

PRACTICAL APPLICATIONS OF CANNABIS IN TREATING POST- TRAUMATIC STRESS DISORDER (PTSD)

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What is Post-Traumatic Stress Disorder?

- The person experiences, witnesses, or is confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others.
- The person's response involves intense fear, helplessness, or horror. Note: in children, it may be expressed by disorganized or agitated behavior.
- The person experiences intrusive recollection in which the traumatic event is persistently re-experienced.

What is Post-Traumatic Stress Disorder?

- The person avoids stimuli associated with the trauma, and experiences numbing of general responsiveness.
- The person experiences persistent symptoms of increasing arousal.
- These disturbances cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (1).

What is Post-Traumatic Stress Disorder?

- PTSD is considered the fourth most common psychiatric disorder, affecting 10% of all men and 18% of women, with rates closer to 40% in high trauma populations, such as combat, and low-income inner-city populations (2).
- PTSD often occurs co-morbidly with other disorders, such as depression, substance abuse, and other anxiety disorders (2).

What is Post-Traumatic Stress Disorder?

- Originally PTSD was considered a normative response, related primarily to stressor intensity. It's now clear that the response of an individual to trauma depends not only on stressor characteristics, but also on neurobiological factors specific to the individual (3).

Symptom Clusters in PTSD

1. Reexperiencing Symptoms

- Intrusive/distressing thoughts
- Recurrent nightmares
- Flashbacks
- Intense emotional upset at reminder
- Intense physical reactions at reminder (4)

Symptom Clusters in PTSD

2. Avoiding and Numbing Symptoms

- Avoiding thoughts/feelings
- Avoiding activities/situations/places
- Inability to recall important aspects of event(s)
- Loss of interest in activities
- Detached/cut-off from others
- Impaired range of emotions
- Changed future plans/hopes (4)

Symptom Clusters in PTSD

3. Hyperarousal Symptoms

- Difficulty sleeping
- Irritability/anger
- Difficulty concentrating
- Overly alert
- Jumpy/easily startled (4)

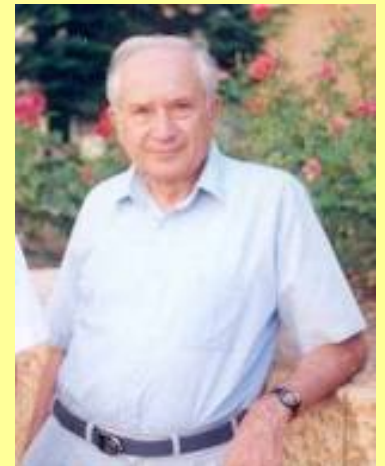
Symptom Clusters in PTSD

- Because of the broad range of symptoms seen in PTSD, it is often difficult to treat with a single medication.
- This often leads to the use of “drug cocktails” that can cause significant adverse effects.
- Cannabis addresses symptoms across all 3 major symptom clusters in PTSD, and does so with few clinically significant adverse effects.

Symptom Clusters in PTSD

“It has been suggested that pharmacological treatments in psychiatry have been overly reliant on neurotransmitter systems and their agonists. In the last several decades, advances in psychopharmacology have reduced side effects but have failed to lead to major disease improvement. The endocannabinoid system may shed new light on the physiological basis of psychiatric diseases leading to new and more effective treatments.” (5)

- Raphael Mechoulam



The Neurobiological Basis of PTSD

- In order to properly treat PTSD, you need to understand the underlying neurobiological processes involved in its etiology.
- PTSD is increasingly understood to involve central neurotransmitter imbalances and neuroanatomical disruptions, along with potential dysregulation of immune, autonomic, endocrine, and cardiovascular function (6).

The Neurobiological Basis of PTSD

PTSD is associated with dysfunction in:

- the amygdala,
- the anterior cingulate cortex (ACC),
- the medial prefrontal cortex (mPFC),
- the hippocampus (7).

The Neurobiological Basis of PTSD

Possible structural impairments in PTSD:

- decreased hippocampal volume (likely precedes PTSD symptoms, and predisposes the person to developing PTSD)
- decreased anterior cingulate cortex volume (likely follows development of PTSD symptoms) (7)

The Neurobiological Basis of PTSD

- The neurocircuitry model of PTSD, emphasizes the role of dysregulation in threat-related processing (7).
- Trauma exposure sets off a cascade of neural changes leading to a state of amygdala hyperresponsivity, triggering hyperarousal and vigilance (7).
- Inadequate top-down control by the mPFC and ACC perpetuates the state of amygdala hyperresponsivity, leading to increased attention to trauma-related stimuli (7).

The Neurobiological Basis of PTSD

- The hypothalamic-pituitary-adrenal (HPA) axis is the central coordinator of neuroendocrine stress response systems, and as such, it has been a major focus of in patients with PTSD (8).
- Upon exposure to stress, neurons in the hypothalamic paraventricular nucleus (PVN) secrete corticotropin-releasing hormone (CRH) which stimulates the production and release of adrenocorticotropin (ACTH) from the anterior pituitary (8).

The Neurobiological Basis of PTSD

- ACTH then stimulates the release of glucocorticoids from the adrenal cortex which modulates metabolism, immune function and brain function to manage stressors (8).
- Sustained glucocorticoid exposure leads to reduced dendritic branching, loss of dendritic spines, and impaired neurogenesis of the hippocampus (8).

Cannabinoids and the Amygdala

- Cannabinoids have a profound effect on function of the amygdala and endocannabinoids are crucial for the extinction of aversive memories (9, 10).
- Activation of CB1 receptors in the amygdala blocks reconsolidation of aversive memories. This suggests that cannabinoids could be useful for the treatment of patients with PTSD, because they may be less likely to relapse after a stressful experience (11).
- THC has a significant and selective impact on amygdala reactivity to signals of threat in humans (12).

Cannabinoids and the Prefrontal Cortex

- The endocannabinoid system plays a significant role in the function of the prefrontal cortex.
- The PFC is highly interconnected with the rest of the brain which allows it to receive and modulate information processing in other regions (13).
- The PFC projects to subcortical arousal systems, regulating monoamine and cholinergic inputs throughout the brain (13).
- Activation of cannabinoid receptors in the mPFC elicits potent antidepressant-like behavior and enhances 5-HT neurotransmission (14).

Cannabinoids and the Prefrontal Cortex

- The antidepressant activity of cannabinoids, likely involves disinhibition of excitatory projections from the mPFC to serotonergic neurons in the dorsal raphe (15).
- It appears that CB1 receptors are involved in not only the extinction of conditioned fear, but also in the adaptation to aversive situations in general (16).
- Enhancing the endogenous cannabinoid system could be a new mechanism for medicines to alleviate depression and related psychiatric disorders (15).

Cannabinoids and the Prefrontal Cortex

- Cannabinoids have diverse effects on hippocampal memory and plasticity (17).
- There is a general consensus that the effects of cannabinoid agonists on anxiety seem to be biphasic, with low doses being anxiolytic and high doses being ineffective or possibly anxiogenic (17).
- However, chronic high dose cannabinoid treatment has been shown to induce hippocampal neurogenesis (18).

Cannabinoids and the Prefrontal Cortex

- This increased hippocampal neurogenesis appears to underlie the mechanism of anxiolytic and antidepressant effects of high dose chronic cannabinoid treatment (18).
- Modulation of hippocampal memory and plasticity by targeting the endocannabinoid system may aid in the treatment of impaired extinction-like processes seen in PTSD (19).

Cannabinoids and the Hypothalamic Pituitary Adrenal (HPA) Axis

- The endocannabinoid system plays a critical role in regulation of the HPA axis.
- Endocannabinoid signaling negatively modulates function of the HPA axis, in a context-dependent manner (20).
- Short term activation of the HPA axis is beneficial to the survival of an organism (20).
- However, long-term activation can impact metabolism, mood, and cognition, and is associated with a variety of neuropsychiatric disorders (20).

Cannabinoids and the Hypothalamic Pituitary Adrenal (HPA) Axis

- Cannabinoids, through action on both limbic and paralimbic brain areas, reduce activity of the amygdala and hypothalamus (21).
- Retrograde endocannabinoid signaling in the hypothalamus is responsible for regulating HPA output (22).
- Acute administration of exogenous cannabinoid ligands also activates the HPA axis indirectly through an increase in serotonergic and noradrenergic neurotransmission (23).

Cannabinoids and the Hypothalamic Pituitary Adrenal (HPA) Axis

- Chronic exposure to desipramine (and perhaps other antidepressant drugs and therapies) upregulates the endocannabinoid system, which in turn, dampens the stress axis in a manner similar to habituation (24).
- Endogenous cannabinoid signaling is essential for stress adaptation, and is fundamental to the intrinsic regulation of the HPA axis (25).

Case Study 1

- Male, mid 20's
- Diagnosed with: PTSD, Profound autism, Intermittent Explosive Disorder
- Medication history includes: Aripiprazole, Lorazepam, Risperidone, Clonidine, Gabapentin, Depoprovera
- Presented with severe behavioral disturbances, assaultive behavior towards others, self destructive behavior, and property destruction.
- He is non-verbal, history comes from parents and support staff.
- Stopped depoprovera and decreased his risperidone.

Case Study 1

- PRN dronabinol was added with positive effect.
- He was tapered off his lorazepam due to possible disinhibition, and routine dosing of dronabinol was initiated at 2.5 mg BID.
- We continued to taper off risperidone and clonidine.
- Parents and staff report significant reductions in frequency and severity of aggressive behavior.
- Sleep patterns have improved.

Case Study 1

- He is better able to transition between activities.
- Patient has now been referred to the medical cannabis program for PTSD.
- He receives standardized doses of cannabis butter at home with his parents, and he remains stable on a combination of dronabinol and dietary supplements in the group home setting.
- His parents hope to transition him from dronabinol to cannabis.

Case Study 2

- Female, early 20's
- Diagnosed with: PTSD, Bipolar II Disorder, ADD
- Medication history: Aripiprazole, Fluoxetine, Citalopram, Lamotrigine, Lisdexamfetamine, Clonazepam, Bupropion, Lorazepam
- Presented with complaints of depression, anxiety, irritability, anger, rapid cycling mood swings.
- Symptoms increased after she was discharged from her previous psychiatric provider for using marijuana.

Case Study 2

- She complained of debilitating depression and anxiety with suicidality.
- She was experiencing hypervigilance, poor sleep with recurring nightmares, mood swings with irritability and anger.
- She was using cannabis occasionally and reported a benefit, but her symptoms were not well managed.
- She was started on aripiprazole which helped stabilize her mood but she had ongoing depression and anxiety so bupropion was added and a PRN for clonazepam.

Case Study 2

- She was referred to the Medical Cannabis Program for PTSD.
- Symptoms improved with medication but she had significant side effects and eventually stopped all other medications except cannabis.
- She went several months with a stable, euthymic mood, improved sleep, no nightmares, decreased anxiety and improved concentration/focus.
- Unfortunately, the Department of Health delayed renewal of her medical cannabis card for several months, and she lost access to a supply of cannabis.

Case Study 2

- She became hypomanic, leading to significant alcohol use and risky behavior, ultimately leading to further trauma.
- Her symptoms have improved since obtaining consistent access to a supply of cannabis and returning to therapy.

Case Study 3

- Male, mid 50's
- Diagnosed with: PTSD, Chronic Paranoid Schizophrenia
- Medication history: Fluoxetine, Risperidone, Benztropine, Haloperidol, Gabapentin, Duloxetine, Propranolol, Olanzapine, Quetiapine
- Patient presented with complaints of auditory hallucinations (with commands to kill himself and others) and visual hallucinations of demons.
- He complained of poor sleep with frequent nightmares, mood swings with irritability and anger, fear, hypervigilance, anxiety.

Case Study 3

- Multiple medical issues including history of traumatic brain injury contributed to his symptoms.
- History of poor medication compliance due to side effects and/or lack of response to medications.
- He frequently went for several months before decompensating enough to return to the clinic.
- He was referred to the medical cannabis program and has reported consistent benefits.

Case Study 3

- His mood has been more stable and he has experienced significant reductions in irritability and anger.
- He has experienced significant reduction in both the positive and negative symptoms of schizophrenia.
- Command hallucinations have ceased and the auditory hallucinations that continue have decreased in severity and frequency.
- He continues to see “shadows” occasionally, but the “demons” are gone.

Case Study 3

- He is able to enjoy spending time with his family and grandchildren.
- He has been consistent with follow up and has been compliant with his other psychotropics since beginning medical cannabis.
- He continues on Risperidone, benztropine, and fluoxetine.

Case Study 4

- Male, mid 60's
- Diagnosed with: PTSD
- Viet Nam Vet.
- Multiple injuries in the field, and additional medical trauma R.T. failed surgeries.
- Now with liver damage due to long term use of pain meds.
- Recently stopped all psychiatric and pain meds, and using cannabis to manage symptoms but has inconsistent access and symptoms worsen when unable to use cannabis.

Case Study 4

- History of alcohol abuse, anxiety, poor sleep with nightmares, irritability/anger, hypervigilance, easily startled, chronic pain and recurring negative thoughts about Viet Nam
- Multiple failed medication trials with VA, including antidepressants, antipsychotics and benzodiazepines.
- He was referred to the medical cannabis program and although access is improved, cost is restrictive.
- He is not using alcohol.
- His mood is more stable.

Case Study 4

- Irritability and anger have been significantly decreased.
- He is sleeping well and nightmares have resolved.
- He continues to experience anxiety in crowds but this is manageable for him.
- He remains off all other psychiatric and pain meds.

Discussion

- I currently manage hundreds of PTSD patients in New Mexico's Medical Cannabis Program.
- Most of these patients have other co-occurring psychiatric and/or medical issues which contribute to their symptoms.
- There is evidence that the endocannabinoid system is involved in the extinction of aversive memories, and PTSD patients claim that cannabis use helps them considerably (26).

Discussion

- The stimulation of cannabinoid receptors in the prefrontal cortex, amygdala, and hippocampus, with the subsequent activation of different signaling pathways, appears to be the first event underlying the effects of cannabinoids on anxious states (27).
- THC may prevent activation of this anxiety circuit (27).
- Changes in levels of CB1 receptors and endogenous CB1 receptor ligands are observed depression (28).
- Stimulation of cannabinoid receptors enhances stress-coping behaviors and increases spontaneous firing of serotonergic and noradrenergic neurons in the midbrain (29).

Discussion

- Phytocannabinoids, including THC, CBD, and CBC, exert antidepressant-like actions (30).
- The CB1 receptor is an important new target in the development of antidepressant drugs (14).
- High rates of suicidal behavior have been found among PTSD patients (31).
- Sensitization of CB1-receptor-mediated G-protein signaling in the prefrontal cortex is one of the neuroadaptive factors in the pathophysiology of suicide, and likely contributes to suicidal behavior (32).

Discussion

- The role of the endocannabinoid system in the pathophysiology of PTSD suggests that cannabinoids may be an effective modality to treat PTSD and suicidal behavior in persons with PTSD (31).
- Inhaled cannabis is generally well tolerated and has been shown to reduce the intensity of pain, decrease anxiety and improve sleep (33).
- Cannabinoids may reduce, or entirely eliminate nightmares, and patients using cannabinoids report improvement in sleep time, quality of sleep, reduction of daytime flashbacks and night sweats (34).

Discussion

- Alcohol abuse has been significantly linked to PTSD (35) and cannabis has been shown to act as a substitute for alcohol (36).
- The majority of the patients I have referred to the medical cannabis program who use alcohol, have reported significantly decreased use, and in many cases, complete cessation of alcohol.
- Cannabinoids have been shown to reduce aggressive behavior (37, 38, 39) which has important implications in PTSD.
- My patients commonly report significant reductions in irritability and anger.

Discussion

- Oftentimes patients are accompanied by family members, friends, and/or treatment team members who confirm reductions in aggressive behavior.
- I have a significant number of patients who use cannabis for PTSD, who have co-occurring psychotic disorders.
- Although use of cannabis in patients with schizophrenia has typically been reported to worsen psychosis (40), increases in population cannabis use have not been followed by increases in psychotic incidence (41).

Discussion

- Dronabinol has been shown to improve symptoms in treatment-refractory schizophrenic patients, including reduction in core psychotic symptoms, with no clinically significant adverse effects (40).
- Schizophrenic patients who use cannabis, and patients with a history of cannabis at first episode of psychosis, have superior neuropsychological functioning compared with nonusing patients (42).
- I have seen consistent benefits with cannabis in reducing both positive and negative symptoms of schizophrenia, with few adverse effects.

Discussion

- Using strains of cannabis containing CBD in addition to THC may be protective against the psychotic-like symptoms that may be induced in some individuals by THC alone (43).
- A comprehensive study of 4 legal medical cannabis patients in the federal Investigational New Drug Program, found only mild changes in pulmonary function associated with long term heavy use (44).
- No functionally significant adverse effects were noted in any other physiological system examined in the study (44).

Discussion

- Cannabis has proven to be the best tolerated and most consistently beneficial medication available to help my patients with PTSD.
- Most of my medical cannabis patients have been able to decrease the use of other medications after beginning medical cannabis, and in some cases they have eliminated other medications entirely.
- Fewer than 1% of patients I have referred to the program have reported stopping due to adverse effects.
- The most commonly reported adverse effects are mild anxiety or mild paranoia.

Discussion

- The vast majority of my patients who do experience occasional adverse effects, report that the benefits outweigh the risk, and choose to continue treatment with cannabis while avoiding strains which are more likely to cause adverse effects.
- The most common reasons reported for discontinuing treatment with cannabis are employer drug testing, high costs of medication, and the stigma associated with cannabis use.

Conclusion

- Cannabis is a safe and effective medication for treating PTSD, even when there are other co-occurring psychiatric disorders.
- The broad range of therapeutic effects seen with cannabis in treating PTSD, suggests it would be an ideal treatment for many psychiatric disorders.
- Rather than simply targeting neurotransmitter systems and their agonists, cannabinoids target the underlying neurobiological processes that lead to imbalances in these neurotransmitter systems, helping to return them to a state of homeostasis.

Conclusion

- Unfortunately, poor access to cannabis may place medical cannabis patients at risk for decompensation, if unable to maintain a consistent and safe supply of medication.
- As medical providers, we have an obligation to our patients to be aware of the therapeutic value of cannabis, and to provide the best possible care, based on the best available scientific evidence.
- We also need to take a more active role in demanding access to this medication, in order to better assure the safety of our patients.

References: See document