis' theory⁴⁴ (which proposes this bidirectional effect is directly related to the dose administered). However, it does not coincide with Zuardi et al.'s study,³⁷ which demonstrated that a dose of 300 mg of CBD decreased subjective anxiety but doses of 100 and 900 mg did not provide anxiolytic effects. These differences between published reports highlight the need for more clinical studies in patients with anxiety disorders that include a larger number of participants and use cognitive therapies together with psychiatric drugs in addition

Table 1. Concomitant treatments and cannabidiol dosage (initial and final) per patient.

Case no.	Medication and dose	Supplement and dose	Cognitive therapy	Cannabidiol dose (mg/day)	
				Initial	Final
1	Topical calcitriol Pantoprazole 40 mg/d	–	–	20	80
2	Citalopram 10 mg/d Levothyroxine 50 µg (Mon–Fri)	–	+	10	33.3
3	Vortioxetine Initial: 7.5 mg/d Final: 0 mg/d (weaning over 4 weeks)	Vitamin C 500 mg/d Vitamin D 2000 IU/d Vitamin E 5000 IU/d Magnesium glycinate 400 mg/d	–	25	33.3
4	Sumatriptan 50 mg	5-Hydroxytryptophan 100 mg/d Glycine 500 mg/d Tryptophan 400 mg/d Chamomile (<i>Matricaria chamomilla</i>) 200 mg/d Lemon balm (<i>Melissa officinalis</i> L.) 200 mg/d Vitamin B6 20 mg/d Magnesium glycinate 400 mg/d	–	20	20

+, presence of concomitant therapy; –, absence of concomitant treatment.

to CBD in order to better evaluate the effects of integrative conventional treatments when combined with this cannabinoid.

The anxiolytic effects of CBD have been observed in animal models for generalized anxiety disorder, social phobias, panic disorders, OCD, and PTSD^{12,15,17,45} as well as in people with generalized social anxiety disorder, PTSD, patients with psychiatric and anxiety disorders and trouble sleeping, patients in drug withdrawal and problematic cannabis consumption, finding a reduction of associated symptoms, and effectively treating anxiety disorders.^{45,46}

In 2016, Shannon et al.¹⁹ evaluated the effectiveness of CBD oil to treat anxiety and insomnia derived from PTSD in a female paediatric patient, noting that CBD was safe at the dose used (25 mg/day + 6–12 mg twice or thrice weekly) during the treatment period (6 months). It helped decrease the patient's anxiety and improved her quality of sleep. Similar to the approach herein, where some patients continued their conventional psychiatric treatments supported with nutritional supplements in addition to CBD to decrease anxiety symptoms and insomnia, the patient treated by Shannon et al.¹⁹ continued to take 25 mg of diphenhydramine at night and a fish oil nutritional supplement (750 mg/day) after starting CBD treatment and eventually managed

to suspend diphenhydramine. The final treatment goal in this particular case report was to gradually decrease the use of CBD, so the patient could eventually stop taking medication and redirect treatment to physical activities that help maintain her anxiety in non-pathological levels, improving her quality and quantity of sleep as well.

CBD has also demonstrated increasing cannabinoid receptor activation indirectly by elevating endocannabinoid levels through its action over endocannabinoid metabolism, such as slowing down breakdown of anandamide by fatty acid amide hydrolase (Figure 1).^{15,20} It is possible that the anxiolytic effects of CBD are partly related to its interaction with the fatty acid amide hydrolase, inhibiting its activity and thus diminishing its degradation of the endocannabinoid anandamide in the brain.^{17,39} Therefore, CBD would indirectly increase CB1R activation because anandamide would be more readily available to bind to these receptors, providing anxiolytic effects. It is believed that CB1R activation mediates the processing of long-term fear learning.^{47,48} This receptor is widely distributed in the central nervous system, with expression occurring mainly in areas closely related to emotion regulation such as the prefrontal cortex, hippocampus, amygdala, basal ganglia, striate nucleus, adrenergic ganglion cells of the mesencephalon, and cerebellum.^{18,49} This receptor is

also expressed in GABAergic, glutamatergic, serotonergic, and noradrenergic axon terminals. Therefore, its activation inhibits neurotransmitter release by temporarily or permanently modulating synaptic transmission. Additionally, CB1R activation produces anxiolytic and antidepressant effects as well as potentiating the effects of classic antidepressants.¹⁸ Endocannabinoid signalling is a part of an endogenous anxiolytic neuromodulating system; therefore, inhibiting fatty acid amide hydrolase activity is a potentially promising therapeutic approach to reduce symptoms related to anxiety,^{12,15,20} suggesting that the ECS plays an important role in modulating anxiety and depression.^{47,48}

A recent 2021 study by Laczkovics et al.³¹ presented the case of a 17-year-old male patient with severe depression, social phobia, narcissistic personality disorder, and multiple substance abuse. After a failed treatment with antidepressants, this patient received CBD capsules starting at a dose of 100 mg/day and increasing the dosage over 8 weeks up to a dose of 600 mg/day. After CBD treatment and suspension of antidepressant medication, the patient showed improvement in his anxiety and depression symptoms, including simple phobias and symptoms of paranoia and dissociation. In addition, the patient stopped abusing illegal drugs without showing abstinence symptoms, showing that CBD may work both as a supplemental treatment as well as a substitute treatment for patients who are refractory or show low responses to conventional medication, possibly avoiding abstinence syndrome, without involving additional risks for the patient if appropriate follow-up is performed. This coincides with Case 3 presented herein, who requested a gradual weaning off vortioxetine without presenting adverse effects from medication weaning or CBD use and presenting improvement of his anxiety and insomnia symptoms.

In order to determine if CBD helps improve sleep and/or anxiety in a clinical population, in 2019, Shannon et al. performed a retrospective evaluation of a wide range of cases²⁹ ($n=72$), belonging to a psychiatric clinic, which involved the administration of CBD as a complement to conventional treatment to improve symptoms of anxiety and sleep problems in these patients. The study noted that, during the first month of treatment, anxiety levels decreased in 79.2% of the patients and that these remained decreased for the duration of treatment. Concordantly, in our study, the four patients performed a self-assessment and reported noticing an improvement even from the first month of treatment, which correlated to HAM-A and PSQI scores obtained in their monthly follow-ups, even when three of the patients required further increases to their doses

due to some ongoing anxiety symptoms. Regarding sleep evaluation in the Shannon et al.²⁹ study, sleep scores improved during the first month for 66.7% of patients, though these fluctuated through time. Our study parallels those results, with four patients reporting improvements during the first month but with variations reported in their sleep patterns that were always associated with anxiety-causing events in their lives, leading to sleep problems. Lastly, Shannon et al.²⁹ reported that CBD was well tolerated by most of the patients, with some reporting fatigue as the main adverse effect. Our clinical cases showed that CBD treatment was well tolerated and no adverse effects were reported. This may be due to the sample sizes, ours only consisting of four patients whilst the retrospective evaluation involved a significantly larger number, which accounts for a larger data sample with greater variability between participants.

According to the report by Moltke and Hindocha in 2021,²³ a significant number of people using CBD do so to treat mental health problems such as anxiety, stress, and problems sleeping. As it can be seen from the clinical cases reported in this text and similarly to the results obtained by Shannon et al.,²⁹ there is a significant degree of comorbidity of sleep alterations and mood disorders (such as depression and anxiety).⁴⁷

In 2019, Klier et al.⁵⁰ published the case study of a 14-year-old female patient diagnosed with Crohn's disease and several phobias, including social phobia. Considering that the minor's guardian had already started CBD treatment on her own, and both mother and daughter refused treatment with selective serotonin reuptake inhibitors, an alternate CBD treatment was proposed for this case. It involved a starting dose of 100 mg/day of CBD, increasing the dose gradually over 19 weeks up to 600 mg/day, achieving a significant clinical improvement, which despite not managing to eliminate the anxiety disorder, did decrease symptoms related to her phobias. This case highlights the problems caused by CBD popularity, which has led to patients, or their guardians, starting treatment without medical guidance or supervision. The patients reviewed in our study did not start CBD therapy on their own, but they were actively seeking physicians who would work with this cannabinoid as a supplemental therapy or as a substitute for conventional medications. Most commonly, patients seek cannabis as a substitute for conventional drugs when they feel these have not provided enough relief to their symptoms when they cause significant side-effects or both. Such is the situation of Case 3, where the patient wanted to stop using vortioxetine against medical advice and wanted to stop abruptly, but once a weaning plan was

devised and CBD treatment was implemented, the patient reported a significant reduction in his anxiety levels.

In patients suffering from insomnia, pioneer studies⁴⁷ with CBD (160 mg/day) indicated that it increases the total sleep time and decreases frequent waking during the night. Interestingly, low doses of CBD increase wakefulness.⁴⁷ However, the cases presented here showed good results over insomnia even when much lower doses than those suggested for treating it were used, which could suggest that the positive effects of CBD over the quality of sleep in these patients were not due to the CBD dose administered but instead due to its effects over anxiety, the primary diagnosis in these patients. It is important to note that, in at least two of these patients, a larger CBD dose at night resulted in beneficial effects over their sleep issues. A few reports have been published regarding CBD treatment for anxiety and sleep disorders presenting together with other ailments. Tartaglia et al.³⁰ presented three clinical cases of patients diagnosed with Fragile X syndrome treated with oral CBD, using doses between 32 and 63.9 mg/day. All three patients showed improvement during treatment with CBD, including significant reduction in social avoidance and anxiety, as well as improvements in sleep, feeding, motor coordination, and speech skills, etc. Two patients showed a reappearance of symptoms (such as anxiety) after CBD treatment was interrupted but improved again once CBD was restarted. Despite our presented patients not sharing the Fragile X syndrome diagnosis, similar symptoms such as anxiety and insomnia improved, with CBD treatment with no adverse effects reported.

In the past few years, the effects of CBD have been studied in illnesses associated with sleep disorders such as anxiety. According to the summarized sleep disorder classification proposed by Monti et al.,⁴⁷ all of the patients presented here would be classified into sleep disorders linked with mental, neurological, or other medical disturbances. Given the positive results obtained after CBD administration in different health conditions, this poses a plausible proposition to explore the medical benefits of CBD on sleep alterations,⁴⁷ particularly in those directly related to anxiety disorders.

Study limitations

The results seen in this study must be carefully interpreted because the sample size is very small, the patients have individual characteristics and personalized treatments that differ from one another, and this is a clinical case review with no control group to compare against. Simultaneous to CBD administration, several of our patients used a combination of

concomitant psychiatric medications, nutritional supplements, and/or other mental health services such as cognitive-behavioural therapy as would happen with routine clinical attention, which limits our ability to correlate causality directly to CBD treatment alone. This is both a limitation and a strength because very few publications have approached this population type and integrative approach. It is important to note that other researchers have pointed out the influence of the placebo effect in patients using cannabinoids and medical cannabis, a key factor in the anxiolytic effects provided by CBD.⁵⁰ Additionally, some of the patients evaluated expressed their desire to reduce, avoid, or suspend the use of psychiatric medications, which could contribute to a greater placebo effect or additional bias. A longer study duration could help diminish this concern in future studies. Additionally, further research could explore the possible selection bias involved in this treatment option. Nonetheless, the results reported here show a tendency towards clinical relief of anxiety and insomnia symptoms when starting treatment with CBD in addition to integrative therapy.

Conclusions

Considering the results observed in the reported cases, it can be concluded that the personalized prescription of CBD can be a treatment option with a wide range of safety and efficacy and, when paired together with cognitive therapies, may aid in reducing anxiety and its related symptoms (such as insomnia), helping to improve patients' quality of life and allowing them to better interact with their environments. Moreover, no adverse effects were observed or reported, whether CBD was administered as a single-drug pharmacological therapy or when used in combination with other drugs, and some patients even showed improvement in other concomitant illnesses. Therefore, the results found in this study add to the existing clinical evidence that supports the safety of CBD use (as long as it is pharmaceutical grade and legally sourced) and suggest that it may be useful for patients with refractory anxiety or low response rates to conventional treatments.

Nonetheless, it is recommended to continue research with randomized and controlled groups of patients with more diverse diagnoses of anxiety disorders in order to determine whether this cannabinoid has any beneficial effects for these ailments as well as to determine the safety and efficacy of long-term CBD treatment. The effects of CBD over sleep modulation still require more research under different experimental designs such as sleep alteration models.

Contributions: FCOR was in charge of the bibliographic research, writing of the original manuscript in Spanish, and formatting of the clinical cases; IGDR provided additional support for the above. IGDR and ESD provided the information, medications, and dosages about the clinical cases. IGDR was responsible for clinical cases 1 and 2, whilst 3 and 4 were the responsibility of ESD. All authors reviewed and contributed to subsequent and final drafts of the manuscript in Spanish and English. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: FCOR and IGDR are remunerated employees at ICAN, an enterprise that owns the compounding pharmacies that formulate Botican brand medications; they both declare not having received any payment or compensation for their participation in this study and having no conflict of interest. ESD declares no conflict of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: <https://www.drugsincontext.com/wp-content/uploads/2022/08/dic.2022-3-2-COI.pdf>

Acknowledgements: Carlos Flores helped with reviewing the original manuscript in Spanish. Mish Castillo reviewed the original manuscript in Spanish and was in charge of the English translation and medical writing, as well as its subsequent review alongside the authors. Zaira Orozco was in charge of adapting the CBD interaction chart (Figure 1).

Funding declaration: There was no funding associated with the preparation of this article. The research did not require funding, it took place in a private practice in Mexico City, Mexico.

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Article URL: <https://www.drugsincontext.com/cannabidiol-as-a-personalized-treatment-for-anxiety-clinical-cases-in-mexico>

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Provenance: Invited; externally peer reviewed.

Submitted: 9 March 2022; **Accepted:** 26 July 2022; **Published:** 19 September 2022.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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