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A Comparative Review of Cannabis-Based Medication and First-Line Pharmacotherapy Treatments for Anxiety Disorders

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A B S T R A C T

Cannabis, with its constituents phytocannabinoids, has been subject of interest in the management of several CNS disorders, particularly conditions related to anxiety. Cannabis is often investigated for two compounds: 9-tetrahydrocannabinol (THC), which is noted as the prime constituent associated for the plant's psychoactive effects; and Cannabidiol (CBD), which is the plant's principal non-psychotomimetic constituent. Findings from studies gathered on different chronic and debilitating anxiety disorder conditions, including Generalized Anxiety Disorder (GAD), Post-traumatic Stress Disorder (PTSD), Obsessive-compulsive Disorder (OCD), Social Anxiety Disorder (SAD), and Panic Disorder (PD), were reviewed with an emphasis to determine and compare the potential benefits of Cannabis-based medications on anxiety disorders over its current first-line pharmacotherapy treatments. The evidence indicates that cannabis-based medicine appears to be beneficial also in the treatment of anxiety disorders as compared to current first-line treatment. There are cases which showed that patients do not react to first-line medications, however cannabis-based medicine can generate anxiolytic outcomes and considerably improve the therapy of those individuals. The study provides an overview of the existing database, which also encompasses current advances in human clinical applications and possible treatments.

Keywords: Phytocannabinoids, Cannabidiols, CBD, Anxiety disorders, SSRI, SNRI

1. Introduction

Anxiety is one of the adaptive responses that is necessary for dealing with threats to one's wellbeing [1]. Anxiety disorders encompass a wide range of chronic, debilitating conditions representing the world's most prevalent mental illnesses [2]. Anxiety affects an estimated 264 million individuals worldwide [3]. The incidence of any anxiety disorder was similar across all age categories, however it is more widespread in females than in males [4].

There are a variety of currently available pharmacological and synthetic treatments in treating anxiety disorders however, most of the first line pharmacotherapy treatments of anxiety disorders are serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI). Medications for anxiety are typically safe and effective, and it is frequently used in combination with therapy. Moreover, medication treatment can be short-term or long-term, depending on the extent of symptoms and underlying medical conditions [5]. Due to the limitations of current treatments, there is a continuous discovery and development of new therapeutics for anxiety disorders.

Moreover, cannabis-based medications have recently been thoroughly investigated for its efficacy, safety, and risk on the treatment or alleviation of anxiety disorders. Cannabis belongs to the plant family Cannabaceae, and it is likely the world's oldest medicine [6-[7]. Cannabinoids present in the cannabis plant are called phytocannabinoids [8]. Among the 11 cannabinoid subclasses, Δ9-tetrahydrocannabinol (THC) is the main psychotropic constituent of the plant [9]. Additionally, Cannabidiol (CBD), a non-psychotropic compound with partially antagonistic effects, is another cannabinoid of current interest [10]. CBD has a wide spectrum of activities that are relevant to a number of symptoms; these effects include panicolytic and anti-anxiety effects, reduction of conditioned fear expression, and increased fear extinction [1]. Both THC and CBD interact differently with the endocannabinoid (ECB) system [9]. Cannabinoid receptors, endogenous cannabinoids, and enzymes make up the ECB system. This system is considered to be a crucial regulatory mechanism involved in major pathophysiological aspects of a person [11-13]. The proper interaction of all the components of this system is essential in the development of the central nervous system (CNS), motor control, stress, synaptic plasticity, and emotional responses [10].

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Cannabis-based medications have sparked interest as a possible anxiolytic treatment in recent years. The article aims to evaluate the effects of cannabis-based drugs on anxiety disorders in comparison to existing first-line pharmacotherapy treatment. It intends to provide an overview of the existing database regarding current breakthroughs in human clinical trials and possible therapies.

2. Methods

This article review uses MEDLINE (PubMed), ResearchGate and Google Scholar databases to recover systematic reviews and clinical trials on the efficiency and safety of cannabis-based medications and first-line pharmacotherapy for anxiety disorders. The researchers assessed the titles and abstracts of articles discovered using search algorithms to determine their suitability for this article's inclusion criteria. The review was done comprehensively to present the potential benefits of cannabis-based medication over first-line pharmacotherapy for anxiety disorders.

3. Pathogenesis of Anxiety Disorders

The development of anxiety disorders involves intricate connections amongst psychological mechanisms, biological variables, and environmental effects [14]. The primary CNS regulators of anxiety disorder symptoms are serotonin, norepinephrine, gamma-aminobutyric acid (GABA), and dopamine [15]. The amygdala in the brain is important for managing fear and anxiety. Anxiety disorder patients frequently have a heightened amygdala reaction to stressors. The prefrontal cortex is linked to the amygdala and other limbic system components. Moreover, amygdala's hyperresponsiveness may be linked with lower activation thresholds when responding to perceived social danger [16]. Many anxiety disorders are heavily influenced by genetic factors. However, the Mendelian method of inheritance is not applicable in anxiety disorders, but it has a complex-genetic pattern of anxiety feature inheritance that involves an interplay of several susceptibility genes with minor specific effects along with environmental influences [17]. Furthermore, external conditions like early childhood trauma and stress can raise the risk of having anxiety disorders in the later age [18]. The pathogenesis of anxiety disorders is presented in Figure 1 [19].

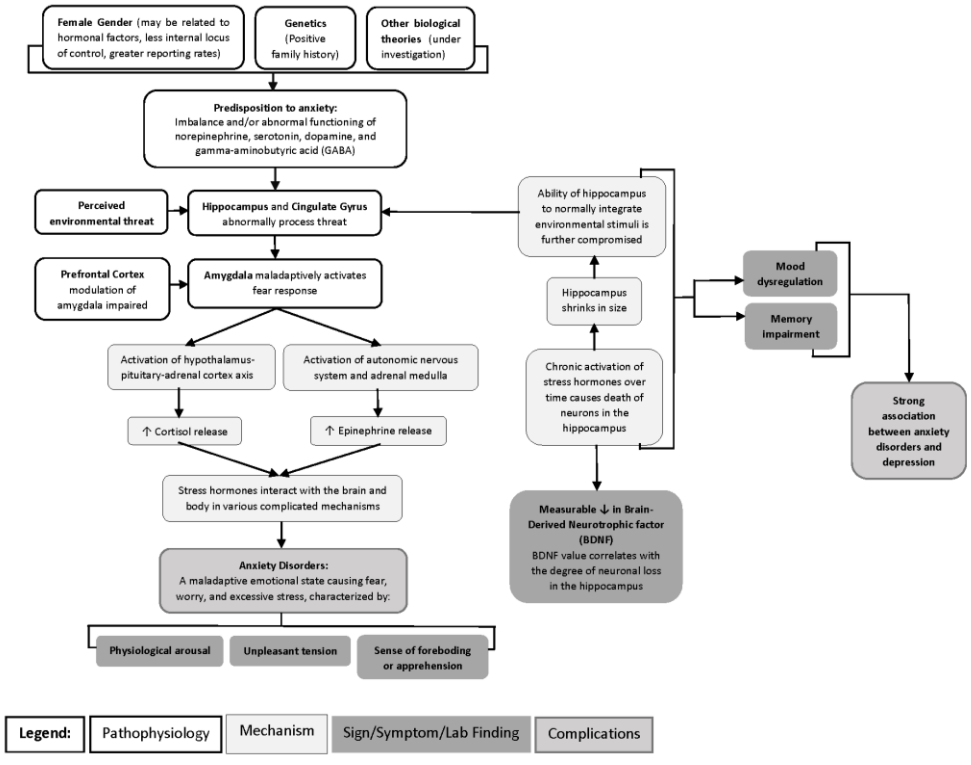

Fig. 1 - Pathogenesis of Anxiety Disorders. Adopted from Yu (2013) [19]

4. Cannabis-based Medication and First-line Pharmacotherapy Treatment Pharmacology Relevant to Anxiety Disorders

4.1.Endocannabinoids (ECB) and Phytocannabinoids Pharmacology

The ECB system is a multidimensional system that has a function in maintaining the human body's homeostasis [22]. One component of the ECB system is the endogenous cannabinoid or endocannabinoids (ECB) such as 2-arachidonoylglycerol (2-AG) and anandamide (AEA) [10-12]. There are several ECBs that are known to have an effect in the ECB system, but the primary ECBs are 2-AG and AEA [22]. ECBs and their receptors are located in all parts of the human body, particularly in the nervous system, internal organs, connective tissues, and immunological cells [20]. ECBs attach to G-protein coupled receptors including CB1 and CB2 cannabinoid receptors to induce its effect [7]. The primary method through which ECBs influence synaptic function is retrograde signaling, in which ECBs (2-AG and AEA) generated by postsynaptic neuron depolarization activates presynaptic CB1 receptors, which leads to the inhibition of neurotransmitter release [23]. CB1 receptors are numerous in both peripheral and central nervous systems, and they are also found in both GABAergic neurons and glutamatergic neurons [7,15]. CB1 receptor activation has anxiolytic benefits in numerous unconditioned fear models, which are related to a variety of anxiety disorder symptoms [24].

Both CBD and THC are constituents of cannabis that have the ability to imitate the activity of ECB [22]. These phytocannabinoids, particularly CBD, have a diverse pharmacological profile that includes interactions with receptors such as CB1 receptor, serotonin 5-HT1A receptor, and transient receptor potential vanilloid type 1 (TRPV1) receptor, which have been recognized to influence fear and anxiety-related responses [1]. These phytocannabinoids are recognized by the body as endocannabinoids since cannabis can function as a mass stimulation to the ECB system [22].

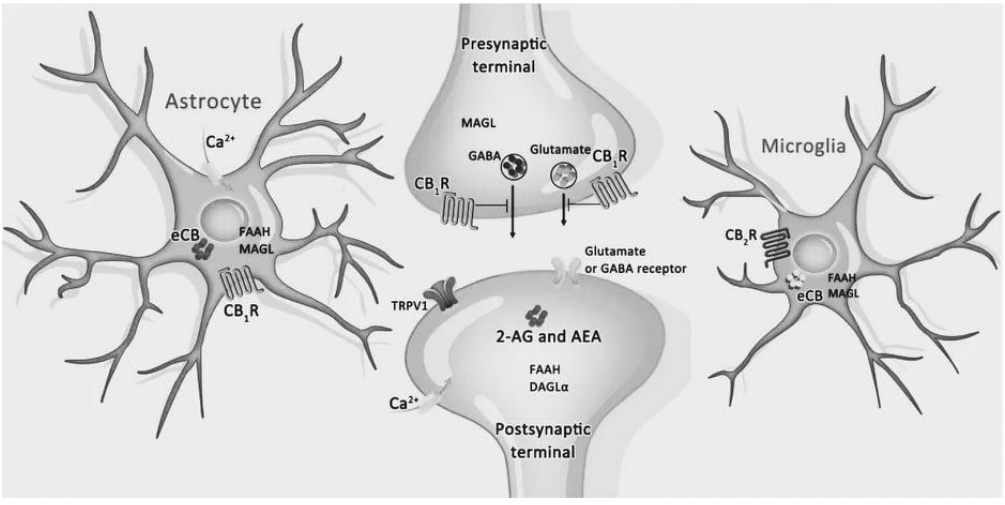

Fig. 2 -Endocannabinoids Action in Anxiety Regulation. Adopted from Yin et. al (2019) [25]

4.2. Pharmacology of Current First-line Pharmacotherapy Treatments

In both physiologic and pathologic anxiety states, many neurotransmitters play a major role. Each of these processes could be a target for therapeutic treatment, but only a few medicines are now utilized to treat anxiety in medical practice [26]. SSRI is advised for people who have never been prescribed medication for anxiety [27]. Almost all anxiety disorders presently consider SSRIs as the first-line medication treatment. The primary function of this class of drugs is to block the serotonin transporter and appear to promote desensitization of postsynaptic serotonin receptors, restoring serotonergic pathway function. This drug class includes sertraline, citalopram, fluoxetine, escitalopram, fluvoxamine, paroxetine, and vilazodone. Despite the fact that SSRIs have fewer adverse effects than other antidepressants, a study found that SSRIs and SNRIs were linked to elevated risk of suicidality [28]. Additionally, the development of sexual dysfunction, a rise in weight after six to twelve months of medication, disrupted sleep, including initial, middle, and late insomnia, and the risk for discontinuation responses when treatment is stopped are all long-term consequences in the use of SSRIs [29]. Alternative first-line agents include SNRIs [27]. When an SSRI fails or does not work, SNRIs are utilized [26]. All existing drugs have been shown to be beneficial in at least one of the anxiety disorders, and the vast majority of them have acquired regulatory clearance for these conditions [27].

5. Types of Anxiety Disorders and its Pharmacotherapy Treatments

5.1. Generalized Anxiety Disorder (GAD)

GAD is a widespread and debilitating condition that is frequently misdiagnosed and undertreated. Chronic anxiety and excessive worrying are one of its symptoms which can cause physical and psychological discomfort [30]. Untreated GAD elevates the incidence of subsequent illnesses, and it can also increase the risk of suicidal behavior [31]. GAD is commonly treated using SSRIs, SNRIs, benzodiazepines and many more psychopharmacologic agents [31,32]. However, SSRIs and SNRIs are regarded as first-line drug therapies for patients with GAD because of their tolerability and efficacy relative to other medications [30,33].

SSRIs have a wide range of effectiveness in both long-term and short-term therapy [34]. No SSRI or SNRI has been found to be superior to another in the treatment of GAD [35]. A fixed-dose controlled research examined sertraline, an SSRI, in young patients with GAD, and improvements in patients administered with sertraline were seen in the fourth week of medication [36]. Another research found that while sertraline was very well-tolerated, the total side effect incidence was higher in patients treated with sertraline monotherapy than those who undergone Cognitive Behavioral Therapy (CBT) or conjunction of both CBT and sertraline [37]. According to a randomized controlled experiment, escitalopram, another first-line medicine for the treatment of GAD, can likewise lessen anxiety symptoms. The research sought to evaluate the effectiveness of escitalopram in older adults suffering from major depressive disorder (MDD) and GAD. The findings revealed that the symptoms of GAD and MDD on the patients administered with escitalopram significantly decreased [38-40]. Additionally, a different study was conducted to evaluate citalopram. Though the study encountered a major limitation in which the patients' average ages was 38, the results of the study showed that an enhancement in the Hamilton Anxiety Rating Scale (HAM-A) occurred, lowering the anxiety level of the patient according to HAM-A [41]. For SNRI's, an example of a drug administered for GAD is duloxetine. It is approved by the DFA to be used for the management of GAD and MDD. Moreover, a pooled analysis conducted on duloxetine suggested that though patients treated with Duloxetine lowered their HAM-A scores and their HAM-A psychic anxiety factor, it did not have a great impact on the HAM-A somatic anxiety factor test [42].

Despite the first-line treatments for GAD, there is still a continuous development and discovery for better treatment. A study found that CBD lowered the stress levels in rats. The behavioral indicators of anxiety in rats were shown to be reduced once CBD had been administered [43]. Moreover, a case study presented a 10-year old patient diagnosed with GAD and was administered with CBD displayed a maintained decrease in anxiety as well as the patient's quality of sleep [44]. However, a descriptive study conducted in Ontario, Canada showed that 66% of the population preferred using medical cannabis for chronic pain, which can be linked with a higher possibility of having anxiety and depression. At least 50% of the total population completed the Generalized Anxiety Disorder -7 item scale (GAD-7) and they were categorized as having a moderate to severe level of anxiety [45]. Moreover, even though CBD has a number of molecular targets, and hence has a wide range of mechanisms involved, it has been discovered to be a powerful activator of serotonin 5-HT1A, which is a target for treating generalized anxiety disorder [46].

5.2. Post-traumatic Stress Disorder (PTSD)

PTSD is a long-term psychiatric disorder that occurs as a result of an abnormal response after a severely traumatic experience [47]. PTSD develops primarily as cognitive symptoms whenever trauma is revisited through intrusive memories and nightmares [48]. However, individuals do not get PTSD as a result of being exposed to a stressful experience. Only around 10% of people who are subjected to a traumatic situation will get PTSD, and only 6.8% will have it for the rest of their lives. Among other psychotherapies and non-pharmacological techniques, exposure therapy, biofeedback, and eye movement desensitization and reprocessing are used to treat PTSD [49-51]. Approximately 40–70% of persons who got these interventions over a short period of time saw a substantial improvement in symptoms as well as the elimination of their learned fear [52,53]. These treatments, however, are not suitable for everyone. Suicidality, alienation, destructive impulsivity, and chaotic life issues are signs that a patient isn't responding well to therapy, prompting doctors to stop using it [54].

Traditional antidepressants and anxiolytics, such as sertraline, paroxetine, and fluoxetine, as well as SNRIs, including venlafaxine, are among the pharmacological treatments approved for PTSD [55,56]. Despite the fact that only around 60% of patients react to SSRIs, with only about 20% to 30% attaining complete recovery, SSRIs have generally been known as the first-line treatment for PTSD [57]. Neurotransmitters such as serotonin, norepinephrine, GABA, glutamate, and dopamine, alter the fear and anxiety circuits of the brain, which are targeted by PTSD treatments. Serotonin, a neurotransmitter, has been associated with the management of various mood and anxiety conditions. Some people with PTSD, for example, have been found to have a problem with serotonin transport in the amygdala. SSRI can control the amount of serotonin in both peripheral and central nervous systems. Moreover, according to research, the maximum effect from SSRI medication is dependent on appropriate dosages and treatment duration, and maintaining treatment adherence is critical to successful PTSD pharmacotherapy [58,59].

One study examined how cannabis usage affects the amygdala response in people suffering from PTSD. The three groups of participants were healthy adults who had not been exposed to trauma, trauma subjected adults without PTSD, and trauma subjected adults with PTSD. THC or a placebo was provided to the participants, who then completed a threat processing scenario while undergoing functional magnetic resonance imaging. According to the study's findings, THC reduced threat-related amygdala reactivity, enhanced mPFC activation during threat, and improved mPFC-amygdala functional coupling in adults with PTSD [60]. Furthermore, preclinical study on CBD usage for the treatment of PTSD has revealed that it improves fear extinction and the therapeutic consolidation of emotional memories [55,61]. Additionally, CBD caused decreased responses to aversive memories and increased their

extinction, improved the outcomes of inhibitory avoidance tasks, and produced anxiolytic effects [62,63]. For example, one case report on a 10-year-old patient who was sexually abused found that a daily oral dose of 12 to 37 milligrams of CBD was associated with a decreased in PTSD-related sleep and anxiety symptoms [44]. In another open-label pilot research, patients with chronic PTSD were given oral THC as an add-on treatment. It examined ten patients with chronic PTSD who were already on stable medication and were being treated with four or more different medications, and results showed that using THC with an initial dose of 2.5mg drops twice a day, and an increasing dose of 5mg drops twice a day improved sleep quality in patients and decreased the occurrence of PTSD-related episodes. Even though patients experienced some moderate side effects, all patients tolerated the add-on therapy [52,64].

5.3. Obsessive-compulsive Disorder (OCD)

Obsessive-compulsive disorder or OCD is an anxiety disorder characterized by obsessive thoughts and compulsive actions. Such manifested behaviors and patterns of thinking are mostly harmless [65]. However, these obsessions and compulsions can dominate one's mental status, leading to functional impairment and the inability to conduct everyday tasks, not to mention the accompanied feelings of anxiety that often come with it. While irresistible urges or intrusive thoughts are experienced by most people to a certain degree, it is only when they reach this severe level of life disruption that a diagnosis for OCD is warranted, as has occurred in a surprisingly large amount of the general population-- roughly 2.5-3% [66]. Little is known about what causes OCD, but older studies, recent genetic sequencing, and meta-analyses suggest that it may involve genetic factors that ultimately lead to the impairment of cortical-striatal neural pathway function, impairment of the dopaminergic and serotonergic systems, which coincides with the use of drugs like SSRIs in its treatment, and possibly an imbalance in glutamate-GABA [66-69].

Currently, the best pharmacologic options for the treatment of OCD is the prolonged administration of SSRIs or clomipramine, although SSRIs are now the preferred first-line agent due to rising concerns regarding the safety and anticholinergic adverse effects of clomipramine, which may rarely include seizures or arrhythmia [70]. Examples of SSRIs typically given to those suffering from OCD include fluoxetine, sertraline, citalopram, and escitalopram. These are usually given in conjunction with exposure and response prevention (ERP) or cognitive behavioral therapy (CBT) [71]. However, it should be noted that up to 40% of patients do not report a response to this first-line treatment, thus highlighting the need to discover new options [72]. Furthermore, in order to elicit an optimal response, higher doses of SSRIs are usually needed compared to other indications, sometimes even above maximal doses, thus requiring careful monitoring of serotonin levels [70]. Under this regimen, it still typically takes between four and six weeks for a patient to notice any substantial improvements in symptoms, although in some cases it may take more than even ten weeks.

Regarding treatment-resistant OCD, one common approach to effectively combat it is combined treatment, which typically involves the augmentation of SSRIs or clomipramine through the addition of an atypical antipsychotic, although the potential benefit may be outweighed by adverse effects unlike SSRI or clomipramine monotherapy, such as weight gain or metabolic syndrome [73]. One review of 792 articles also found that the adjunctive use of neuroleptic drugs and other neuromodulatory approaches may help in cases of treatment-resistant OCD. Additionally, it found preliminary evidence suggesting that certain other agents, specifically memantine, N-acetylcysteine, celecoxib, and ondansetron, as well as glutamate-modulating drugs such as topiramate, ketamine, riluzole, and lamotrigine, may be safe to use in combination with SSRIs or as monotherapy in treating OCD, but the efficacy of such drugs remains to be established [72,74].

Meanwhile, research on the effects of cannabis on pure OCD remains limited, but one case study on a male patient, a 24-year-old, comorbid with bipolar disorder and diabetes, showed that the administration a synthetic variant of THC known as dronabinol led to the gradual decline of his Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores from 39 to as low as 10, significantly ameliorating quality of life. This also led to the patient being able to tolerate CBT for the first time [75,76] These positive results align with an older study on dronabinol which found a marked improvement in symptoms even in treatment-resistant OCD [77]. Similarly, a recent trial researching the use of cannabinoids suggested that while nabilone, another synthetic form of cannabis, produced little change in symptoms alone, it significantly augmented the effects of exposure-based psychotherapy in that it facilitated fear extinction, thus also leading to a significant decrease in Y-BOCS scores-- nearly twice the reduction observed in patients who received exposure-based psychotherapy alone [78,79]. This reduction was still observed in the follow-up one month after the study protocols were completed. Furthermore, the same study also showed that cannabis relieved compulsive behaviors and anxiety in animal models, and that the endocannabinoid system may have some involvement in OCD's pathophysiology. In general, the utilization of nabilone was well-tolerated, with the adverse effects communicated by the participants mostly rated "mild" in nature and none greater than "moderate". These effects consisted of symptoms such as dry mouth, disorientation, difficulty concentrating, and forgetfulness, all of which improved over time. Additionally, no cases reported euphoria, which may indicate that nabilone's potential for abuse is low.

5.4. Social Anxiety Disorder (SAD)

One of the most prevalent psychiatric disorders is social anxiety disorder (SAD), which is linked to a substantial burden of illness [80]. It is a type of anxiety condition that causes intense dread of being judged by others in social situations [81,82]. Excessive anxiety in circumstances where an individual may be assessed and criticized when performing and communicating with others is a sign of having SAD. This disorder can be treated effectively through psychotherapy and/or pharmacotherapy [83].

There are various treatment options for this condition, which depends on the condition's severity. Studies showed that SAD can be treated through cognitive behavioral therapy (CBT), psychotropic medications, or a combination of both [80-85]. Also, SSRI and SNRI have been thoroughly investigated and proven to be useful in the treatment of SAD [80,86]. Additionally, both are considered to be the first line treatments for SAD, and its effectiveness extends well beyond depression and encompasses social anxiety disorder and have become the treatment of choice, particularly, sertraline with a starting dose of 50-200mg/day and Paroxetine in the dose of 20-60mg/day, for the medication treatment of SAD. These medications are also often well tolerated, but have a number of side effects including sexual dysfunction as the more long-term and troublesome side effect of both SSRIs and SNRI, which can be addressed with complementary therapy. Patients may experience antidepressant-induced jitteriness or anxiety that may be caused by an early surge in serotonin which produces anxiety, however this can be lessened by longer escalation or the use of benzodiazepines [87]. In a concept of randomized controlled trials assessing paroxetine's efficacy and tolerability in individuals with SAD, it was effective in reducing dread and avoidance symptoms while also increasing social interaction. Paroxetine has been demonstrated to be usually well-tolerated in terms of tolerance or acceptance [88]. Moreover, escitalopram was also found to be efficacious in another placebo-controlled and flexible-dosage study for the treatment of SAD. Escitalopram's tolerability in the 10mg to 20mg dosage range was equivalent to that previously observed in the treatment of depression. Escitalopram is a viable pharmacotherapeutic choice in the treatment of individuals with SAD because of the low withdrawal rate in this trial and its efficacy/tolerability profile [89]. Furthermore, modern antidepressants and pregabalin are highly suggested. However, in daily clinical practice, a number of factors must be considered [90].

Furthermore, preclinical research backs up cannabidiol's efficacy as a treatment for anxiety disorders. CBD usage in the treatment of SAD has been connected to stress induction and reduction. People with social anxiety who were given CBD had an increased blood flow to the cingulate cortex, which is important for interpreting others' reactions, while decreasing blood flow to the hippocampus and parahippocampal gyrus, which are involved for memory formation and recollection, as well as perceiving faces [91]. A clinical research on the benefits of CBD oil on teenagers suffering from SAD was conducted. The placebo treatment was olive oil, whereas the CBD treatment had 300mg of CBD oil. The findings showed that individuals who got CBD therapy had less anxiety than those who received a placebo treatment [87]. Also, CBD has been shown to be both safe and beneficial in social anxiety studies during public speaking activities. Additionally, evidence from human tests involving healthy volunteers and those with SAD, CBD appears to have anxiolytic qualities [92].

5.5. Panic Disorder (PD)

Panic disorder is a type of anxiety condition that produces panic episodes on a regular basis. A person having panic attacks experiences fear and anxiety, as well as physical symptoms. Some patients develop agoraphobia where they avoid situations and things that they find difficult to escape in order to avoid experiencing another panic attack [93]. However, the direct cause of panic attacks and panic disorders are still not clear but there are factors such as genetics, stress and emotional sensitivity that might possibly cause the disorder [94].

In the management of panic disorder, CBT is also effective and has been a golden standard treatment [95]. On the other hand, medications are also used to manage the effects of the disorder. Both SSRI and SNRI are first-line drugs as these drugs work effectively in relieving the symptoms of panic disorder. In fact, a review concluded that both drugs are efficient in the management of anxiety disorders, and higher doses of SSRIs are linked to better treatment effect, however, SNRIs in higher doses do not exhibit the same as SSRIs [96]. SSRI is an antidepressant commonly recommended as the first choice in treating panic disorders. SSRI medications such as paroxetine and sertraline have already been in use for panic disorder treatment in certain doses [87]. A review states that a result from 57 meta-analyses concludes that SSRI have a great efficacy for treating anxiety disorders, and SSRI doses on the upper side of the therapeutic range are associated with improved PD symptoms [97,98]. Clinical studies have stated that SSRIs like citalopram, fluvoxamine, and paroxetine, as well as SNRIs like venlafaxine and duloxetine, are beneficial in treating panic disorder both acutely and long term [99]. These drugs also come with side-effects, with common ones such as nausea, vomiting, insomnia, headache as wells decreased sex drive. SSRI also has less common side effects but worse adverse effects such as birth defects, QT prolongation, rash, hyponatremia, cataracts and serotonin syndrome [98].

Furthermore, cannabis has been claimed to be a good alternative in treating anxiety disorders. The anxiolytic effects of CBD are also revealed in a study, however, the anxiolytic effects were only present in certain doses. In this study, 57 of the respondents were healthy male and were given CBD capsules of three different doses (150mg, 300mg and 600mg) and a placebo before proceeding in a simulated public speaking test to induce anxiety. Results showed that the subjects who took 300mg of CBD capsules notably reduced their anxiety, as for the subjects who took the placebo, 150mg and 600mg, there was no significant difference in their anxiety levels [100]. Moreover, a research found that CBD can affect the activity of brain regions such as the medial and left temporal lobes, prefrontal cortex, and insula, all of which have been shown to be modified in patients with PD [101].

6. Discussion

Existing research finds that cannabis-based medicine yields promising results in the treating and management of all five major anxiety disorders: GAD, PTSD, OCD, SAD, and PD. However, its ability to reduce anxiety behaviors and its unique system of mechanisms suggest that cannabis may also be a powerful tool in the management of a broad range of other anxiety and psychiatric disorders. Cannabis boasts a high safety profile with good tolerability, with only mild side effects, for instance dry mouth or drowsiness. This is important considering that firstline treatments for anxiety disorders, typically SSRIs, are capable of producing serious or long-term adverse effects in certain individuals such as sexual dysfunction, seizures, metabolic syndrome,

cataracts, and more, which may themselves warrant the need for additional therapy. Additionally, in order to be effective in anxiety disorders, SSRIs may need to be administered at higher doses compared to their other indications, thus leading to an increased incidence of side effects. Further worth noting is that there are many cases in which patients are unresponsive to first-line modes of treatment, whereas cannabis-based medicine is able to elicit anxiolytic responses directly or significantly augment the therapy of the same individuals.

Still, while the studies, survey data, and animal models discussed above generally suggest positive outcomes, it should be noted that this field of research is still in its infancy [92]. There exists very little documentation on the anxiolytic effects of cannabis in clinical populations, with existing studies on cannabis' effects on mood and anxiety symptoms being small in scope or limited to healthy populations. On a similar note, there exists only a small number of studies with standardized approaches to determine the proper dose, and the measurement of clinical outcomes. As a result, the drawing of sound conclusions regarding the application of cannabis in the clinical treatment and management of anxiety disorders in humans is restricted by the lack of well-controlled, high-quality studies [102-104]. However, the untapped potential demonstrated by the available research should only further demonstrate the need to continue evaluating the application of cannabis as a therapeutic option for anxiety disorders, as well as the need to question if cannabis truly deserves its illegality and the accompanying stigma in certain countries.

7. Conclusion

Cannabis-based medications and current first-line pharmacotherapy treatments on anxiety disorders have been comparatively reviewed. Based on the evidence seen, cannabis also has beneficial effects in managing anxiety disorders as compared to its current first-line pharmacotherapy treatments. However, more data and extensive research are needed to proceed in such creation of treatment to assure its efficacy and safety. Hence, it can be an increasing interest and great potential candidate in developing cannabis-based medications to treat anxiety disorders.

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