IDPH Iowa Department of Public Health

BEFORE THE IOWA MEDICAL CANNABIDIOL BOARD

Petition by *(Your Name)*

for the **(addition or removal)** of

Panic Disorder

(medical condition, medical treatment or debilitating disease) to the list of debilitating medical conditions for which the medical use of cannabidiol would be medically beneficial.

PETITION FOR
ADDITION or **REMOVAL**
(Circle one)

Petitioner's Information			
Name (First, Middle, Last or Name of Organization):			
Home Address (including Apartment or Suite #):			
City:	State: IA	Zip Code:	
Telephone Number:	Email Address:		
Is this the person/ organization to whom information about the petition should be directed?	**Yes** ☒	**No** ☐	

Representative's Information *(If applicable)*			
Name (First, Middle, Last):			
Mailing Address (including Apartment or Suite #):			
City:	State:	Zip Code:	
Is this the person/ organization to whom information about the petition should be directed?	**Yes** ☐	**No** ☐	

RECEIVED
OCT 18 2019
Office of Medical CBD
Iowa Dept. of Public Health

Telephone Number:	Email Address:

1. Please provide the name of the specific medical condition, medical treatment, or debilitating disease you are seeking to add to or remove from the list of debilitating medical conditions for which patients would be eligible to receive a medical cannabidiol registration card. *Please limit to **ONE** condition, treatment, or debilitating disease per petition.*

Recommended Action	Condition or Disease
☒ Add ☐ Remove	Panic Disorder

2. Please provide a brief summary statement that supports the action urged in the petition. *Attach additional pages as needed.*

"In the present review, we included both experimental laboratory animal and human studies that have investigated the putative anti-panic Properties of CBD.
Taken together, the studies assessed Clearly suggest an anxiolytic-like effect of CBD in both animal models and healthy volunteers."

RECEIVED
OCT 18 2019
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Iowa Dept. of Public Health

IDPH Iowa Department of Public Health

3. Please provide a brief summary of any data or scientific evidence supporting the action urged in this petition. *Attach additional pages as needed*
See attached.

4. Please provide a list of any reference material that supports your petition.
Evidences for the Anti-panic actions of cannabidiol By: Vanessa P. Soares and Alline C. campos. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5412699/)

5. Please provide a list of subject matter experts who are willing to testify in support of this petition (if any). The list of subject matter experts must contain names, background, email addresses, telephone numbers, and mailing addresses. *Attach additional pages if needed.*			
Name	(1)	(2)	(3)
Background			
Email address			
Telephone number			
Mailing address			

6. Please provide the names and addresses of other persons, or a description of any class of person, known by you to be affected by or interested in the proposed action which is the subject of this petition. *Attach additional pages if needed.*

7. Please indicate whether you have attached a brief in support of the action urged in the petition.	Yes	No
	X	☐

8. Please indicate whether you are asking to make an oral presentation of the contents of the petition at a board meeting following submission of the petition.	Yes	No
	☐	X

9. Acknowledgement and Signature

By signing this document I certify that the information provided in this petition is true and accurate to the best of my knowledge.

Signature _____ Date (mm/dd/yyyy) 10/14/2019

- Please fill out each section that is applicable to your petition. Failure to conform to what is required in this petition may result in a denial of consideration by the board.
  - You do not need to fill out sections asking for your representative's information if you do not have one.
  - For section **2**, please provide a short, essay-like summary of your argument.
  - For section **3**, please provide a short, essay-like summary of the articles and evidence that supports your position (if any).
  - For section **4**, please provide a list of articles that are in support of your position (if any).
  - For section **5**, please provide a list of experts that would be willing to testify in support of your position (if any). In the background section, please provide the reasons why they should be considered experts in the area: education, credentials, field of study, occupation, etc. This section is optional but will greatly aid in helping the board consider your petition.
  - For section **6**, please provide information about groups of people that will be affected if the petition were approved. This could include people suffering from a specific disease, advocacy groups, local government officials, etc.
  - Sections **7** and **8** are optional but may aid the board in considering this petition.
- Please be aware:
  - The board may request that you submit additional information concerning this petition. The board will notify you of the requested materials in the event that more information is needed.
  - The board may also solicit comments from any person on the substance of this petition. The board may also submit this petition for a public comment period where any interested person may comment.
  - The board has six months after you submit this form to either deny or grant the petition. If approved, you will be notified in writing that the board has recommended the addition or removal of the medical condition, treatment, or debilitating disease to the board of medicine. If denied, the board will notify you in writing the reasons for denial.

- If the board denies your petition for failure to conform to the required form, you will be allowed to correct the errors and resubmit for consideration.
- **After you have completed this petition, please make sure that you sign, date it, and email, mail, or hand deliver to:**

Iowa Department of Public Health
Office of Medical Cannabidiol
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Evidences for the Anti-panic Actions of Cannabidiol

Vanessa P. Soares and Alline C. Campos

Abstract

BACKGROUND

Panic disorder (PD) is a disabling psychiatry condition that affects approximately 5% of the worldwide population. Currently, long-term selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for PD; however, the common side-effect profiles and drug interactions may provoke patients to abandon the treatment, leading to PD symptoms relapse. Cannabidiol (CBD) is the major non-psychotomimetic constituent of the Cannabis sativa plant with anti-anxiety properties that has been suggested as an alternative for treating anxiety disorders. The aim of the present review was to discuss the effects and mechanisms involved in the putative anti-panic effects of CBD.

METHODS

electronic database was used as source of the studies selected selected based on the studies found by crossing the following keywords: cannabidiol and panic disorder; canabidiol and anxiety, cannabidiol and 5-HT1A receptor).

RESULTS

In the present review, we included both experimental laboratory animal and human studies that have investigated the putative anti-panic properties of CBD. Taken together, the studies assessed clearly suggest an anxiolytic-like effect of CBD in both animal models and healthy volunteers.

CONCLUSION

CBD seems to be a promising drug for the treatment of PD. However, novel clinical trials involving patients with the PD diagnosis are clearly needed to clarify the specific mechanism of action of CBD and the safe and ideal therapeutic doses of this compound.

Keywords: Animal models, cannabidiol, human studies, 5-HT1A receptors, panic disorder, serotonin

1. INTRODUCTION

Panic disorder (PD) is a chronic and disabling psychiatric disorder that is characterised by unexpected and recurrent panic attacks and affects approximately 0.8-5% of all people worldwide and may vary according to socio-demographic factors [1]. PD patients experience psychosocial impairment and a high risk of psychiatric co-morbidities and suicide [2]. In the early 1960s, Donald Klein described the efficacy of the tricyclic antidepressant imipramine in blocking panic attacks [3]. Currently, selective serotonin reuptake inhibitors (SSRIs) are the first-line compounds in the treatment of PD, although other drugs, such as tricyclic antidepressants and highly potent benzodiazepines, are also indicated. Less than half of the patients who suffer from PD show complete and sustained remission of the symptoms after long-term treatments with the currently available treatments [2]. This apparent discrepancy might be due to genetic variations in PD etiology that could affect the pharmacological responses and side effects [2]. Thus, the development of more effective drugs with a better pharmacological profile than the current ones used to treat this psychiatric condition is needed.

Over the last two decades, the therapeutic potential of cannabinoids has been extensively studied. Although cannabis abuse is

connected to marked anxiety, panic attacks, depersonalisation, and emotional liability (primarily due to the psychotropic effects of Δ^9-THC) [4], a growing body of evidence suggests that non-psychotomimetic phytocannabinoids could be useful as therapeutic tools. The most promising of these compounds is cannabidiol (CBD), the major non-psychotomimetic constituent of *Cannabis sativa*. Different from the endogenous ligands anandamide and 2-arachidonylglycerol act as agonists of CB1/CB2 receptors [5, 6], CBD has a very low affinity for these receptors *in vitro* [7, 8] but it can facilitate endocannabinoid signalling by inhibiting the cellular uptake and enzymatic hydrolysis of endocannabinoids [7]. Finally, CBD can also promote the blockade of adenosine uptake or act as an agonist of vanilloid (TRPV1) or 5-HT1A serotonergic receptors [9-12]. Pre-clinical studies have shown that systemically administered CBD induces anxiolytic-like effects in several animal models that have been associated with generalised anxiety (GAD), such as the elevated plus maze (EPM), the Vogel conflict test and aversive conditioning [7]. Reinforcing these findings, human studies have suggested that the drug decreases generalised anxiety symptoms [7]. The specific effects and the relevance of each of these mechanisms for the putative anti-panic effects of CBD are discussed in this review. MEDLINE/PubMed (www.pubmed.com) electronic database was used as source of the studies selected for this review (from 1990 to July 2015). Works were selected based on the studies found by crossing the following keywords: cannabidiol and panic disorder; Cannabidiol and anxiety, Cannabidiol and 5-HT1A receptor.

2. ANTI-PANIC EFFECTS OF CBD IN HUMANS

In humans, responses related to PD have been assessed in both healthy volunteers and panic patients submitted to controlled conditions of psychological or chemical-nature stimuli [15, 16]. For instance, in the simulated public speaking (SPS) test, the participant must prepare a speech and talk in front of a video camera [17]. Indices of anxiety and other emotional states during the test are obtained by applying scales, such as the Visual Analog Mood Scale (VAMS; [17]) and the Self-Statements during Public Speaking Scale [18].

Fear of public speaking is accepted to increase anxiety in healthy people, irrespective of their trait anxiety level [16]. Classical benzodiazepines decrease the VAMS indices before and after the speech, without affecting speech preparation or performance (which is associated with "fear of speaking"). Conversely, speech preparation and performance are reduced by antidepressants [15]. Based on pharmacological studies, it has been proposed that the neural networks activated by SPS are involved in anxiety disorders [16] and, thus, that the fear of speaking provoked by the SPS test can be helpful in understanding the brain areas involved and potential new drugs targets for PD.

Regarding CBD, the work of Zuardi and coworkers [14] showed that a single dose of CBD (300 mg, p.o.) decreased anxiety after the SPS test in healthy volunteers. In another study, Bergamaschi *et al.* [19] showed that social anxiety disorder patients presented higher anxiety, cognitive impairment and discomfort, as well as increased alertness during their speech performance when compared with healthy controls. After CBD (600 mg, p.o.) treatment, however, a significant reduction in anxiety-related measures obtained during their speech performance was observed. These results have encouraged new approaches in the study of the putative effects of CBD on PD.

3. EFFECTS OF CBD IN ANIMAL MODEL

Animal models of panic attacks are supported by the observation of Blanchard and co-workers that, depending on the presence or absence of the predator and its distance from the prey, animals display different defensive strategies [20]. According to this hypothesis, panic attacks would be related to the flight and freezing defensive responses elicited by proximal threats. Thus, the flight/escape and freezing responses generated by a stimuli, such as natural predators, open/unprotected spaces and electrical/chemical stimulation of brain areas (such as the dorsal periaqueductal grey (dPAG) or the medial hypothalamus), have been used to study several aspects of PD [21].

For instance, the encounter between the mouse and the wild snake *Epicrates cenchria crassus* elicited several defensive behaviours. Of note, the acute administration of CBD (0.3-30 mg/Kg, i.p.) decreased the expression of panic-related behaviours, such as defensive immobility, explosive escape and total escape of the mice [22].

The anti-panic effect of CBD was also observed in rats submitted to the open arm of the elevated T-maze or to the electrical stimulation of the dPAG. The local administration of CBD (30–60 nmol, intra-dPAG) inhibited the escape response generated by both tests [23]. Recently, the effects of CBD on experimental PD were reinforced by Campos and colleagues [24], who demonstrated that the chronic (5 mg/kg, i.p., 21 days), but not acute (5, 10 and 20 mg/kg, i.p.), peripheral administration of CBD was able to reduce the escape response of rats submitted to the elevated T-maze. These latter studies also provided new evidence regarding the brain sites and mechanisms involved in the anti-panic effects of CBD.

4. MECHANISIMS OF THE EFFECTS OF CBD ON PANIC

4.1. Brain Sites

Although the network involved in the anti-panic effects of CBD remain largely unknown, both preclinical and clinical studies have suggested some brain areas related to panic disorder [16, 25] as possible sites for the therapeutic actions of this compound (Table 1, Fig. 1).

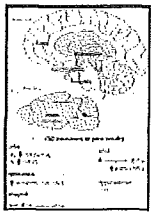

Fig. (1)
Possible neurobiology network brain sites involved in the mechanism of action of cannabidiol in panic disorder. CER: results based on Contextual Fear Conditioning test.

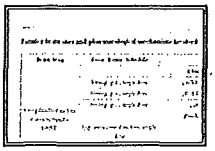

Table 1
Putative brain sites and pharmacological mechanisms involved in the anti-panic effects of CBD.

Structural differences have been described in the amygdala, hippocampus, hypothalamus, cingulated cortex and parahippocampal gyrus of PD patients [26]. Functional magnetic resonance imaging studies have revealed the activation of the amygdala during spontaneous panic attacks [27-29]. Other neuroimaging studies have presented increased activity in the hippocampus, hypothalamus and posterior cingulated cortex in PD patients or during panic anticipation [25]. These results indicate the amygdala, hippocampus, hypothalamus and cingulate cortex as possible brain sites for the panicolytic action of CBD. Crippa and colleagues [30] conducted a functional neuroimaging study to investigate the brain areas recruited after CBD administration in humans. A single dose of CBD, administered orally in Healthy volunteers, promoted a reduction in anxiety evoked by a tracer injection and scanning procedure. CBD also altered resting activity in limbic and paralimbic brain areas. Of note, CBD decreased the activity of the left amygdala-hippocampal complex, hypothalamus and posterior cingulated cortex while increasing the activity of the left parahippocampal gyrus compared with placebo.

Regarding the parahippocampal gyrus, although its deactivation has been observed after panic attacks induced by lactate [31] or cholecystokinin-4 [32], spontaneous panic attacks have also been associated with the activation of this area [25]. Because the study

of Crippa and colleagues [30]

was conducted in healthy volunteers, it would be of interest to test whether CBD would also alter the activity of those limbic and paralimbic areas in PD patients.

In healthy volunteers treated with CBD and submitted to a model of the presentation of fearful faces, a decreasing of the amygdala and anterior and posterior cingulate cortex activities and a disruption in the connections between the amygdala and the anterior cingulated cortex were observed [13, 33]. Interestingly, previous studies have suggested that the anterior cingulated cortex is connected to the amygdala in response to fear and anxiety [30], suggesting these brain areas as candidates for the action of CBD on PD. However, as noted by Kowal and colleagues [35], the effects of CBD on anterior cingulate cortex activity might depend on the nature of the task used in imaging studies. While verbal paired associate learning is associated with cognition, facial expressions task seems to be more related to emotion. These different tasks might differently recruit cingulate cortex. Thus, the effects of CBD in this area might be dependent on the task (emotion vs cognition). In addition to the attenuation of anterior cingulate cortex activity [13, 33], other studies have failed to detect changes in the activity of the anterior cingulate cortex by CBD [36- 38].

These apparent discrepancies, however, could be explained by the fact that CBD may increase the activity in a brain area depending on the stimuli presented to the volunteers and on the anxiety disorder under observation. Preliminary data involving generalized social anxiety disorder patients suggested that CBD decreased VAMS anxiety scores with a concomitant reduction in the left parahippocampal gyrus activation and an increase in the right posterior cingulate gyrus activation, in contradistinction to the previously described results [30]. According to the authors, these discrepancies might be related to differences in the activity of the parahippocampal gyrus and cingulated gyrus in healthy individuals versus patients with anxiety disorders [39].

Imaging studies have also demonstrated that CBD can alter the activity of brain areas such as the medial and left temporal lobes, prefrontal cortex and insula [36, 40], regions that were also found to be modified in PD patients [25]. Moreover, the participation of other brain structures also related to PD [41], such as the midbrain areas, caudal pons and medulla, on the anti-panic effects of CBD cannot be ruled out. However, these brain areas are significantly smaller, and the detection of small alterations during neuroimaging studies could be difficult [42]. One example of a small area that is strongly related to panic responses is the dPAG [42]. Previous studies conducted in humans demonstrated that midbrain stimulation, which was evaluated many years ago while attempting to produce pain relief in patients, induced neurovegetative changes (such as increases in the heart beat and respiratory frequency), followed by feelings of imminent death and suffocation, which is very similar to a panorama described by patients during a panic attack [43].

Aiming to investigate the role of dPAG in the panicolytic-like effect of CBD, Soares and colleagues [23] injected different doses of CBD (30–60 nmol, 0.2 μL) into the dPAG and successfully inhibited escape responses generated in two animal models: the electrical stimulation of the dPAG and the exposure to the open arm of the elevated T-maze. In addition, the anti-panic effects of the chronic treatment of CBD, observed in animals tested in the elevated-T maze, are mediated by serotonergic mechanisms located in the dPAG [24].

4.2. Pharmacological Mechanisms of CBD on PD

So far, several mechanisms of action have been associated with CBD effects [7]. Although many of the described mechanisms are not directly connected to anxiety disorders, the type 1A serotoninergic receptor has been extensively reported to be a key partner in the anti-anxiety and anti-panic effects of CBD [7, 23, 24, 44].

In mice, the panicolytic-like effect of CBD was prevented by the peripheral administration of a 5-HT1A receptor antagonist, WAY-100635 (0.1–0.9 mg/kg, i.p.) [44]. Accordingly, in rats, intra-dPAG CBD administration impaired escape responses generated by the open arm of the elevated T-maze and by the electrical stimulation of the dPAG; in both cases, the effects were prevented by the

administration of WAY-100635 (0.37 nmol) [23]. Later, Campos and coworkers [24] suggested that the panicolytic-like effect promoted by the repeated peripheral administration of CBD in rats was also mediated by 5-TH1A receptors located in the dPAG. Interestingly, the effect of CBD on the dPAG seems to be dependent on its actions on the 5-HT1A receptor rather than the modulation of serotonin release or 5-HT1A and 5-HT2C expression, as observed after antidepressant treatment.

In fact, the activation of 5-HT1A receptors in the dPAG has been proposed to reduce panic-like responses and to be involved in the mechanism of action of antidepressants [45]. In addition to the dPAG, preclinical studies have noted the amygdala and the dorsomedial hypothalamic nucleus as other brain sites for the panicolytic-like effect mediated by 5-HT1A receptor activation [46, 47]. In patients with a PD diagnosis, studies have shown that both presynaptic and postsynaptic 5-HT1A receptor binding is reduced in the anterior cingulate, posterior cingulate, raphe, orbitofrontal cortex, temporal cortex and amygdala [48]. Other genetic studies propose an association between 5-HT1A receptor gene polymorphisms and PD [49].

CBD has been suggested to activate 5-HT1A receptors in several brain regions, such as the basal ganglia [50], the bed nucleus of stria terminalis [51], the prelimbic prefrontal cortex [52] and the dorsal raphe nucleus [53, 54]. Although the molecular mechanism by which CBD favours 5-HT1A activation remains unclear, it might involve the allosteric modulation of this receptor, the ability of CBD to facilitate the 5-HT1A agonist-related stimulation of [35S]GTP$_\gamma$S binding [12] or the indirect recruitment or formation of heterodimers consisting of 5-HT1A and other receptors, such as CB1 [55].

In addition to serotonin, other mechanisms might be involved in the anti-panic effects of CBD. For instance, chronic treatment with CBD can increase the anandamide levels within the hippocampus with concomitant increases of hippocampal neurogenesis [56]. CBD may also favour neurogenesis during the aging process by activating PPARγ [57]. Other receptors may also be involved in the actions of CBD, such as CB1, adenosine 1, TRPV1 and TRPA1 [7]. For instance, after chronic (21 days) treatment, CBD reduced 5-HT2A receptor binding in the substantia nigra [58] and increased mitochondrial complex and creatine kinase activity in the prefrontal cortex, hippocampus and striatum of rats [59]. However, the contribution of the aforementioned mechanisms in the anti-panic actions of CBD has yet to be investigated.

5. CONCLUSIONS AND PERSPECTIVE:

Taken together, the results presented in this chapter, which were derived from both laboratory animal and human studies, support the notion that CBD exhibits anti-panic properties. Despite the described panic response reported as a result of cannabis use, it is important to note that CBD does not present psychoactive effects; it is safe and well-tolerated *via* the oral route (up to 1,500 mg/day) [19]. Moreover, because this compound does not induce dependence, tolerance and abstinence symptoms, it can be, in the future, a good alternative as a substitute for high potency benzodiazepines and antidepressant drugs in PD patients who are resistant to the current treatments. However, it is important to stress that we are just in the first steps in the route to get a possible final approval of CBD for the treatment of PD. Several clinical trials using CBD alone or in combination with other cannabinoids are under development. The GW compound Epidolex®, that basically has CBD in its formula, is currently in phase 3 trial for the treatment of orphan pediatric epilepsy syndrome. Therefore, new studies conducted with a reasonable number of PD patients (phase 2 and phase 3 studies) are necessary to demonstrate the efficacy and the dose range of CBD for the treatment of this anxiety disorder.

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The authors declare that they have no conflicts of interest in the research.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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