BEFORE THE IOWA MEDICAL CANNABIDIOL BOARD

Rebecca Lucas
**Petition by** *(Your Name)*

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

Post-Traumatic Stress 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): Rebecca Lucas | | | |
| Home Address (including Apartment or Suite #): 1953 E Market street | | | |
| City: Des Moines | State: IA | Zip Code: 50137 | |
| Telephone Number: 515-509-4556 | Email Address: Rebecca.Lucas@Medpharmiowa.com | | |
| 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** |

| 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<br>☐ Remove | Post-traumatic stress disorder (PTSD) |

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

please see attached 50 + pages including references & appendices. Thanks.

| 3. Please provide a brief summary of any data or scientific evidence supporting the action urged in this petition. *Attach additional pages as needed* |
| --- |
| There is a summary w/ in the attached<br><br>" |

| 4. Please provide a list of any reference material that supports your petition. |
| --- |
| There ~~are~~ is a reference list on the attached<br><br>" |

| 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.* |
|---|
| Those suffering from PTSD<br>- veterans<br>- Sexual assault survivors<br>- Traumatic event survivors<br>- Domestic abuse survivors |

| 7. Please indicate whether you have attached a brief in support of the action urged in the petition. | Yes | No |
|---|---|---|
| | ✓ | |

| 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 |
|---|---|---|
| | ✓ | |

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.

7-15-2019

*Signature* *Date (mm/dd/yyyy)*

- 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.

# Post-Traumatic Stress Disorder Petition

## 8/2/2019

A note and acknowledgement:

A special thanks goes out to all of those suffering with PTSD that are brave enough to tell their story, whether that is courage to escape domestic assault, courage to feel safe after sexual assault, or just courage to support and listen others. You are not alone, you are not forgotten, and there are people fighting with you.

As a special note to our service members, I want to thank you. As a former Company Commander's wife, I understand the sacrifice you go through, but we as Americans have failed you.

We put forth and build up our veterans and servicemembers when it is convenient for us to do so. We subject them to things people shouldn't ever have to see or experience, and we do this from the comfort of our own lives. We get to live how we do because they fight for us, however, when our service members return, we in essence abandon them. We potentiate a stigma that it is strange for people to not just "be ok." We don't acknowledge the hurts that we can't physically see, and therefore we miss the signs of people around us that need help. This is unacceptable, as Americans, as Iowans, and as human beings. We have a duty to remember that sacrifice, and to help those around us get back to living a lifestyle that they fought to protect.

This petition is written to help people that are suffering. Life is not always a beautiful place, but it is worth living. The goal of this petition is to allow access to tools that may present an avenue of control to those that feel out of control. It is to allow access to tools that can help affect therapy outcomes and sharing of guilt and trauma feelings, allowing a bridge into a more positive quality of life.

**Therefore, the following is a petition to approve Post-Traumatic Stress Disorder to the list of approved conditions in the state of Iowa for access to Medical Cannabis.**

**Questions may be sent to: Rebecca.Lucas@Medpharmiowa.com**

## Table of Contents:

## 1. Summary:

When inhaled or delivered orally, cannabinoids activate endogenous cannabinoid receptors, modulating neurotransmitter release and producing a wide range of central nervous system effects, including increased pleasure and alteration of memory processes. These effects provide a pharmacologic rationale for the use of cannabinoids to manage the core Post Traumatic Stress Disorder (PTSD) symptom clusters. Both animal and human trials show potential in mitigating symptomatic effects of PTSD such as fearful memory, chronic pain, sleep disruption, and anxiety.

With over 28 states currently including PTSD as an approved condition within their medical programs, many sufferers of PTSD have the option to try this form of relief. While the petition in Iowa was initially denied in 2018, we hope that this new petition can allow both a scientific and compassionate care vote of "yes" to allow PTSD as an approved condition in Iowa. Included in Appendix 2 are some letters of some people in Iowa that could be positively affected.

## 2. PTSD background

PTSD was first identified in 1941 as a psychological and physical response to trauma[53]. It was then added to Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in 1980 following the Vietnam war.

PTSD (ICD-20 F43.10) is defined as chronic activation of the stress response as a result of experiencing a traumatic event[1]. PTSD refers to a class of traumatic stress disorders with symptoms lasting one month or more[2]. These generally follow traumatic events such as military combat, domestic violence, sexual assault, or natural disaster. Symptoms of PTSD include anxiety, depression, and chronic pain. Chronic pain can be caused by the traumatic experience or more frequently as a co-morbidity to constant stress.

DSM-5 includes four sets of symptom clusters and two subtypes, as well as requirements around duration of symptoms, how it impacts one's functioning, and ruling out substance use and medical illnesses.

These criterion include[1]((Appendix A)

- Occurrence of a traumatic event
    - Can be direct, witnessed, indirect (such as having a close friend experience the event)
- "Intrusion or Re-experiencing"
    - patients re-experience the event through intrusive thoughts or memories, nightmares related to the traumatic event, flashbacks and the feeling that the event is happening again, and/or psychological and physical reactivity to reminders of the traumatic event
- "Avoidant Symptoms"
    - Ways someone may attempt avoidance of memories of the event
    - Must include avoiding thoughts or feelings connected to the event, or avoidance of people or situations connected to the event
- "Negative alterations in mood or cognitions"
    - Decline in someone's mood or through patterns including
        - Memory problems exclusive to the event

        - Negative thoughts or beliefs about one's self or work
        - Distorted sense of blame for one's self related to the event
        - Being stuck in severe emotions
        - Severely reduced interest in pre-trauma activies
        - Feeling detached, isolated, or disconnected from other people
- "Increased arousal symptoms"/"Hyperawareness"
    - Difficultly concentrating
    - Irritability/increased anger
    - Difficultly falling or staying asleep
    - Hypervigilance
- Additional
    - Symptoms must last at least a month
    - Symptoms must seriously affect one's ability to function
    - Symptoms are connected to the traumatic event

PTSD can also manifest in two types of dissociation, depersonalization (a feeling of disconnection from oneself), and de-realization (a disconnection from the reality of one's surroundings).

## 3. PTSD Statistics

PTSD can have a profound effect on a patient's ability to participate in social settings and professional environments. When compared to members of the workforce without PTSD, those with PTSD have greater occurrence of work absenteeism, more medical visits, increased unemployment or underemployment, lower hourly pay, and a greater difficulty in keeping up with work tasks. [46]

PTSD can happen to anyone and is not a sign of weakness.

- PTSD in general
    - 7-8% of the US population will have PTSD at some point in their lives[42]
        - 8 million adults will have PTSD any given year
        - High prevalence in first responders, police officers, military combat exposure, women experiencing sexual or domestic violence
- PTSD in women
    - Women are twice as likely to develop PTSD than men
    - Interpersonal violence leads to more PTSD than impersonal trauma
    - 50% of sexual assault and rape victims develop PTSD[70,71]

- PTSD prevalence in veterans[42]
    - Vietnam: 30% estimated lifetime prevalence
    - Gulf War: 12%
    - Iraqi Freedom: 14%
    - In 2016 60% of veteran suicides were among veterans age 55 and older

Though PTSD affects groups other than veterans, veterans make up a subset who are tracked by the VA for suicide figures[42].

In the latest VA suicide report, it is reported that veterans make up[42]:

- 21 service members suicides/day
    - 80% veterans; 20% active service members
    - **7,519 suicides per year**
        - **Larger than Iowa's entire Army National Guard**
- Veterans who screened positive for PTSD were more than 4x as likely to have suicidal ideation than non-PTSD veterans.[44]

A survey of recent Iraq and Afghanistan veterans showed 12.5% reported contemplating suicide in the 2 weeks prior to the survey.[45] Positive screens for PTSD and depression were associated with suicidal ideation, where post-deployment social support, sense of purpose, and sense of control were negatively associated.

## 4. Pathophysiology – Neurobiological basis

PTSD and its related symptoms have neurological basis within the human body, including both the physical responses of the brain and nervous systems. The process by which traumatic memories consolidate is recognized to be an abnormal interaction between glucocorticoid hormones and norepinephrine, both stress hormones.[19] Physical manifestations of PTSD are likely linked to increased levels of gluco-corticoid-hormone facilitated Norepinephrine, but also activity of a2-adrenergic receptors, which counteractively impede the release of neurotransmitters from adrenergic presynaptic neurons.

Changes in memory function associated with PTSD differ from those seen in other forms of stress. Below are some important pieces of the brain that play a role in PTSD.

### 4.1 Amygdala

PTSD is caused by disturbances in the function of several biological systems. The amygdala is the area of the brain that plays a role in processing of emotional information, consolidation of emotional memories, generation of stress response, cognitive function, and stimulation of the sympathetic nervous system. The amygdala is also involved in recognition of, and response to, threatening stimuli in the environment.

In patients with PTSD, the amygdala becomes hyper-reactive to physically or emotionally stressful situations resulting in a heightened reaction and behavior in response to stress or trauma.[18] During moments of perceived danger, or constant moments of perceived danger, then amygdala cause be overloaded, resulting in excessive outputs to the rest of the brain. In fact, it is seen in research that during symptomatic states, those suffering with PTSD have heightened amygdala responsivity, both while processing trauma and non-trauma related information.[19]

### 4.2 Hippocampus

The hippocampus is involved in explicit memory formation and the placement of context around fear conditioning. The hippocampus is also responsible for permanent storage of memories as well as the flexible interpretation of recalled information. In animals, hippocampal cell damage or misfunctioning can result from high levels of stressors and can be associated with memory impairment.

In humans, damage to this area of the brain can also result in greater polarization in response to people's immediate behavior, because of lack of recall for prior behavior to contextualize.[16,20]

Researchers can describe traumatic experience on the hippocampus as "allostasis". While responses to severe stress in life-threatening situations help survivability in the short term, if recovery from those stress responses is not adequate, these responses can cause deleterious effects on psychological and physiological function, termed "allostatic load". In those with PTSD this stress response can become dysregulated and hyperactivity of the system sets in.[21]

The predominant finding of a majority of neuroimaging studies of the hippocampus is decreased hippocampal volumes in PTSD compared to healthy controls. Hippocampal volumes have been inversely associated with verbal memory deficits, combat exposure severity, dissociative symptom severity, depression severity, and PTSD symptom severity, meaning those with the most severe symptoms and trauma tend to have the smallest hippocampal volumes. [15,20]

4.3 Pre-frontal Cortex

The prefrontal cortex is well connected to the amygdala and is involved in the disposal of fear and fear memories. When the prefrontal cortex is damaged, or is less responsive, the normal reduction of fear and fear memories is not seen. In essence the Pre-frontal cortex can be thought of as the counter to the amygdala. The amygdala creates fear and the pre-frontal cortex removes fear that is no longer helpful.

In neuroimaging studies, the medial prefrontal cortex appears to be volumetrically smaller and appears hyporesponsive (less responsive) in PTSD patients with performance of emotional cognitive tasks, continuous performance tasks, and emotional word retrieval tasks. Medial prefrontal cortex responsibility is inversely associated with PTSD symptom severity. This finding would be in line with PTSD symptoms of exhibiting persistent and inappropriate fear responses.[20]

## 5. Cannabinoids

The endocannabinoid system within humans is made up of:

- Cannabinoid receptors as part of a neuro-modulatory lipid system (CB1 and CB2 as primary)
- Endogenous cannabinoids (eCBs)
    - Anandamide and 2-arachidonyl-glycerol (2AG)
- Enzymes involved in synthesis and breakdown of the eCBs

eCBs are synthesized "on-demand" by the body at the post-synaptic sites of neurons after an increase in neural activity and calcium ion influx. Their main function at this site appears to function as retrograde neurotransmitters, modulating other neurotransmitter systems. Increasingly there is also research that implicates a potential endocannabinoid deficiency as a role in some disease states.[29]

Cannabinoid type 1 (CB1) receptors are some of the most abundant G-protein-coupled receptors in the CNS, found in almost all neuronal types in the brain with high concentrations within the amygdala-hippocampal-cortico circuit. As seen above, structures like the amygdala are responsible for coordinating fear-related behaviors. While primary effects of CB1 receptors appear to be regulation of fast synaptic transmission, recent research has implicated mediation of glucocorticoid action by CB1 receptors. If we recall, the consolidation of traumatic memories is driven by glucocorticoid-hormone

potentiation of norepinephrine inputs. Therefore, there may be a role of CB1 receptor interaction in PTSD.[19]

There are also non-CB receptor targets of eCB molecules, including peroxisome proliferator-activated receptor and transient receptor potential vanilloid type 1 (TRPV1), though these have not been as well studied in relation to PTSD.[64]

Further reading on the specific expression sites within the brain as well as cannabinoid signaling and PTSD can be found further in:

- Akirav "*The role of cannabinoids in modulating emotional and non-emotional memory processes in the hippocampus*"[14]
- Hill et al "*Integrating Endocannabinoid Signaling and Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder"*[64]
- Ney et al "*Cannabinoid interventions for PTSD: Where to next*?"[77]

## 6. Conventional Treatments:

Conventional treatments for PTSD include psychological therapies, cognitive therapies for desensitization, and pharmaceutical interventions.

Common pharmaceutical interventions for PTSD with their side effects can be seen below. For a comparison, the side effects of Sativex, a 1:1 ratio of CBD to THC can also be seen below. The side effects for Sativex can be found in GW literature describing this European and Canadian approved pharmaceutical[3,4]

| Drug | Common side Effects | Uncommon side effects | Rare side effects |
|---|---|---|---|
| Citalopram (Depression)(SSRI)[5] | Decreased Sex Drive<br>Drowsiness<br>Nausea<br>Insomnia<br>Fatigue<br>Dry Mouth | Agitation<br>Blurred Vision<br>Confusion<br>Fever<br>**Lack of Emotion**<br>**Memory changes**<br>Head and Body aches | Seizures<br>Unusual weakness<br>Irregular heartbeat<br>Swelling<br>Aggression<br>Depersonalization<br>**Suicidal ideation** |
| Clonazepam (panic attacks)[6] | Aches and Pains<br>Difficulty breathing<br>Feeling sad or empty<br>Shakiness<br>Drowsiness<br>Trouble concentrating | Memory changes<br>Changes in Urination<br>Mood or mental changes<br>Changes in Speech<br>Vomiting<br>**Depression** | Confusion<br>Lack of emotion<br>**Suicidal thoughts** |
| Prazosin (insomnia and nightmares)[7] | Dizziness<br>Headache<br>Fatigue<br>Urination changes<br>Heartbeat changes | Light-headedness<br>**Depression**<br>Vertigo | Perceptual disturbances<br>**Depersonalization**<br>**Hallucinations**<br>Distortion of body image |
| Risperdal (anti-psychotic)[8] | Fatigue<br>Vomiting | Pain and numbness<br>Sexual disturbances | **Confusion**<br>Weak heartbeat |

| | | | |
|---|---|---|---|
| | Fever<br>Parkinsonism<br>Anxiety<br>Tremor | Difficulty breathing<br>**Aggressive behavior**<br>Memory problems<br>Dizziness | Unusual Bleeding<br>Spasms<br>Vision problems |
| Lamotrigine (Mood stabilization)[9] | Changes in vision<br>Unsteadiness<br>Headache<br>Nausea<br>Vomiting<br>Tremor | Anxiety<br>Confusion<br>**Depression**<br>Seizures<br>Trouble sleeping | Fever<br>Memory loss<br>Muscle cramps<br>Pain or weakness<br>Trouble breathing<br>**Suicidal ideation** |
| Paroxetine (anti-depressant)[10] | Headache<br>Nervousness<br>Restlessness<br>Dizziness<br>Insomnia<br>Sexual disturbances | Agitation<br>Confusion<br>Difficulty breathing<br>Heartbeat changes | **Suicidal ideation**<br>Seizures<br>Twitching<br>Decrease in body movement<br>Inability to move eyes |
| Sativex (1:1 ratio of CBD: THC | Fatigue<br>Nausea<br>Dizziness | Disorientation<br>Mood changes<br>Dissociation<br>Euphoria<br>Heartbeat changes<br>Dry Mouth | Suicidal ideation<br>Paranoia<br>Hypertension<br>Hypotension<br>Memory disturbance |

*For those with figures available, Common = > 1 in 10; Uncommon = ~1 in 100; Rare = <1 in 100 patients

The medications chosen above are commonly prescribed medications from within the various categories of medications used to treat PTSD. This is not an exhaustive list of side effects, but rather an example of the side effects faced by patients currently treated by these types of medications. In addition, many of these drugs have serious withdrawal symptoms that include seizures, psychotic episodes, and depression.[2]

Many of these medications have similar acute side effects, as well as similar amounts of conflicting data showing effectiveness/ineffectiveness in certain populations[18]. It is interesting to note that all anti-depressants can carry the risk of increased anxiety and depression, but a risk-benefit analysis is needed if these medications are also providing benefit.

The broad range of symptoms observed in PTSD make treatment challenging. Selective serotonin reuptake inhibitors (SSRIs) have the strongest empirical support in treatment literature, however even then, fewer than 50% of PTSD patients improve on them.[60]

Interestingly, some research seems to relay that those experiencing single or short-lived traumatic events tend to respond better to standard pharmacotherapy, whereas individuals experiencing constant, ongoing, or reoccurring traumatic situations show less benefits from standard pharmacotherapy.[65,66,67] Combat PTSD especially would seem to fit in a chronic or long-term stress environment and may be an apt environment for introduction of adjunctive or alternative therapies, especially with the high percentage of patients that do not tolerate/respond well to conventional treatment options for PTSD.[51]

## 7. PTSD Symptoms holding Cannabis Potential

It is seen in many papers that patients recording high PTSD scores generally have increased rates of coping-oriented use of cannabis than those recording low PTSD severity scores.[60,62,63] This may be due to positive effects within cannabis for specific symptoms of PTSD. Below are some descriptions of symptoms in which cannabinoid therapy could be helpful. Below that section are 2 sections detailing non-exhaustive lists of papers supporting these claims both in animals and humans. An excellent review can be found as Appendix 5.[57]

7.1 Fear-Memory

Research within this area includes three main areas where cannabinoids may play a part that are explored in detail in the studies section:

- dampening the cue-elicited fear response
- blocking consolidation of fear memories
- facilitating fear-memory extinction[30]

7.2 Anxiety

Cannabinoids have shown promise in the management of generalized anxiety via reduction of anxiety-like behavor.[30,31] While it is well-known that anxiety or paranoia can also be increased at higher levels, this is likely due to a biphasic effect of cannabis at appropriate vs. inappropriate dosages. More current work has looked at varying ratios of CBD:THC as a way to address some of these side effects, however on the whole we see an anti-anxiety effect that could be helpful for those with PTSD.

Patients within Iowa's program are titrated through low-dosing to a dose where side effect profiles are known to the patient before going to standardized dosing. In this way the lowest appropriate dose can be found, and a lower potential side-effect profile could be attained.

7.3 Depression

Depressive and non-depressive effects are less studied in humans, however in a few new animal studies, administrations with CBD were associated with reductions in the loss of interest in pleasurable behavior and/or exploratory behavior. This means animals that were administered CBD were more interested in positive behaviors and exploring. This is likely through increased glutamate availability via 5-HT1A receptor activation. This is an area that could be expanded upon in human research, but animal models are positive about the potential for using cannabinoids as modifiers to negative mood-behaviors.[30]

There is some discussion about whether cannabis use exacerbates or initiates depressive feelings, or if we simply see persons with depressive feelings tending to self-medicate more with cannabis. In a 3-year population (non-PTSD) based study there were no longitudinal associations between cannabis use and incidence of depression or anxiety. It is likely that studies looking at worse symptoms between those using cannabis with PTSD and those non-using are likely due to the self-selection of those with worse symptoms tending to self-medicate more than those with less severe symptoms. [51,52]

7.4 Sleep

This area explores use of THC, CBD and THC + CBD on sleep, specifically for quality of sleep and also for decrease in nightmares. Though there are some studies that show inconsistent effect generally due to

dose variances, on the whole, there is research to suggest that cannabinoids can help with sleep quality and the reduction of distressing dreams in PTSD models.

In studies looking at use of marijuana for coping in post-traumatic stress, there was a strong correlation between the severity of PTSD-related sleep disturbances and the amount of cannabis use, suggesting that using cannabis for coping reasons is more central to PTSD system severity and comorbidity of sleep problems, then using it for other reasons.[61,62]

7.5 Chronic Pain

Chronic pain in PTSD populations can be caused by the actual traumatic event and/or the chronic stress associated with this condition. For some people whose pain is caused by the traumatic event, this pain may actually serve as a reminder of the traumatic event, which can make other PTSD symptoms even worse.[40] In fact, people with chronic pain and comorbid PTSD report more severe pain, poorer quality of life, and more depressive symptoms than those with chronic pain alone.[42] Those with pain diagnoses are also often prescribed opioids.

Among US Veterans of Iraq and Afghanistan, mental health diagnoses like PTSD were associated with an increased risk of receiving opioids for pain, high-risk opioid use, and adverse clinical outcomes associated with this[79] Veterans are twice as likely as non-veterans to die from overdoses of painkillers, reflecting high levels of chronic pain among vets.[38] Within our experience at two dispensaries in Iowa, many chronic pain patients have been able to reduce their dosages of opioid-like pain-killers. This is mirrored in other research.[47]

According to the National Academies of Science, there is conclusive or substantial evidence that cannabis and/or cannabinoids are effective for treatment of chronic pain in adults, and therefore may be positive in relieving some of the PTSD symptoms that are associated with chronic pain.[41] Likely due to this pain, those with PTSD tend to struggle with opioid use at higher rates than the general public.[17]

7.6 Traumatic Brain Injury (TBI)

According to the Veterans Affairs website, combat conflicts in the Middle East have resulted in increased amount of veterans that have TBI. The cause of this can be blasts, motor vehicle accidents, gunshot wounds, and general injury. In fact, PTSD and TBI often co-exist because brain injuries are often sustained via a traumatic experience, in both veteran and general populations. Recent evidence suggests that this lingering symptomology may be due to stress reactions after TBI, with about 5% of those sustaining a TBI experiencing persistent functional difficulties.[70]

Traumatic brain injury can also trigger accumulation of harmful mediators that may lead to secondary damage, with unknown effects on PTSD. There is increasing research that endocannabinoids as well as other molecules that interact with the cannabinoid receptors may have neuroprotective effects following brain injury. While most of these effects' papers explore the short time frames since injury, it may be possible that neuroprotection could assist in lingering symptomology. [72,73,74,75,76]

## 8. Studies

The below work will discuss literature and potential benefits associated with medical cannabis. This is in no way comprehensive of all the in vitro, animal, or human work available in the scientific realm, and is

meant to give an overview. As with all areas of science, more data is always better. With more and more large scales trials being investigated, this area of research will only grow.

In summary: Patients using cannabis may experience relief from anxiety, flashbacks, and nightmares. Symptomatically patients may have increased quality of sleep, as well as assistance of other symptoms such as pain and depression.

## *8.1 Animal*

### *Marsicano et al "The Endogenous Cannabinoid System Controls Extinction of Aversive Memories"*[23]

In this mouse model, CB1 deficient mice were generated and tested against CB1 positive mice in auditory fear conditioning tests. This test is dependent on the amygdala and allows us to see different phases of fear memory formation such as acquisition, consolidation, and extinction (removing the fear memory). Mice are given a foot shock that is associated with a tone, and over time their "freeze" response is measured as an indicator of aversive memory.

- CB1 deficient mice were more likely to
    - Show non-exploratory activity in open arm maze
    - Show increased time of fear response to shocks, even when tone was presented with no shock (no diminished freezing response)
        - CB1 mice may have diminished ability to remove fear memories
        - Blocking CB1 in wildtype mice had the same effect
    - No differences in the memory acquisition, consolidation, or recall
    - **Results indicate an involvement of the endogenous cannabinoid system in extinction of aversive memories**

### *Pamplona et al "Short and long-term effects of cannabinoids on the extinction of contextual fear memory in rats"*[24]

Rats were subjected to the foot shock test with and without cannabinoid agonist drugs. Agonists are those that activate the cannabinoid receptors.

- Cannabinoid agonists facilitated short-term fear memory extinction
- Enhancement of endocannabinoid levels via metabolism inhibitors also enhanced fear memory extinction
    - **Would indicate that adding mimetic cannabinoids may enhance removal of fearful memories**

### *Cinar et al "Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity"*[25]

This paper explores anandamide (the body's endocannabinoid mimetic molecule of THC) and its role in stress-reactivity via mouse model of fear and use of AM3506, a FAAH inhibitor, leading to larger amounts of anandamide.

- Variations in FAAH gene may predict individual differences in amygdala threat-precession
- FAAH variant mice exhibited quicker habituation of amygdala reactivity
    - May explain inter-human variability to stress response
- Augmenting amygdala anandamide enables extinction-driven reductions in fear in mice
- **Supplementing with endocannabinoid like molecules (like THC) may promoting stress-coping in humans**

### *Burstein et al "Cannabinoids prevent depressive-like symptoms and alterations in BDNF expression in a rat model of PTSD"*[35]

Examination of a rat model of PTSD investigating whether cannabinoids could prevent the long-term depressive-like symptoms induced by exposure to shock and situation reminder model of PTSD.

- Cannabinoids prevented the shock-induced alteration in social recognition, locomotion, passive coping, anxiety-like behavior, and fear extinction
- Cannabinoids decreased brain-derived neurotrophic factor (BDNF) in the brain
    - Significant correlations were found between depressive—like behaviors and BDNF levels in the brain
- **Findings suggest cannabinoids may help prevent depressive and PTSD-like symptoms following exposure to severe stress**

### *Bluett et al "Endocannabinoid signaling modulates susceptibility to traumatic stress exposure"*[36]

Laboratory mice with their innate individual differences in stress-susceptibility were used to explore the role of endogenous cannabinoid 2-arachidonoylglycerol (2-AG) in stress resilience

- **Systemic 2-AG endocannabinoid) augmentation is associated with a stress-resilient phenotype and enhances resilience I previously susceptible mice**
- 2-AG depletion of CB1 receptor blockade increases susceptibility in previously resilient mice
- Amygdala-specific 2-AG depletion impairs successful adaptation to repeated stress
- **Findings suggest that systemic endocannabinoids and their healthy tone play a role in and may be responsible for differences in stress-resilience among individuals.**

Many other papers support these papers, as well as animal models showing the contribution of CB1 cannabinoid agonists to improvement of stress induced anxiety and depressive behaviors in animals.

Additional reading can be found in the following sources

- Haller et al. "*CB1 cannabinoid receptors mediate anxiolytic effects: convergent genetic and pharmacological evidence with CB1-specific agents*"[27]

- Resstel et al. "*5-HT$_{1A}$ receptors are involved in the cannabidiol-induced attenuation of behavioral and cardiovascular responses to acute restrain stress in rats*"[54]

- Ching Lin et al. "*Effects of intra-amygdala infusion of CB1 receptor agonists on the reconsolidation of fear-potentiated startle"*[55]

- Chhatwal et al. "*Functional Interactions between Endocannabinoid and CCK Neurotransmitter Systems May be Critical for Extinction Learning*"[56]

- Campos et al. "*Predator threat stress promotes long lasting anxiety-like behaviors and modulates synaptophysin and CB1 receptors expression in brain areas associated with PTSD symptoms*"[58]

- Pamplona et al. *"The cannabinoid receptor agonist WIN 55,212-2 facilitates the extinction of contextual fear memory and spatial memory in rats*"[59]

- Xing et al. "*Cannabinoid receptor expression and phosphorylation are differentially regulated between male and female cerebellum and brain stem after repeated stress: Implication for PTSD and drug abuse"*[68]

- Haller et al. "*The effects of genetic and pharmacological blockade of the CB1 cannabinoid receptor on anxiety*"[26]

- Fidelman et al. "*Chronic treatment with URB597 ameliorates post-stress symptoms in a rat model of PTSD*"[78]

- Stern et al. "*Cannabidiol disrupts the consolidation of specific and generalized fear memories via dorsal hippocampus CB1 and CB2 receptors"*[80]

## *8.2 Human*

### *Greer et al "PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program"*[13]

This paper was conducted using PTSD patients in New Mexico. It uses the CAPS scoring criteria, a frequently used instrument created by the National Center for PTSD. On this form, symptom criterion including intensity are combined to create a total CAPS score. This study looked at 80 patients over 2 years, and study procedures were approved by the IRB at Harbor UCLA Medical center.

- Observational, in that patients were not limited to dose or form of cannabis
- Cannabis use vs no-cannabis use showed statistically significant ($p<0.01$) reductions in CAPS scores

- **Patients CAPS scores showed over 75% reduction in all three PTSD symptom clusters**
    - **Reexperiencing, avoidance, hyperarousal**
- Limitation: Pre-cannabis reflections were retrospective; self-selected group of those that would participate in the study.

### *Elliot et al "PTSD and Cannabis-Related Coping Among Recent Veterans in New York City"*[11]

This paper explores interview and focus group of veterans and their use of coping strategies. While anecdotal, it is of interest that this paper also explored experiences with pharmaceuticals in comparison to cannabis for PTSD. Questioning on PTSD and Cannabis were elicited separately, and recruitment and data collection were approved by the National Development and Research Institutes institutional review board.

- Patients described PTSD as "managing a stream of unending thoughts and hyperarousal"
    - Relaxation/calming effects of Cannabis is of greater significance in alleviation of symptoms than cannabis simply "providing distraction"
- Participants universally spoke to the strong personal dedication required to overcome the challenges of PTSD
- Patients reported only negative experiences of alcohol use in regard to PTSD symptoms
- Most patients reported cannabis as mitigating stress and anxiety
- **Effects noted on pain relief for patients with cannabis use**
- **Prevent of decrease unwanted flashbacks and disruptive memories**
- **Help with establishment of supportive social structures**

### *Thomas Johnston II "The Treatment of Post Traumatic Stress Disorder Utilizing Cannabis Sativa as an Adjunctive Pharmacologic Agent"*[18]

This clinical research thesis submitted to the American School of Professional Psychology provides a comprehensive survey of the literature and critical analysis related to PTSD and cannabis. Findings support:

- **Cannabis can be an efficacious pharmacological agent especially with "talk therapy"**
    - **Decreased side effects allowing patients to be present during therapy sessions**
    - **Increased discussion and re-connection with self**
    - **Reduced timeframe to reach clinical doses**
- Effectiveness of cannabis for chronic long-term sufferers of PTSD
    - Standard psychotropic medications have been less effective with this population
- Cannabis when taken correctly has a better side effect profile than other pharmaceuticals for PTSD.

*Neumeister et al. "Elevated Brain Cannabinoid CB1 Receptor Availability in Posttraumatic Stress Disorder: A Positron Emission Tomography Study*[19]

This *in vivo* imaging study compares individuals with untreated PTSD to healthy controls with trauma history (TC) and healthy controls without trauma histories (HC) using PET scanning with CB1-selective radioligands.

- Compared to controls, patients with PTSD had reduced levels of endocannabinoid anandamide ($p<0.05$)
    - Suggest lower anandamide tone in PTSD patients
- Compared to controls, patients with PTSD had upregulated CB1 receptor ($p<0.05$)
    - May result from receptor upregulation due to lower levels of endogenous endocannabinoids
- **Results suggest that patients with PTSD present abnormal CB1 receptor mediated anandamide signaling**
    - **Supplementation with external cannabinoids may help mediate system**

*Fraser, Neuroscience and Therapeutics "The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder"*[22]

Canadian open-label clinical trial to evaluate the effects of nabilone, an endocannabinoid receptor agonist for treatment of nightmares

- Nabilone – synthetic cannabinoid similar to THC
- Patients were not on any other psychotropic medications during study
- **72% of patients receiving the synthetic cannabinoid experienced either cessation of nightmares of significant reduction intensity**
- Subjective improvement of quality of sleep and day-time flashbacks were also noted by some patients

*Trezza and Campolongo "The Endocannabinoid System as a Possible Target to Treat both the Cognitive and Emotional Features of Post-Traumatic Stress Disorder"*[28]

Review identifying research about cannabis and PTSD as well as endocananbinoid neurotransmission in emotional memory processing

- Research indicating illicit cannabis use in relation to PTSD patients
    - Could be because of self-coping done by those with treatment resistance
- Data about effects of cannabinoids in fear memory extinction fairly prevalent
    - **Compounds mimicking endocannabinoids may facilitate PTSD recovery**

*Akirav "The role of cannabinoids in modulating emotional and non-emotional memory processes in the hippocampus"*[14]

Review looking at research on cannabinoids and their effects on hippocampal memory and plasticity via exploration of agonists and antagonists of the cannabinoid receptors.

- Effects of cannabinoids on memory and plasticity are complex and dependent on several different factors
    - Nature of task (emotional vs non-emotional)
    - Stage of memory (acquisition, retrieval, extinction)
    - Experimental model used
- Behavioral effects can vary as a function of dose, route of administration, and specific cannabinoid used
- **eCB system modulates unconditioned stress and anxiety-like responses**
    - **inhibition of eCB signaling increases stress and anxiety**
    - **moderate increases in eCB signaling decreases stress and anxiety**
        - Important to find correct dose
    - **modulating anxiety-like responses may help in PTSD**

*Roitman et al. "Preliminary, Open-Label, Pilot Study of Add-on Oral D9 THC in Chronic Post-Traumatic Stress Disorder"*[32]

Short communication looking at 10 outpatients with chronic PTSD on stable medication and the add-on of THC for sleep

- No side effects leading to discontinuation
- **Statistically significant improvement in**
    - **Global symptom severity**
    - **Sleep quality**
    - **Decreased frequency of nightmares**
    - **Decreased PTSD hyperarousal symptoms**

*Jetly et al "The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares – a preliminary randomized, double-blind, placebo-controlled cross-over design study"*[33]

Clinical trial to investigate the efficacy of nabilone (synthetic THC) in reduced frequency of nightmares in Canadian male military personnel with PTSD. These patients have despite receiving standard treatment continued to experience trauma-related nightmares. Though a small sample size, these are the findings

- **Significant improvements in distressing dream scores as measured by CAPS**
- Improvements in sleep for those with PTSD
- No adverse events that were severe or resulted in a drop-out

*Russo et al "Cannabis, Pain, and Sleep: Lessons from Therapeutic Clinical Trials of Sativex, a Cannabis-based Medicine"*[34]

Review examining modern studies on the effects of THC and CBD on sleep especially in the context of medical treatment of neuropathic pain using a product that is plant derived with a 1:1 ratio of CBD:THC.

- Data from over 2000 subjects in numerous Phase I-III studies
- **3mg-300mg Sativex per day (1.5-150mg THC/day)**
    - **Up to 27g/90 day supply**
- **Markedimprovement in subjective sleep parameters in patients with wide variety of pain conditions**
- Acceptable adverse event profile
- No tolerance to the benefit of Sativex on pain or sleep
- No need for dosage increases have been noted in safety extension studies up to 4 years.

*Tikun Olam "6 month questionnaire of PTSD symptoms before and after treatment"*[37]

This was a questionnaire surveying patients in Israel with PTSD symptoms before an after 6 months of treatment, including pain intensity, aversive memory frequency and general quality of life

- **96% of those who completed 6 months of treatment reported moderate to significant improvement in their symptoms**
- 54% of patients reduced the number of medications they took
- Acceptable adverse side effect profile
- Significant improvements in pain control, quality of life, and ability to deal with stress
- **Patients took an average of 200mg THC/day (within the form of smoking 1g flower)**
    - **Some patients smoking 3.3g/day of Alaska strain (30% THC)**
        - **Max dosage of 990mg THC/day**
    - **Up to 90g/90 day supply**

*Cameron et al "Use of a Synthetic Cannabinoid in a Correctional Population for Posttraumatic Stress Disorder – Related insomnia and nightmares, chronic pain, Harm reduction, and other indications"*[39]

A retrospective study of 104 male inmates with serious mental illness given nabilone, a synthetic THC

- **Significant improvements in**
    - **PTSD symptoms**
    - PTSD associated insomnia and nightmares
    - Global Assessment of Function
    - Subjective improvements in chronic pain

*Hill et al "Integrating Endocannabinoid Signaling and Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder"*[48]

Review of the current state of knowledge regarding the effects of cannabis and cannabinoids in PTSD and the preclinical and clinical literature on the effects of cannabinoids and endogenous cannabinoid signaling systems in the regulation of biological processes.

- Authors propose that a state of endocannabinoid deficiency could present a stress susceptibility endophenotype
- Could indicate stress susceptibility in humans related to trauma is interlaced with endocannabinoids
- **Provide biologically plausible support for the self-medication hypothesis used to explain high rates of cannabis use in patients with trauma-related disorders**

*Mashiah, MD, MHA Deputy Director of Abarbanel Mental Hospital Israel (2012) "Medical Cannabis as a Treatment for Chronic Combat PTSD – Promising Results in an Open Pilot Study"*[49]

Unpublished open pilot study at the Abarbanel Mental Hospital in Israel presented by the doctor in charge of licensing PTSD participants in Israel. The study was designed to test the effects of smoked cannabis on symptoms of chronic combat PTSD.

- Amount limit was 100grams of flower/30 days
  - **Patients could take 730mg/day THC**
  - **Equates to 63g/90 days THC**
- Symptom reduction was seen in second CAPS assessment
- **Patients still had PTSD symptoms, but cannabis use was associated with a reduction in these symptoms**

*Tull et "Marijuana Dependence Moderates the Effect of Posttraumatic Stress Disorder on Trauma Cue Reactivity in Substance Dependent Patients"*[50]

Individuals with PTSD are at heightened risk for marijuana use. This study explores the ways in which marijuana may affect in-the-moment emotional responding among individuals with PTSD. In this way emotional reactivity was measured in those with PTSD (n=202) that were cannabis users compared to those with PTSD that were not cannabis users, compared to those without PTSD

- PTSD vs non-PTSD showed greater emotional reactivity
- **Emotional reactivity to adverse memories was higher in the PTSD group that did not use cannabis**
- Cannabis using patients reported less PTSD emotional reactivity during interviews where negative affect was studied
- No effects were seen on cortisol levels

9. **Other states.**

Over 28 States' Medical Programs contain PTSD as a condition approved for medical use. This includes Minnesota, and Illinois, states that border Iowa. With this many states including PTSD as an approved condition within their medical programs, many veterans do have the option to try this form of relief, but of course it was not always an easy decision for these states in the beginning.

Arizona's director of Health services (Dr. Christ) initially denied the original PTSD petition for the state at the time (2013) due to "lack of scientific evidence". However, after subsequent papers published in 2014, the director changed their position stating, "In other words, the information presented by the Petitioners at the hearing and the subsequent published study provided evidence that marijuana may be helpful in the *palliative care* of PTSD in some patients." PTSD is now an approved condition in Arizona.[12]

With our bordering states Minnesota and Illinois both serving those with PTSD it is imperative that we provide such a compassionate alterative to our PTSD communities as well.

10. **Iowa as a "right to try" state**

In 2017 Governor Branstad signed into law SF404 "A bill for an act relating to the use of experimental treatments for patients with a terminal illness" better known as Iowa's "right to try" act. This bill was passed unanimously through both the house and senate before being signed into law.

As of August 2018, 41 states have enacted "right to try" laws that allow terminally ill patients access to therapeutics that have not been approved by the FDA, under the auspice of compassionate care.

While many may argue that PTSD is not a terminal illness, for those that are part of the shocking suicide statistic of 21 veteran suicides per day, one could argue that for these people PTSD is a terminal illness and that PTSD is a potentially fatal disorder. With this mindset, any therapeutic that could make a difference should be allowed under a compassionate care and right to try.

11. **Conclusion:**

**Cannabinoids are a promising method for pharmacological treatment of PTSD symptomology. Both animal and human trials show potential in mitigating symptomatic effects of PTSD such as fearful memory, chronic pain, sleep disruption, and anxiety.**

**References:**


1. Betthauser, Kevin, et al. “Use and Effects of Cannabinoids in Military Veterans with Posttraumatic Stress Disorder.” *American Journal of Health-System Pharmacy*, vol. 72, no. 15, 2015, pp. 1279–1284., doi:10.2146/ajhp140523

2. Maren Schroeder “Minnesota Medical Cannabis Program Petition to Add PTSD” 2016

3: Sativex oromucosal spray pharmaceutical monograph – accessed at: https://www.nps.org.au/assets/medicines/c6e1d13b-cc33-45a4-8e43-a82600bbc31d-reduced.pdf

4. Bayer Sativex oromucosal spray monograph accessed at: https://www.bayer.ca/omr/online/sativex-pm-en.pdf

5. Citalopram pharmaceutical monograph accessed at: https://www.sandoz.ca/sites/www.sandoz.ca/files/Citalopram_TAB_Monograph.pdf

6. Klonopin pharmaceutical monograph accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017533s053,020813s009lbl.pdf

7. Prazosin hydrochloride pharmaceutical monograph accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017442s033lbl.pdf

8. Risperdal pharmaceutical monograph accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020272s056,020588s044,021346s033,021444s03lbl.pdf

9.Lamictal pharmaceutical monograph accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020241s037s038,020764s030s031lbl.pdf

10. Paroxetine hydrochloride monograph accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020031s060,020936s037,020710s024lbl.pdf

11. Elliott, Luther, et al. “PTSD and Cannabis-Related Coping Among Recent Veterans in New York City.” *Contemporary Drug Problems*, vol. 42, no. 1, 2015, pp. 60–76., doi:10.1177/0091450915570309.

12: Christ, Cara. “Director's Decision: Cannabis & Palliative Care for PTSD.” *AZ Dept. of Health Services Director's Blog*, 2014, directorsblog.health.azdhs.gov/directors-decision-cannabis-palliative-care-for-ptsd/.

13. Greer, George R., et al. “PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program.” *Journal of Psychoactive Drugs*, vol. 46, no. 1, 2014, pp. 73–77., doi:10.1080/02791072.2013.873843.

14. Akirav, Irit. “The Role of Cannabinoids in Modulating Emotional and Non-Emotional Memory Processes in the Hippocampus.” *Frontiers in Behavioral Neuroscience*, vol. 5, 2011, doi:10.3389/fnbeh.2011.00034.

15. Logue, Mark, et al. “Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results from Posttraumatic Stress Disorder Consortia.” *Biological Psychiatry*, vol. 83, no. 3, 1 Feb. 2018, pp. 244–253., doi:doi:10.1016/j.biopsych.2017.09.006.

16. Rubin, Rachael D., et al. “The Role of the Hippocampus in Flexible Cognition and Social Behavior.” *Frontiers in Human Neuroscience*, vol. 8, 2014, doi:10.3389/fnhum.2014.00742.

17. Bohnert, Kipling M., et al. “Positive Posttraumatic Stress Disorder Screens among First-Time Medical Cannabis Patients: Prevalence and Association with Other Substance Use.” *Addictive Behaviors*, vol. 39, no. 10, 2014, pp. 1414–1417., doi:10.1016/j.addbeh.2014.05.022.

18. Johnston , Thomas. “The Treatment of Post Traumatic Stress Disorder Utilizing Cannabis Sativa as an Adjunctive Pharmacological Agent.” *Argosy University*, 2010. accessed at: https://www.researchgate.net/publication/215757449_The_Treatment_of_Post_Traumatic_Stress_Disorder_Utilizing_Cannabis_Sativa_as_an_Adjunctive_Pharmacological_Agent

19. Neumeister, Alexander, et al. “Elevated Brain Cannabinoid CB1 Receptor Availability in Posttraumatic Stress Disorder: A Positron Emission Tomography Study.” *Molecular Psychiatry*, vol. 18, no. 9, Sept. 2013, pp. 1034–1040., doi:doi:10.1038/mp.2013.61.

20. Shin, L. M., et al. “Amygdala, Medial Prefrontal Cortex, and Hippocampal Function in PTSD.” *Annals of the New York Academy of Sciences*, vol. 1071, no. 1, 2006, pp. 67–79., doi:10.1196/annals.1364.007.

21: Charney, Dennis S. “Psychobiological Mechanisms of Resilience and Vulnerability: Implications for Successful Adaptation to Extreme Stress.” *American Journal of Psychiatry*, vol. 161, no. 2, 2004, pp. 195–216., doi:10.1176/appi.ajp.161.2.195.

22. Fraser, George A. “The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD).” *CNS Neuroscience & Therapeutics*, vol. 15, no. 1, 2009, pp. 84–88., doi:10.1111/j.1755-5949.2008.00071.x.

23. Marsicano, Giovanni, et al. “The Endogenous Cannabinoid System Controls Extinction of Aversive Memories.” *Nature*, 2002, doi:10.1038/news020729-6.

24. Pamplona, Fabrício A., et al. “Short- and Long-Term Effects of Cannabinoids on the Extinction of Contextual Fear Memory in Rats.” *Neurobiology of Learning and Memory*, vol. 90, no. 1, 2008, pp. 290–293., doi:10.1016/j.nlm.2008.04.003.

25. Gunduz-Cinar, O, et al. “Convergent Translational Evidence of a Role for Anandamide in Amygdala-Mediated Fear Extinction, Threat Processing and Stress-Reactivity.” *Molecular Psychiatry*, vol. 18, no. 7, 2012, pp. 813–823., doi:10.1038/mp.2012.72.

26: Haller J, Bakos N, Szirmay M, Ledent C, Freund TF. The effects of genetic and pharmacological blockade of the CB1 cannabinoid receptor on anxiety. Eur J Neurosci. 2002; 16(7):1395–1398.

27: Haller J, Varga B, Ledent C, Freund TF. CB1 cannabinoid receptors mediate anxiolytic effects: convergent genetic and pharmacological evidence with CB1-specific agents. Behav Pharmacol. 2004; 15(4):299–304

28. Trezza, Viviana, and Patrizia Campolongo. "The Endocannabinoid System as a Possible Target to Treat Both the Cognitive and Emotional Features of Post-Traumatic Stress Disorder (PTSD)." *Frontiers in Behavioral Neuroscience*, vol. 7, 2013, doi:10.3389/fnbeh.2013.00100.

29: Russo, Ethan B. "Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes." *Cannabis and Cannabinoid Research*, vol. 1, no. 1, 2016, pp. 154–165., doi:10.1089/can.2016.0009.

30. Loflin, Mallory Je, et al. "Cannabinoids as Therapeutic for PTSD." *Current Opinion in Psychology*, vol. 14, 2017, pp. 78–83., doi:10.1016/j.copsyc.2016.12.001.

31: Sethi, B.b., et al. "Antianxiety Effect of Cannabis: Involvement of Central Benzodiazepine Receptors." *Biological Psychiatry*, vol. 21, no. 1, 1986, pp. 3–10., doi:10.1016/0006-3223(86)90003-x.

32: Roitman, Pablo, et al. "Preliminary, Open-Label, Pilot Study of Add-On Oral Δ9-Tetrahydrocannabinol in Chronic Post-Traumatic Stress Disorder." *Clinical Drug Investigation*, vol. 34, no. 8, 2014, pp. 587–591., doi:10.1007/s40261-014-0212-3.

33 Jetly, Rakesh, et al. "The Efficacy of Nabilone, a Synthetic Cannabinoid, in the Treatment of PTSD-Associated Nightmares: A Preliminary Randomized, Double-Blind, Placebo-Controlled Cross-over Design Study." *Psychoneuroendocrinology*, vol. 51, 2015, pp. 585–588., doi:10.1016/j.psyneuen.2014.11.002.

34. Russo, Ethan B., et al. "Cannabis, Pain, and Sleep: Lessons from Therapeutic Clinical Trials of Sativex®, a Cannabis-Based Medicine." *ChemInform*, vol. 38, no. 47, 2007, doi:10.1002/chin.200747254.

35. Burstein, Or, et al. "Cannabinoids Prevent Depressive-like Symptoms and Alterations in BDNF Expression in a Rat Model of PTSD." *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 84, 2018, pp. 129–139., doi:10.1016/j.pnpbp.2018.01.026.

36. Bluett, Rebecca J., et al. "Endocannabinoid Signalling Modulates Susceptibility to Traumatic Stress Exposure." *Nature Communications*, vol. 8, no. 1, 2017, doi:10.1038/ncomms14782.

37. Tikun Olam "Report of Tikun-Olam's PTSD Patients" Accessed at: https://tikunolamusa.com/ptsd_studies/

38. Goldberg, Rueters health "Opioid abuse crisis takes heavy toll on US Veterans accessed at: https://www.reuters.com/article/us-usa-veterans-opioids/opioid-abuse-crisis-takes-heavy-toll-on-u-s-veterans-idUSKBN1DA1B2

39. Cameron, Colin, et al. “Use of a Synthetic Cannabinoid in a Correctional Population for Posttraumatic Stress Disorder–Related Insomnia and Nightmares, Chronic Pain, Harm Reduction, and Other Indications.” *Journal of Clinical Psychopharmacology*, vol. 34, no. 5, 2014, pp. 559–564., doi:10.1097/jcp.0000000000000180.

40. US Department of Veterans Affairs “Chronic Pain and PTSD: A guide for Patients” accessed at: https://www.ptsd.va.gov/understand/related/chronic_pain.asp

41. National Academies of Science – Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda “The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research” *The National Academies Press* 2017. Doi: 10.17226/24625

42: Morasco, Benjamin J., et al. “The Relationship between PTSD and Chronic Pain: Mediating Role of Coping Strategies and Depression.” *Pain*, vol. 154, no. 4, 2013, pp. 609–616., doi:10.1016/j.pain.2013.01.001.

43: US Department of Veterans affairs “VA National Suicide Data Report 2005-2015” Accessed at: https://www.mentalhealth.va.gov/mentalhealth/suicide_prevention/data.asp

44: Jakupcak, Matthew, et al. “Posttraumatic Stress Disorder as a Risk Factor for Suicidal Ideation in Iraq and Afghanistan War Veterans.” *Journal of Traumatic Stress*, vol. 22, no. 4, 2009, pp. 303–306., doi:10.1002/jts.20423.

45: Pietrzak, Robert H., et al. “Risk and Protective Factors Associated with Suicidal Ideation in Veterans of Operations Enduring Freedom and Iraqi Freedom.” *Journal of Affective Disorders*, vol. 123, no. 1-3, 2010, pp. 102–107., doi:10.1016/j.jad.2009.08.001.

46: American Psychiatric Association Foundation – Center for Workplace Mental Health. Accessed at : http://workplacementalhealth.org/Mental-Health-Topics/Posttraumatic-Stress-Disorder

47. Schleider, Lihi Bar-Lev, et al. “Prospective Analysis of Safety and Efficacy of Medical Cannabis in Large Unselected Population of Patients with Cancer.” *European Journal of Internal Medicine*, vol. 49, 2018, pp. 37–43., doi:10.1016/j.ejim.2018.01.023.

48. Hill, Matthew N, et al. “Integrating Endocannabinoid Signaling and Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder.” *Neuropsychopharmacology*, vol. 43, no. 1, 2017, pp. 80–102., doi:10.1038/npp.2017.162.

49. Mashiah M. “Medical cannabis as treatment for chronic combat PTSD: Promising results in an open pilot study” *Presentation at Patients Out of Time Conference,* Tucson, AZ; 2012 April 28 accessed at: http://www.maps.org/research-archive/presentations/Mashiah-MotiApril27.pdf

50: Tull, Matthew T., et al. “Marijuana Dependence Moderates the Effect of Posttraumatic Stress Disorder on Trauma Cue Reactivity in Substance Dependent Patients.” *Drug and Alcohol Dependence*, vol. 159, 2016, pp. 219–226., doi:10.1016/j.drugalcdep.2015.12.014.

51: Shishko, PharmD. Residency Rounds Final Report “Medical Marijuana for the Treatment of Posttraumatic Stress disorder: Real symptom Re-leaf or just High Hopes” South Texas Veterans Health Care System – University of Texas

52: Danielsson, Anna, et al. “Cannabis Use, Depression and Anxiety: a 3-Year Prospective Population-Based Study.” *Journal of Affective Disorders*, vol. 193, 2016, pp. 103–108.

53. Kardiner, Abram. *The Traumatic Neuroses of War*. Martino Fine Books, 1941.

54. Resstel, Leonardo, et al. “5-HT1A Receptors Are Involved in the Cannabidiol-Induced Attenuation of Behavioural and Cardiovascular Responses to Acute Restraint Stress in Rats.” *British Journal of Pharmacology*, vol. 156, 2009, pp. 181–188., doi:10.1111/j.1476-5381.2008.00046.x.

55. Lin, H.-C., et al. “Effects of Intra-Amygdala Infusion of CB1 Receptor Agonists on the Reconsolidation of Fear-Potentiated Startle.” *Learning & Memory*, vol. 13, no. 3, 2006, pp. 316–321., doi:10.1101/lm.217006.

56. Chhatwal, Jasmeer P, et al. “Functional Interactions between Endocannabinoid and CCK Neurotransmitter Systems May Be Critical for Extinction Learning.” *Neuropsychopharmacology*, vol. 34, no. 2, 2008, pp. 509–521., doi:10.1038/npp.2008.97.

57. Berardi, Andrea, et al. “The Endocannabinoid System and Post Traumatic Stress Disorder (PTSD): From Preclinical Findings to Innovative Therapeutic Approaches in Clinical Settings.” *Pharmacological Research*, vol. 111, 2016, pp. 668–678., doi:10.1016/j.phrs.2016.07.024.

58. Campos, Alline Cristina, et al. “Predator Threat Stress Promotes Long Lasting Anxiety-like Behaviors and Modulates Synaptophysin and CB1 Receptors Expression in Brain Areas Associated with PTSD Symptoms.” *Neuroscience Letters*, vol. 533, 2013, pp. 34–38., doi:10.1016/j.neulet.2012.11.016.

59. Pamplona, Fabrício A., et al. “The Cannabinoid Receptor Agonist WIN 55,212-2 Facilitates the Extinction of Contextual Fear Memory and Spatial Memory in Rats.” *Psychopharmacology*, vol. 188, no. 4, 2006, pp. 641–649., doi:10.1007/s00213-006-0514-0.

60. Segev, Amir, and Irit Akirav. “Cannabinoids and Post-Traumatic Stress Disorder: Clinical and Preclinical Evidence for Treatment and Prevention.” *Behavioural Pharmacology*, vol. 27, Aug. 2016, pp. 561–569.

61. Metrik, Jane, et al. “The Mediating Roles of Coping, Sleep, and Anxiety Motives in Cannabis Use and Problems among Returning Veterans with PTSD and MDD.” *Psychology of Addictive Behaviors*, vol. 30, no. 7, 2016, pp. 743–754., doi:10.1037/adb0000210.

62. Bonn-Miller, Marcel O., et al. “Sleep Problems and PTSD Symptoms Interact to Predict Marijuana Use Coping Motives: A Preliminary Investigation.” *Journal of Dual Diagnosis*, vol. 6, no. 2, 2010, pp. 111–122., doi:10.1080/15504261003751887.

63. Kevorkian, Salpi, et al. “Associations among Trauma, Posttraumatic Stress Disorder, Cannabis Use, and Cannabis Use Disorder in a Nationally Representative Epidemiologic Sample.” *Psychology of Addictive Behaviors*, vol. 29, no. 3, 2015, pp. 633–638., doi:10.1037/adb0000110.

64. Hill, Matthew N, et al. “Integrating Endocannabinoid Signaling and Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder.” *Neuropsychopharmacology*, vol. 43, no. 1, 2018, pp. 80–102., doi:10.1038/npp.2017.162.

65. Stein, Murray B., et al. “Adjunctive Olanzapine for SSRI-Resistant Combat-Related PTSD: A Double-Blind, Placebo-Controlled Study.” *American Journal of Psychiatry*, vol. 159, no. 10, 2002, pp. 1777–1779., doi:10.1176/appi.ajp.159.10.1777.

66. Van der Kolk, BA, et al. “Fluoxetine in Posttraumatic Stress Disorder.” *Journal of Clinical Psychiatry*, vol. 55, no. 12, Dec. 1994, pp. 517–522.

67 Reist, C et al. “A controlled trial of desipramine in 18 men with Posttraumatic Stress Disorder. “ *The American Journal of Psychiatry*, 146(4), 1989; 513-516.

68. Xing, Guoqiang, et al. “Cannabinoid Receptor Expression and Phosphorylation Are Differentially Regulated between Male and Female Cerebellum and Brain Stem after Repeated Stress: Implication for PTSD and Drug Abuse.” *Neuroscience Letters*, vol. 502, no. 1, 2011, pp. 5–9., doi:10.1016/j.neulet.2011.05.013.

69: US Department of Veterans Affairs “Traumatic Brain Injury and PTSD” Accessed at: https://www.ptsd.va.gov/understand/related/tbi_ptsd.asp

70. Bryant, Richard. “Post-Traumatic Stress Disorder vs Traumatic Brain Injury.” *Dialogues in Clinical Neuroscience*, vol. 13, 2011, pp. 252–262.

71. Chivers-Wilson, Kaitlin. “Sexual Assault and Posttraumatic Stress Disorder: A Review of the Biological, Psychological and Sociological Factors and Treatments.” *Medical Journal of Malaysia*, vol. 9, no. 2, 2006, pp. 111–118.

72. Mechoulam, R. “Cannabinoids and Brain Injury: Therapeutic Implications.” *Trends in Molecular Medicine*, vol. 8, no. 2, 2002, pp. 58–61., doi:10.1016/s1471-4914(02)02276-1.

73. Mechoulam, R., and E. Shohami. “Endocannabinoids and Traumatic Brain Injury.” *Molecular Neurobiology*, vol. 36, no. 1, 2007, pp. 68–74., doi:10.1007/s12035-007-8008-6.

74. Elliott, Melanie B., et al. “Acute Effects of a Selective Cannabinoid-2 Receptor Agonist on Neuroinflammation in a Model of Traumatic Brain Injury.” *Journal of Neurotrauma*, vol. 28, no. 6, 2011, pp. 973–981., doi:10.1089/neu.2010.1672.

75. Lopez-Rodriguez, A. B., et al. “CB1 And CB2 Cannabinoid Receptor Antagonists Prevent Minocycline-Induced Neuroprotection Following Traumatic Brain Injury in Mice.” *Cerebral Cortex*, vol. 25, no. 1, 2015, pp. 35–45., doi:10.1093/cercor/bht202.

76. Panikashvili, David, et al. “An Endogenous Cannabinoid (2-AG) Is Neuroprotective after Brain Injury.” *Nature*, vol. 413, no. 6855, 2001, pp. 527–531., doi:10.1038/35097089.

77. Ney, Luke J., et al. “Cannabinoid Interventions for PTSD: Where to next?” *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 93, 2019, pp. 124–140., doi:10.1016/j.pnpbp.2019.03.017.

78. Fidelman, Sharon, et al. “Chronic treatment with URB597 ameliorates post-stress symptoms in a rat model of PTSD.” *European Neuropsychopharmacology,* vol 28, no. 5, May 2018, pp. 630-642

79. Seal, Karen, et al. “Association of Mental Health Disorders with Prescription Opioids and High-Risk Opioid Use in US Veterans of Iraq and Afghanistan.” *JAMA*, vol. 307, no. 9, Mar. 2012, pp. 940–947.

80. Stern, Cristina A.j., et al. “Cannabidiol Disrupts the Consolidation of Specific and Generalized Fear Memories via Dorsal Hippocampus CB 1 and CB 2 Receptors.” *Neuropharmacology*, vol. 125, 2017, pp. 220–230., doi:10.1016/j.neuropharm.2017.07.024.

# APPENDIX 1

**DSM-IV-TR Criteria for Posttraumatic Stress Disorder**

- **Criteria A**
  - The person has been exposed to a traumatic event in which both of the following were present:
  1. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.
  2. The person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior.
- **Criteria B**
  - The traumatic event is persistently reexperienced in one (or more) of the following ways:
  1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
  2. Recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.
  3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience; illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). Note: In young children, trauma-specific reenactment may occur.
  4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
  5. Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
- **Criteria C**
  - Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
  1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
  2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
  3. Inability to recall an important aspect of the trauma
  4. Markedly diminished interest or participation in significant activities
  5. Feeling of detachment or estrangement from others
  6. Restricted range of affect (e.g., unable to have loving feelings)
  7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal lifespan)
- **Criteria D**
  - Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
  1. Difficulty falling or staying asleep

2. Irritability or outbursts of anger
3. Difficulty concentrating
4. Hypervigilance
5. Exaggerated startle response

- **Criteria E**
  - Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.
- **Criteria F**
  - The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**APPENDIX 2: Iowa Letters**

7-6-2019

To whom it may concern,

My name is [redacted]. My story begins around [redacted] 2007. This is when I was sworn in as a Police Officer for the [redacted] Police Department. I was sent to the Iowa Law Enforcement Academy where I graduated [redacted] Policing is what I wanted to do. I wanted to help people and uphold the law. It is engrained in my DNA to obey the law and tell the truth. I guess that is why I enjoyed catching criminals who lied and/or broke the law.

In the spring of 2010, I noticed something was seriously wrong. I was not the same person anymore at home or on the job. I was irritable, angry, short tempered, and anxious to name a few. On the job, I would start shaking, I was becoming more aggressive, I was having homicidal thoughts and increasing suicidal thoughts so I sought help. Through doctors, therapists and psychologists it was determined that I had Post Traumatic Stress Disorder and given a disability retirement from the [redacted] Police Department in [redacted] of 2010.

Over the next seven years, I would seek out help from doctors whom would prescribe medications that would have bad side effects and I would stop taking the medication. I had to quit 3 different jobs because my symptoms from PTSD would cripple me to the point I was unable to continue. I went through several different periods of depression and the suicidal thoughts would come back. The only reason I did not kill myself was because I did not want my kids to grow up without a father.

I pressed on trying on my own to fight the anxiety, anxiousness, anger, irritability, fear of large crowds, fear of certain places in [redacted], emotional numbness, difficulty sleeping, difficulty concentrating and fear of leaving the house. Through these 7 years of doctors, counselors, medications and fighting these symptoms on my own, I lost hope that I would ever be or feel 'normal' again.

My sister-in-law, [redacted], moved to Colorado in 2014 due to her child, [redacted], having uncontrollable seizures to seek help through the use of medical marijuana to treat her daughter. She had mentioned to me a few different times to try cannabis oil as it helps people with PTSD. It had been so engrained in me throughout my policing background that marijuana was bad so I refused. Heck, I even put people in prison because they had and/or were selling marijuana. I was simply against it and, I mean, I was strongly against it.

However, after years of doctors, counselors, medications and fighting myself internally, I got to a point where I broke down and was willing to try anything to get better.

In May of 2017, I started taking Charlotte's Web by the Stanley Brothers. This cannabis oil is extremely low in THC (the hallucinogenic part of the plant) and high in CBD. After only 2 to 3 weeks I started noticing a big difference. My PTSD symptoms were drastically improving. My anxiety, anxiousness, irritability, fears and depression had subsided drastically. For the first time in almost 10 years I felt 'normal' again. I felt like I have my life back!

I have talked with my wife about wanting to share my story with others, especially veterans, emergency responders, or even people who may have even suffered abuse who are experiencing PTSD symptoms. They may not know about cannabis oil as doctors do not prescribe this. I would love to share my story to help others as I believe cannabis oil can literally help save lives especially those fighting PTSD. It's so important for them know they are not alone and that there are other options even when you feel like there is no other way.

[redacted]

[redacted]

Tuesday, July 2, 2019

To Whom It May Concern:

I'm [redacted], and I'm a medical cannabis cardholder in Iowa. Although I was approved for untreatable pain due to fibromyalgia and myofascial pain, PTSD is another condition that I suffer with, and am able to treat successfully with cannabis.

I'll give you guys a back story, on where my trauma comes from. It's pretty personal, but I don't mind sharing, because I want everyone to know how much cannabis helps.
For me, I've been through a lot.

In [redacted], I was walking to the train station in [redacted] from my dorm with my friend, when suddenly two men came up to us and said, "Hey give me your purse, or I'll shoot you." Right after that, my friend was stabbed right in front of me by one of these men. That's when my PTSD started.

The second incident was when a man pulled a gun on me, in my apartment building's hallway, and chased me out of the building. I was with a friend and we safely made it to her car and to the police station to file a report. This was in 2008.

I won't go into much detail about the next 3, but I was sexually assaulted by 3 separate people. Twice in one year. The third one happened years later.

The last experience that I will explain here was by far the most traumatizing of all and what haunts me the most. I'm a domestic violence survivor. I was in a relationship with a transwoman for a year and a half. In the beginning things were normal. We moved to Colorado Springs together, pretty early on in our relationship, because I needed access to medical cannabis. I had only been using cannabis for 10 months when I moved there, and realized it was something that brought my many health conditions under control, unlike any other medication. I wanted to be legal. I'm legally disabled, by the way.

Soon after I moved to Colorado with my ex, her anger started to get out of control. We had a roommate at the time, so that helped me stay safe for a while. Once we moved into our own apartment, that's when things really got bad.

My ex would scream at the top of her lungs, throw and break things (even punched a hole in the wall and smashed her phone into pieces). She was always calling me horrible names. She was extremely controlling and manipulative. I wasn't allowed to do the things I wanted, or hang out with friends alone, without her permission. I was sexually abused for a very long time by her. Finally it got physically abusive, although the vast majority of the abuse was emotional, verbal and psychological.

When I ended things with her in September of 2018, my PTSD went out of control. I had moved to Iowa a month prior, so I had to give up my medical cannabis that I was using in Colorado.

Things already were bad- I was previously having nightmares about my other trauma. Cannabis was

helping that while I was in Colorado, but I went 7 months in Iowa before getting approved for a medical card. I suffered greatly the entire time. 4-5 times a week I was having severe nightmares about the trauma with my ex. Sometimes multiple times a night. In between all that I would still have nightmares about other trauma I have endured. A lot of flashbacks too. Overall, my mental health was out of control because of the trauma. The domestic violence trauma is also what caused my fibromyalgia, according to my doctor.

My psychiatrist prescribed me Prazosin, because she said it would take away the intrusive nightmares. It never once helped. Not even when she increased the dosage. I finally quit taking it because it was not helping my PTSD one bit.

In [redacted] of 2019, I saw a doctor in [redacted], who had an Iowa medical license, and was able to certify that I had untreatable pain, so I could obtain my medical cannabis card. Ever since then, my PTSD has been 100% under control.

I no longer have nightmares and intrusive thoughts. I'm able to function and work part-time without calling in "sick" all the time. I'm able to walk by myself, and not be afraid of getting jumped or shot at. I'm able to hear fireworks and not be alarmed. I'm able to sleep and have restful sleep, instead of waking up at 1am from a scary dream and not being able to fall back asleep because my anxiety is so high. I'm no longer afraid to live my life. Finally, I'm not suffering, and it's all thanks to using medical cannabis everyday.

Specifically, I take the Comfort capsules at night, because I feel as though the higher dosage of THC helps keep my PTSD under control better when I'm asleep. During the day, the Harmony and Comfort tinctures help with symptoms of PTSD that I experience during the day.

Thank you guys for hearing me out, and I do apologize that this was so long, but I do hope that PTSD becomes an approved condition for suffering Iowans. It helps me, so I would love for other people to be able to be helped too.

Thanks again,

[redacted]

**APPENDIX 3: Select letters from Drs in other states[2]**


# LIFE MEDICAL, PA

**4201 Excelsior BLVD, Saint Louis Park, MN 55416**
**Tel. 952-933-8900 Fax 952-945-9536**
**www.LifeMedical.US**


## Section G

7-10-16

Michelle Larson, MPA
Director
Office of Medical Cannabis
Minnesota Department of Health
Golden Rule Building
85 E. 7th Place, Suite 220
PO Box 64882
St. Paul, MN 55164-0882

RE: Adding PTSD to the list of conditions qualified for medical cannabis in Minnesota

Dear Ms. Larson,

I support inclusion of Post-Traumatic Stress Disorder in the list of conditions qualified for medical cannabis in Minnesota. Multiple encounters with people using cannabis for medical reasons in my clinic confirm that PTSD symptoms often respond well to cannabis. These patients often indicate reduced need for antidepressants and anti-anxiety agents to treat their symptoms if they have cannabis. Many of them prefer cannabis because it provides them with better symptoms relief with fewer side effects than the conventional drugs.

Sincerely,

Jacob Mirman, MD


**Leon B. Frid, DC Jacob I. Mirman, MD**

**WC Kleis, MS, LP, LLC**
**1610 14th ST NW, Ste 201**
**Rochester, MN 55901**
**wckleis@gmail.com**
**Ph: 507-281-2115**

July 2016

## CANNIBAS AS A TREATMENT ALTERNATIVE FOR PTSD

I have been a licensed psychologist since 1993. I have no personal experience with using cannabis, so all my thoughts are based upon what I have seen and heard and read in my years of practice. I have a few premises, so I would encourage anyone reading this to stop if you disagree with any of them.

-Anxiety is a symptom of some unresolved fear.
-It makes sense to treat symptoms instead of just DSM diagnoses.
-Ultimately, the cause of the symptoms must be resolved.
-Addiction is a serious concern for extended prescriptions for anxiety and pain today.
-Cannabis takes motivation away from immature users in proportion to its frequency of use.

Given these premises, I believe cannabis could be a valid prescription alternative for treatment of PTSD (Posttraumatic Stress Disorder) if it is monitored properly. Most often today, the person prescribing the medication is not the person helping resolve the anxiety, i.e., making the underlying problem become historical or without emoting debilitating anxiety. This suggests better communication between the prescriber and the therapist than is generally present today. If there is no improvement toward remission and consequently a better family, personal, and business life, it wouldn't make sense to continue with this prescription. And if there was improvement, it would make sense to terminate the prescription as soon as the PTSD is in remission.

I like the phrase: "That was then, and this is now." It is amazing how quickly soldiers are expected to re-enter a "normal" life in the United States these days after a tour of duty. If anyone is suffering from PTSD today, it would be reasonable to prescribe cannabis. It would be normal to then determine if the individual was making progress with remission of the acute aspects of PTSD and remaining motivated to overcome the trauma and resume life as it was for him or her before the onset of this illness.

Ideally, cannabis would have the THC component removed and still be effective. I do not know if that is possible based upon statements I have read from both sides of the issue. To the extent it is not possible, cannabis would still be less addictive than the most of the benzodiazepines generally prescribed today.

Sincerely,

WC Kleis, MS, LP

Written for the MN Petition for PTSD July 27, 2016

To Whom It May Concern:

I was a practicing Arizona Physician for 14 years in internal medicine and psychiatry. I served as clinical faculty at St. Joseph's Hospital internal medicine clinic and also worked at the University of Arizona, College of Medicine. As a board certified psychiatrist, I have a long-standing interest in psychiatry and substance abuse. My practice is filled with many combat veterans and first responders with treatment resistant PTSD. That is why I now serve as principal investigator of an FDA-approved randomized controlled trial looking at the safety and efficacy of marijuana in treating PTSD.

I mention all of this as there are so many conflicting opinions, so much misinformation, so many vested interests, that it is important to consider the source when evaluating what you hear or read. And, on my part, when I read medical articles and studies I look for solid, peer reviewed studies, by reputable researchers from unimpeachable institutions. Examples would include studies from the our own government's National Institute of Mental Health, articles from our top medical schools, like the University of California, New York University, the University of Arizona and the Mayo Clinic.

I have no financial ties to the medical marijuana industry. I am not a dispensary owner nor a certifying physician. I do not use medical marijuana nor recreational marijuana.
I have never even tried it. Not once. But from my scientific background and clinical experience, I do believe that medical marijuana, for some patients, and for some conditions, may be the best and most effective form of treatment.

As one that cares for combat vets, I have had several patients that were killed or injured in various conflicts over the years.

Of those that came home, several have suffered from PTSD, hence my strong interest in today's subject.

But while that is my personal motivation, it is important to remember that military service members, or firemen, or policemen, are not the only people that suffer from PTSD. Any traumatic life event or loss can trigger PTSD, and more women than men suffer from PTSD.

**Post Traumatic Stress Disorder (PTSD)**
About 50% of all American adults will encounter a severely stressful event at least once in their lives. This could be combat, a bad accident, a beating, sexual abuse, rape, an

earthquake, fire, a severe health issue, or other similar happening. A person may experience it directly or they may see a friend or loved one as the victim of such event.

When faced by such a traumatic or life threatening situation, our bodies immediately go into a fight or flight response. Our bodies focus totally on survival. Nothing else matters. We have a heightened awareness, our heart beats fast, our blood flows to our muscles, our hormones surge. We are ready for the fight of our lives.

Now, if that person survives that severely stressful encounter, over the next few hours the physical responses will return to normal. And in a few days, weeks or months our memory, and emotional response to that stress will fade.

But for some people, about 15% of those exposed to such major stress, memory and emotions don't fade and adapt. Instead they continue to react as if the original event was reoccurring, time and time again. The reaction that served them well during the original stressful event now becomes a problem in their everyday life. This abnormal, or delayed, reaction may last for years. And the initial re-occurrence of the stress reaction may occur years after the initial stress.

Heart beating out of your chest, muscles tense, epinephrine cascading through your body, eyes dilated, ready to fight...all good if you are confronted by maximum danger...a snarling tiger...but not so good if just reacting to the family cat plopping on your lap. This is PTSD. Abnormal reactions to everyday stimuli, as if a person is experiencing the original event.

**How Common is PTSD?**

Of those Americans that do encounter, and survive, a major stressful happening, most adapt normally with eventual fading of the memory and emotions. But for about 15% of those people this does not occur. These are people with PTSD. About 7% of all adult Americans will suffer PTSD at some time in their life. And in any one year almost 3% of adult Americans will suffer with PTSD. That is around 6,000,000 adults.

So, PTSD is pretty common. It can also affect children and teens. And, even though we often think of wars and combat veterans when we think of PTSD, there are actually more women suffering from PTSD than men. But, for those who have served in combat, both the frequency and toxicity of PTSD is increased.

**What is PTSD?**

It is the failure to adapt to the original stress. Victims re-experience the original stress time after time. In memories, flashbacks and dreams. They try to avoid situations and stimuli that might trigger such memories. The have heightened arousal, have difficulty sleeping, can't concentrate and may be irritable. They are hyper vigilant and fearful. They are feeling danger. What's around that corner?

**What does PTSD lead to?**

Individuals with PTSD suffer a decreased quality of life. Anxiety increases along with depression. They are at increased risk of poor health. Relationships suffer, divorce rates increase, success in school fades and many become unemployed. At this moment, over 100,000 veterans, many with PTSD, are homeless.

PTSD leads to an increased risk of suicide. Combat related PTSD is particularly severe and difficult to treat. Every day in the USA, 22 veterans commit suicide. That is a shocking number.

**Is there good current therapy for PTSD?**
Not really. The current uses of SSRI type anti-depressants and anti-anxiety medications, as the mainstay of treatment, are of limited value for many patients. Either they don't work well or the side effects, such as obesity, grogginess, or decreased sexual function, cause many patients to discontinue therapy. Psychotherapy may be helpful for some, but is of limited availability. An additional pharmacological agent to treat PTSD could be very beneficial for many patients.

**What is the role of medical marijuana in treating PTSD?**
A review of the current medical literature demonstrates many recent articles on PTSD. They share a common theme. Current therapy is not adequate for many patients. And in particular SSRIs do not treat, or help extinguish, toxic memories, the core problem of PTSD.

Here is a typical quote. It appears in an article by Drs. Trezza and Campolongo in *Frontiers in Behavioral Neuroscience* (FBN), August 2013: "Although SSRIs emerge as the first line treatment to treat the anxiety symptoms of PTSD, a large proportion of those patients fail to respond to those medications. Furthermore, no treatment is currently available to treat the mal-adaptive cognitive features of PTSD... Studies point to the endo-cannabinoid system as a possible ideal therapeutic target to treat both the emotional and cognitive dysfunction characterizing PTSD."

Another 2013 article, by Dr. Akirav in *FBN*, September 2013, states "The endo-cannabinoid enhancers may be the ideal pharmacologic treatment for PTSD by blocking the pathological over-consolidation and continuous retrieval of the traumatic event on the one hand, and enhancing its extinction and reducing the anxiety symptoms on the other hand. These effects fit well with the concept of reducing fear memory."

In 2012 Drs. Emrich et al, in Drug Test Analytics, July-August 2012 writes "This review shows that recent studies provided supporting evidence that PTSD patients may be able to cope with their symptoms by using cannabis products. Cannabis may dampen the strength or emotional impact of traumatic memories through synergistic mechanisms that might make it easier for people with PTSD to rest or sleep and feel less anxious and less involved with flashback memories."

Recent research with functional MRIs and PET scanners demonstrate that PTSD is more than just an emotional or psychological condition. It is a process that affects both neuro-hormones and functional neuroanatomy.

Dr. Rabinak, of the University of Michigan, reports a human study, using functional MRI, in *Neuro-biological Learning*, September 2013. It states, "This study provides the first evidence that pre-extinction administration of THC modulates the prefrontal-limbic circuits during fear extinction in humans."

Good, double-blind prospective research studies on the effectiveness of medical marijuana are very difficult to perform in the United States due to the well known opposition to these studies by NIDA and the DEA.

But, we have a very good retrospective study from the State of New Mexico Medical Advisory Board. New Mexico was the first state to approve PTSD as a qualifying condition for treatment under their medical cannabis program.

The study is known as "PTSD Symptom Reports of Patients Evaluated for the New Mexico Medical Cannabis Program." It is attached for review.

This study was approved for study by the Institutional Review Board of UCLA. It states, "The Clinician Administered Post-traumatic Scale (CAPS) was administered retrospectively and symptom scores were collected and compared in a chart review of the first 80 patients evaluated.

"Results: Greater than 75% reduction in CAPS symptom scores were reported when patients were using cannabis than when they were not... There is extensive evidence that cannabinoids may facilitate extinction of aversive memories." The New Mexico report concludes, "There are currently 3350 patients enrolled in the PTSD program. To date, there have been no incidents or adverse events."

Briefly, on the subject of adverse events and risk factors, it appears that medical marijuana is rather safe when used under informed medical supervision. The NYU Institute of Human Development states, "While marijuana is not physically addicting it is habit forming. Regular users sometimes experience withdrawal symptoms such as grogginess, irritability, nausea, insomnia and agitation. These generally wear off in one to two days." It also states, "It is nearly impossible to overdose on marijuana."

It should be noted that marijuana does become habit forming in about 9% of users. Youth are at an increased risk for habituation and proper caution should be observed. Also note the rate of habit formation is much lower than for tobacco and alcohol.

**To conclude:**
PTSD is a common but serious disorder, which affects almost 6,000,000 Americans each year. It is a disabling condition leading to a poor quality of life, and many patients become depressed and are at increased risk of suicide.

Combat related PTSD is particularly toxic and hard to treat, and tragically, 18 US veterans commit suicide every day.

Unfortunately, conventional treatments are of limited value.

New research is showing the value of medical marijuana, not only in treating symptoms, but possibly treating the root cause of PTSD — the inability of some people to extinguish traumatic memories.

Writing in the *Mayo Clinic Proceedings*, February 2012, Dr. Raphael Mechoulam, the Israeli scientist that first synthesized THC, and who led the team that discovered the endo-cannabinoid system in humans, said "I believe that medical marijuana as a therapeutic entity is here to stay. It is being used in numerous medical conditions, at times with considerable success. Are we entitled to neglect such a valuable drug?"

I strongly encourage approval of PTSD as a qualifying medical condition under the Minnesota's Medical Cannabis Program.

Thank you

Sue Sisley MD

## Appendix 4: Select letters from those in other states

7/7/2019

I have been asked to write a quick letter about my story and how cannabis has helped my PTSD, also how legal access to cannabis has helped since I live in a legal state for cannabis, both recreational and medicinal. Here is that story, I'll try to make it quick, or short.

I enlisted in the US Army in [redacted] with a Military Occupational Specialty of Military Police, 95B. During my enlistment of 5 years I travelled to and lived in places all over the world, including Germany, Panama, and my last deployment to Haiti in [redacted] in support of Operation Uphold Democracy and the UN Mission in Haiti.

PTSD started for me while deployed and seemed to get worse after my return home from Haiti. My term of service was completed shortly after returning from Haiti in [redacted]1995, and I was out of the Army, out of work, and living at home with my parents, along with my wife and son by the end of September 1995. Only a 3 month period of time between daily traumatic exposure of an incredibly extreme nature as a US Army Soldier until I was home, as a civilian, and expected to just be normal, act as if I hadn't been exposed to daily homicides and murders, daily riots and physical engagements of a violent nature. I put more humans in body bags than I can even begin to deal with on a personal level, and this was a daily continual exposure. Now I was home?

Nightmares started for me the second night after I returned from Haiti and affected me even as a soldier, I was hardened, I was bitter, and I was aware of the evil that is in this world. Seeking help for something of this nature, PTSD, wasn't even talked about in 1995 in the active army, at least I was never told about it. I believed that to say openly that I was having problems with nightmares, anger, rage, or drinking/self-medicating, it would have been looked down on and it possibly could have affected my discharge in a negative way had I mentioned it. Nobody talked about it, and nobody asked about it.

I started seeking help from the Department of Veterans Affairs in 2005 and was instantly given a laundry list of prescription medications, with a promise that I would feel better, that the medications would help. You see, I had been self-medicating with alcohol for my nightmare and sleep problems, and my overwhelming inability to engage socially, since 1995, 10 years. I treated PTSD by drinking and over working, I worked 70-80 hours a week and drank nearly every single night, just hoping that I would have that one in a million-night, free of nightmares and yelling, kicking and punching in my sleep. Working so many hours kept my mind busy and was like a block to the intrusive memories from my deployment, which were there, just beyond the veil, every time I slowed down, closed my eyes, or tried to rest. I was a wreck, and over time the medication from the VA only compounded my problems. Simply put, the effects of the medications stole from me even my will to live. By the summer of 2012 I had been through an in-patient PTSD treatment program and the list of prescribed medications seemed to grow longer at every visit, I was a zombie, made that way by the legal medications prescribed to me by health care professionals at the VA. I rarely left my home at that point, I couldn't, I had no balance, my vision was blurry, I had no energy, I didn't feel safe even driving my own vehicle, I was (age redacted), and I wanted to die. All this thanks to prescription medications, recommended and prescribed by doctors at the VA. It was then that I decided that I wanted to live. I tossed all the medications in the trash and accessed cannabis for the first time, illegally.

What this medicine does for me is something that no other medication was able to do, I could sleep, nightmare free. Cannabis allowed me to live again, to relax, to take a long-needed break from the hyper vigilance, anxiety, and depression that accompanied my PTSD, for the first time in 17 years. No longer was I plagued every single time I closed my eyes with images from that hellish deployment, I finally could rest, and so could my family. You see, PTSD doesn't only affect the service member, or the traumatized person, it affects their entire family. This medicine, Cannabis, allows me to be a better human, a better father, a better husband. No longer does my wife have to either jump out of bed in the middle of the night to escape my kicking and yelling in my sleep or try

to awaken me as I slip into one of those trauma filled nightmares. Just this one aspect, real sleep, real rest, is something that I couldn't find in any other way, prior to Cannabis. I am able now to be active, and engage with my children in a real way, without all the negative symptoms from PTSD or the negative affects of the prescription medication.

I do live in a legal state, Oregon, for cannabis consumption, both recreationally and medicinally, and because of that I am able to take care of providing my own medication. Simply stated, I grow my own medicine, and it makes me feel better, it makes me feel alive, and helps me to be a better citizen, a better father, and a better husband. Because I live in a legal state, I can treat legally my service-connected disability with Cannabis medicine. I do not have to be concerned that the medicine that works for me could also land me behind bars and fill my life with legal problems that would make worse my struggles with PTSD, anxiety, and depression.

[redacted]

US Army Military Police

Pharmacological Research 111 (2016) 668–678

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Perspective

# The endocannabinoid system and Post Traumatic Stress Disorder (PTSD): From preclinical findings to innovative therapeutic approaches in clinical settings

Andrea Berardi[a], Gustav Schelling[b], Patrizia Campolongo[a,*]

[a] Dept. of Physiology and Pharmacology, Sapienza University of Rome, 00185 Rome, Italy
[b] Department of Anaesthesiology, Ludwig-Maximilians University, 81377 Munich, Germany

ARTICLE INFO

*Article history:*
Received 11 April 2016
Received in revised form 30 June 2016
Accepted 21 July 2016
Available online 22 July 2016

*Keywords:*
Memory consolidation
Memory retrieval
Memory extinction
Memory of emotionally arousing experiences
Endocannabinoid system
Traumatic stress disorder
URB597
WIN55,212-2
JZL184
FAAH
MAGL
Anandamide
2-arachidonoylglicerol

ABSTRACT

Post-Traumatic Stress Disorder (PTSD) is a psychiatric chronic disease developing in individuals after the experience of an intense and life-threatening traumatic event. The post-traumatic symptomatology encompasses alterations in memory processes, mood, anxiety and arousal. There is now consensus in considering the disease as an aberrant adaptation to traumatic stress. Pharmacological research, aimed at the discovery of new potential effective treatments, has lately directed its attention towards the "so-called" cognitive enhancers. This class of substances, by modulating cognitive processes involved in the development and/or persistence of the post-traumatic symptomatology, could be of great help in improving the outcome of psychotherapies and patients' prognosis. In this perspective, drugs acting on the endocannabinoid system are receiving great attention due to their dual ability to modulate memory processes on one hand, and to reduce anxiety and depression on the other. The purpose of the present review is to offer a thorough overview of both animal and human studies investigating the effects of cannabinoids on memory processes. First, we will briefly describe the characteristics of the endocannabinoid system and the most commonly used animal models of learning and memory. Then, studies investigating cannabinoid modulatory influences on memory consolidation, retrieval and extinction will be separately presented, and the potential benefits associated with each approach will be discussed. In the final section, we will review literature data reporting beneficial effects of cannabinoid drugs in PTSD patients.


## 1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a chronic psychiatric disease characterized by marked alterations in cognition, mood, emotion and social abilities, developing in individuals after the experience of a traumatic and/or life-threatening event. In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) PTSD has been included in the new category of "trauma and stressor-related disorders", where the abnormal adaptation to a traumatic experience is considered as a specific pathogenetic starting point [1]. Among the different characteristics of PTSD, much attention has been lately given to the study of abnormalities in fear memory elaboration, which are thought to be causally linked to symptoms such as spontaneous recollections, flashbacks, enhanced reactivity to trauma-related cues, dissociative amnesia [2–4]. One of the reasons that makes PTSD so persistent and resistant to pharmacological interventions is the substantial lack of treatments targeting memory alterations [5,6]. The inability to extinguish learned fear responses [7], to suppress episodic traumatic retrieval [8], to acquire safety signals [9] or to dampen the over-consolidation process taking place right after re-experiencing symptoms [10], may account for the great stability of PTSD symptomatology over time, thus PTSD can hardly be affected by traditional antidepressant and anxiolytic medications [5]. Non-pharmacological treatments such as Cognitive Behavioral Therapy (CBT) and Eye Movement Desensitization and Reprocessing (EMDR) seem to be more effective in the treatment of PTSD [11,12], but the high drop-out rates observed in *meta*-analysis studies suggest that their procedures may need further refinements [13,14]. The limitations in PTSD treatment make it urgent the discovery of new drugs with the ability to diminish the expression of the multifaceted nature of the post-traumatic symptomatol-

* Corresponding author.
*E-mail address:* patrizia.campolongo@uniroma1.it (P. Campolongo).

http://dx.doi.org/10.1016/j.phrs.2016.07.024
1043-6618/

ogy. Much attention has been lately directed to cannabinoid drugs because of their dual ability to modulate memory processes for emotional experiences on one hand [5,6,15] and to reduce anxiety on the other [5,6,16,17]. Moreover, literature evidence demonstrating alterations of the endocannabinoid system in PTSD patients is continuously increasing [18–22]. The modalities through which cannabinoid compounds could exert beneficial effects on PTSD are various. First, cannabinoid administration in the immediate aftermath of a trauma could reduce the impact of the subsequent traumatic memory by interfering with the memory consolidation process (i.e. that process taking place in a limited time window starting immediately after an experience and that allows an initially labile memory trace to be stabilized into a form of long term memory) [23–26]. Secondly, cannabinoids could reduce traumatic memory by interfering with the memory retrieval process (also named recollection, recall or reactivation, i.e. that process that brings out stored information from the long-term memory into consciousness) [15,27]. After a memory trace has been reactivated, it becomes labile again requiring a new wave of consolidation (or re-consolidation) to get updated in the long term memory [26,28,29]. And a poorly retrieved memory is less prone to be re-consolidated. Finally, yet importantly, cannabinoids could enhance extinction learning (i.e. the form of learning that allows a stimulus previously paired with a negatively valenced emotional experience that trigger fear and anxiety responses, to become non-threated again) [30]. The potentiation of extinction learning is probably the most promising perspective in the application of cannabinoid drugs for the treatment of PTSD since extinction mechanisms are thought to be engaged in exposure-based psychotherapies [31]. Enhancing the efficacy of exposure therapy by means of cannabinoids and other substances represents a new intriguing therapeutic opportunity attracting the attention of clinicians and scientists [6,32]. In this review, we will first briefly describe the endocannabinoid system and the most commonly used animal models for learning and memory testing. Subsequently, we will review experimental data from both human and animal studies describing therapeutic properties of cannabinoid drugs on PTSD, with a particular focus on the target of each of the aforementioned memory phases. In the final section, we will review studies examining the ameliorative effects of cannabinoids on PTSD-affected populations not strictly related to memory modulation.

## 2. The endocannabinoid system

The discovery of the endocannabinoid system followed the identification in the early Sixties of the major psychoactive constituent of *Cannabis* namely Delta-9-tetrahydrocannabinol (THC) [33,34]. This lipophilic compound binds and activates a particular class of G-protein coupled metabotropic receptor, called cannabinoid-receptor type 1 (CB1) [35]. The discovery of the cannabinoid-receptor type 2 (CB2), through homology cloning [36], completed the picture of cannabinoid receptors identification. In the following years, the two major endogenous cannabinoids were also identified: the N-arachidonoyl ethanolamine (anandamide) [37], which acts as a partial agonist of both receptors [38], and the 2-arachidonoyl glycerol (2-AG) [39], which acts as a full agonist of both receptors [40]. Endocannabinoids are synthesized from lipidic membrane precursors [41–43] and released "on demand" by the post-synaptic terminals in an activity-dependent fashion. From the synaptic cleft they travel retrogradely to activate receptors presinaptically located [44]. Once the receptors have been activated, endocannabinoids are recaptured into neurons by still poorly identified mechanisms [45–47], where they undergo enzymatic degradation. The principal degrading enzymes for endocannabinoids are the fatty acid amide hydrolase (FAAH) [48] and the monoacylglycerol lipase (MAGL) [49,50] for anandamide and 2-AG, respectively. The CB1 receptor is the most abundant G-protein coupled metabotropic receptor in the mammalian brain [51], it is widely expressed in the prefrontal-limbic system including areas such as the amygdala, hippocampus and prefrontal cortex [52], and it is the principal mediator of the psychoactive effects of THC and of the many behavior-altering effects observed in experimental studies (see below). In contrast, the CB2 receptor is mainly expressed in peripheral immunological tissue [36], although its presence in the central nervous system has been also recently documented in regions such as the amygdala, hippocampus, striatum, substantia nigra and cortex [53]. Both the cannabinoid receptors are coupled to $G_{i/o}$ proteins which inhibit adenylate cyclase and voltage-gathed calcium channels, activate mitogen-activate protein kinases (MAPK) and inward rectifying potassium channels [54,55]. These molecular events usually result in a general inhibition of neurotransmitters release from pre-synaptic terminals of neurons where cannabinoid receptors are expressed. These include GABAergic interneurons within the limbic system [56] as well as glutammatergic [57], serotoninergic [58,59], noradrenergic [60] and dopaminergic [58] neurons.

## 3. Commonly used rodent models of learning and memory

Over several decades, many different preclinical models have been developed in order to deepen our knowledge of the biological, neurochemical and neurophysiological correlates of mammalian memory functions. In this section, we will briefly describe the most relevant behavioral paradigms for memory processes that can also be useful to mimic some of the PTSD symptoms. It is worth noting that given the high complexity of psychiatric disorders such as PTSD, animal models can only reproduce some aspects of the pathology. Therefore, the translation of conclusions coming from animal studies to humans should be always made by keeping in mind their suggestive rather than deterministic value.

### 3.1. Fear conditioning and extinction

A typical fear conditioning protocol, involves the simple pavlovian association between a neutral stimulus (context, sound, light, odor) and an aversive stimulus (footshock, predator scent). Following one or more pairings of the neutral stimulus with the aversive unconditioned stimulus (US) carried out during the training or conditioning session, the animal will learn the association between the two stimuli. As a result, the animal will begin to express the freezing response at the delayed presentation of the neutral stimulus only (now conditioned stimulus, CS) during the test or retention session. The total freezing response duration expressed by the animal during the retention session is the test variable, with longer durations interpreted as indicative of stronger memory traces [61]. A protocol of extinction involves the new learning that the CS no longer predicts the aversive US. In other words, the rodent will learn to suppress his fear responses elicited by a CS, when the CS is repeatedly presented in the absence of the following US [62]. It is now widely accepted that extinction does not represent an erasure of the previous CS-US association [30]. Indeed, the previous fear association can re-emerge spontaneously after a certain time (spontaneous recovery), after a change in the context (renewal), after the exposure to the US (reinstatement), and it is rapidly re-acquired after the exposure to a new CS-US pairing (rapid re-acquisition) [63].

### 3.2. Inhibitory (passive) avoidance

The inhibitory or passive avoidance test involves the natural aversion of rats and mice for bright spaces. Indeed, in a typical step-through inhibitory avoidance protocol a rat is introduced into

a bright context connected to a darker context by a guillotine door. After a fixed amount of time, the door is opened and the rat is allowed to freely move into the dark compartment of the apparatus. Once in the dark context, the door is closed and a single footshock is delivered (training session). After a fixed retention interval, the rat is again placed in to the bright context with the door opened, and the latency to step through the door is recorded (test session). A longer latency to step into the dark compartment is interpreted as a stronger memory [64]. In another version of the task, namely the step-down inhibitory avoidance, the rat is placed on an elevated platform, the shock is delivered once the rat steps down from the platform and the test variable consists in the latency to step down the platform [65].

### 3.3. Fear-Potentiated startle

The fear-potentiated startle paradigm involves the conditioning of the rodent to a light cue (CS) and a footshock (US) delivered in a particular apparatus connected to a platform sensitive to rodents' movements. Once the conditioning has been established and following a certain retention interval, the animal, placed back into the apparatus, will receive sudden unpredicted loud noise bursts. The noise bursts are delivered both in the presence (light-noise trials) and in the absence of the CS (noise-alone trials), and the startle reactions of the animals are recorded. The mean startle amplitudes for light-noise trials and noise-alone trials are then averaged across trials. Significant greater amplitudes for the light-noise trials versus the noise-alone trials will indicate a successful memory retention [66]. The relevance of behavioral paradigms involving the startle response in PTSD studies comes from enhanced startle reactions on human subjects suffering for PTSD and other anxiety disorders [67,68].

### 3.4. Morris water maze

Differently from the paradigms described so far, the Morris Water Maze test does not involve fear learning. Rather, it involves spatial learning under the aversive/stressful condition represented by being placed into water without escaping possibilities. In this test, a rodent placed into a water-filled swimming arena is trained under multitrial sessions to find a hidden platform. After the training phase, in the retention (probe) trial the platform is removed and the latency to reach the position, the time spent in the quadrant (target), the numbers of crossing of the area where the platform was located together with other possible measures are recorded. A shorter latency to reach the platform position, a greater time spent in the target quadrant and a greater number of crossings are interpreted as a measure of increased memory [69].

### 3.5. Novel object recognition

The Novel Object Recognition test is a learning task involving neither aversive stimuli nor highly stressful conditions. It is based on the rodent natural tendency to explore environmental elements that they had never encountered before. In the training trial a rodent, placed into an arena with two identical objects, is free to explore them for a fixed time interval. After a certain retention interval, the rodent is placed back into the arena where one of the objects is replaced by a novel never-encountered object. The time the subject spends in the exploration of the two objects is recorded, and a significantly longer exploration of the novel object over the familiar one is indicative of a better memory retention [70].

### 3.6. Radial maze

The radial maze test is an appetitively motivated learning task where rodents are trained to remember the arms of an asterisk-shaped 8-arm maze where they will find a food reward. During the retention session, the entries of the animals into arms that have never been rewarded is interpreted as a memory error, therefore the memory index is represented by the percentage of correct entries (i.e. entries in the rewarded arms) over the total number of entries in a fixed amount of time [71].

## 4. Early intervention in the aftermath of a trauma: effects of cannabinoids on consolidation of stressful experiences

The use of cannabinoid preparations in the immediate aftermath of a trauma is probably the most controversial and less promising approach in terms of efficacy in the treatment and prevention of PTSD after exposure to a traumatic event, for a number of reasons. The first is related to the unpredictable and devastating nature of a traumatic experience, which does not easily allow the clinician to organize for a well-designed therapeutic approach. Elements such as the informed consensus, patient's anamnesis and medical history, a standardized time interval to perform drug administrations, might be difficult to obtain in an emergency situation (see below a for discussion on anesthetics in intensive care units, ICUs). Another, and perhaps most important reason, as stated by Vermetten and colleagues [26], is that only a small subgroup of people exposed to a trauma ultimately develops PTSD and it is currently impossible in such an early stage to distinguish a person needing treatment from those who do not. The third reason is related to the effects of cannabinoids on memory consolidation themselves. Indeed, conflicting and often opposite effects of cannabinoid agonists/antagonists administrations have been reported in animal studies investigating memory consolidation, depending on factors such as the tested brain area, doses used and/or the behavioral paradigms especially when involving different levels of stress and/or emotional arousal (see Ref. [15] for an updated review).

### 4.1. Animal studies

As stated literature data regarding cannabinoid effects on memory consolidation are controversial.

#### 4.1.1. Agonists

In the contextual fear conditioning paradigm, the CB1 receptor agonist HU-210 was found to impair consolidation when systemically administered in rats [72]. In the inhibitory avoidance test, the non-selective CB1/CB2 agonist WIN55,212-2 was found to impair consolidation when infused into hippocampal CA1 area [73–77] and central amygdala [78] but the same drug on the same task was found to enhance consolidation when infused into basolateral amygdala [79]. Also the endocannabinoid anandamide when infused into hippocampal CA1 immediately after Inhibitory Avoidance training enhanced the consolidation of the task [80]. However, when systemically administered, anandamide impaired consolidation of Inhibitory Avoidance training [81–83]. In a fear-potentiated startle experiment, WIN55,212-2 infused into basolateral amygdala, but not into medial prefrontal cortex, impaired the consolidation of the test [84]. Systemic WIN55,212-2 also showed biphasical opposite effects on short-term memory retention of rats performing a Novel Object Recognition test when administered post-training in two different conditions [85]. In particular, the drug impaired 1-h retention of rats trained under high arousal (no prior habituation to the test apparatus) while it enhanced 1-h retention performance of rats trained under low arousal conditions (extensive prior habituation to the apparatus)

[85]. Interestingly, the same dose that impaired 1-h retention on non-habituated rats, enhanced memory consolidation in rats trained under the same arousal condition as assessed by a 24-h retention session [85]. URB597 elevates anandamide levels at active synapses through inhibition of its principal degrading enzyme FAAH [86]. We have recently demonstrated that this drug enhances consolidation of Inhibitory Avoidance training when infused into basolateral amygdala, hippocampus and prefrontal cortex, through indirect activation of cannabinoid receptors [87]. The anesthetic drug propofol, apart of its GABAergic action [88], is an inhibitor of the FAAH enzyme [89], thus inducing similar central effects of those induced by URB597 in terms of activation of the endocannabinoid system. Interestingly, we observed enhanced consolidation of Inhibitory Avoidance training in rats systemically administered with anesthetic doses of propofol: the effects were mediated by indirect cannabinoid receptor activation, and not related to GABA activity [90].

#### 4.1.2. Antagonists

A few studies investigated the effects of cannabinoid antagonists on memory consolidation. One of these studies showed that the CB1 antagonist AM251 impaired Inhibitory Avoidance consolidation when either infused in hippocampal CA1 region [91], and another study observed the same effect when AM251 was infused into basolateral amygdala [79]. Basolateral amygdala-infused AM251 also impaired consolidation of contextual fear conditioning in rats [92].

#### 4.1.3. PTSD models

The studies above described can account for the effects of cannabinoids on the consolidation for aversive experiences, partly modeling the memory consolidation of a traumatic event, but failing to provide useful information on the stress-related trauma-induced alterations in behavior. To address this issue, studies involving validated preclinical model of PTSD are more informative. Unfortunately, to date only a few studies examined the effect of post-stress cannabinoid administration specifically in PTSD models. In one of these studies, rats were exposed to the single-prolonged stress model [93] that involves a series of subsequent discrete stressor able to induce in exposed rats long-term behavioral alterations such as: enhanced Inhibitory Avoidance conditioning, impaired Inhibitory Avoidance extinction, potentiation of acoustic startle response, inhibition of the hypothalamic-pituitary-adrenal (HPA) axis and increased anxiety [94]. The administration of the synthetic cannabinoid agonist WIN55,212-2, 24 h after the Single Prolonged Stress procedure, was found to prevent the observed alterations in Inhibitory Avoidance conditioning and extinction, acoustic startle response potentiation and HPA inhibition [94]. Interestingly, alterations in Inhibitory Avoidance and acoustic startle response were prevented also when WIN55,212-2 was infused into the basolateral amygdala, an effect that was blocked by co-administration with the cannabinoid antagonist AM251 [94]. The same authors further investigating this subject in another study where post-stress WIN55,212-2 successfully blocked the Single Prolonged Stress-induced alterations also when infused into hippocampus but not in the prefrontal cortex [95]. In addition, the observed ameliorative effects of WIN55,212-2 where blocked by inhibition of glucocorticoid receptors in the basolateral amygdala and hippocampus [95]. In another study, rats were exposed to a single footshock with a classical Inhibitory Avoidance training, followed by situational reminder on subsequent days, which consisted in placing the animals in the light compartment without access to the dark conditioned compartment in order to avoid extinction [96]. In this experiment, animals exposed to shock and to situational reminders on later days, differently from animals exposed to shock only, showed impaired extinction, enhanced startle latency, altered hippocampus-accumbens pathway plasticity, altered CB1 and glucocorticoid receptors expression in prefrontal cortex, hippocampal CA1 and basolateral amygdala [96]. Much of these effects were prevented by post-training systemic injection of WIN55,212-2, and co-administration with AM251 blocked the ameliorative effects of WIN55,212-2 [96].

These studies seem to prove a certain efficacy of post-stress administration of cannabinoid agonists in preventing the stress-induced alterations on behavior. However, contrasting findings were reported in a recent study that examined the effects of systemic injections of the CB1/CB2 agonist THC, the principal active constituent of cannabis plant, and the CB1 antagonist AM251 [97]. In particular, when THC was given to rats immediately after exposure to predator scent stress, it was able to reduce anxiety measured in the acoustic startle and elevated plus maze tests only in the short-term, with no effects on the long-term neither on anxiety nor on contextual freezing [97]. Conversely, the CB1 antagonist AM251 reduced both anxiety levels and contextual freezing in the long-term showing PTSD-preventing properties [97]. To conclude, given the impossibility to know in advance if someone will develop PTSD after the exposure to a traumatic experience, and given the contrasting results arising from animal studies discussed so far, further studies are needed to clearly demonstrate the utility to administer cannabinoid drugs in the aftermath of a trauma.

### 4.2. Human studies

Human data concerning cannabinoids effects on consolidation of traumatic experiences are hard to collect and few studies are available in the literature. However, there are cases of patients treated with anesthetic drugs in ICUs after accidents and other situations requiring emergency surgery. In such cases, anesthetics are often administered during the time window where memory consolidation occurs, in close proximity to the traumatic experience. Two different studies, which examined different cohorts of ICU patients treated with propofol in the aftermath of a traumatic experience, reported correlative data between propofol use and the enhanced risk to develop PTSD and PTSD symptoms severity [98,99]. In particular, the retrospective cohort study by Usuki and coworkers (2012), examined a cohort of 300 motor vehicle accident survivors who were treated with propofol within 72 h from the trauma. They controlled for confounding factors such as alcohol consumption, use of midazolam, ketamine or morphine within 72 h from the accident and history for psychiatric illness [99]. PTSD diagnosis and symptoms severity were formulated through the administration of the Clinician-Administered PTSD Scale (CAPS) at 1 and 6 months from the accident [99]. The results showed that patients treated with propofol, had an enhanced risk for full or partial PTSD at 1 month and 6 months from the accident [99]. Moreover, propofol-treated patients also showed increased PTSD symptoms severity (i.e. higher scores at the items of the CAPS scale) at 6 but not 1 months from the accident [99]. Although the limitations of a retrospective study has to be taken into account, taken together these data suggest that the use of propofol after accidents and other traumatic experiences should be avoided since it might enhance the risk of subsequent PTSD development [100]. Nevertheless, what all of this has to do with cannabinoids? The anesthetic properties of propofol, like many other related anesthetics, are mediated by the facilitation of GABA-mediated inhibitory transmission and a specific propofol binding side on mammalian GABA-A receptor has been identified [88]. The sedative, hypnotic and amnesic actions as well as its pharmacokinetic properties, make propofol a very versatile and widely used anesthetic in the clinical practice [100]. However, propofol, as stated above, also inhibits the FAAH enzyme causing an increase of anandamide levels and this property differentiates proprofol from all the other clinically used anesthetics [89]. The authors of the reported study

speculate, also on the basis of preclinical data obtained by our group in rats [90] that the observed enhanced risk of PTSD development, linked to propofol use, might be mediated by the enhanced endocannabinoid transmission through anandamide levels elevation [99] and thus by the facilitation of traumatic memory consolidation [100]. To conclude, the mixed results of cannabinoids effects on consolidation do not seem to point out with certainty that post-trauma administrations of cannabinoids could be beneficial or even detrimental for later PTSD symptoms development.

## 5. "Reducing the re-experiencing of traumatic memories": the effects of cannabinoids on memory retrieval

Differently from memory consolidation studies, much consensus exists in the literature regarding the effects of cannabinoids on memory retrieval. Indeed, data from different research groups all seem to point out to an impairing effect on memory retrieval induced by cannabinoid agonists [15]. Given this, and the possible clinical applications involved, the paucity of studies examining this issue on preclinical PTSD models and on clinical trials with PTSD patients appears surprising. Indeed, by attenuating the retrieval of traumatic memories it should be theoretically possible to reduce re-experiencing symptoms thus reducing the subsequent over-consolidation which characterize PTSD patients, thus also leading to a reduced impact that those memories have on anxiety and mood. Besides, the update of the original memory trace occurring after its reactivation, known as re-consolidation, could weaken the trace making it less persistent [101]. Interestingly, this approach has already proven to be helpful in reducing phobic fear, when glucocorticoids (which share with cannabinoids the ability to impair memory retrieval) were administered to phobic patients 1 h before retrieval of fearful information [102].

### 5.1. Animal studies

All animal studies investigating cannabinoid effects on retrieval reported impairing effects of agonists. For example, systemic THC was found to impair retrieval of the Inhibitory Avoidance task [103]. The same treatment along with exposure to marijuana smoke, were also found to impair retrieval of Morris Water Maze task [104] and these effects were blocked by the CB1 antagonist rimonabant [104]. Morris Water Maze retrieval was also impaired by systemic treatment with administration of the cannabinoid agonist CP-55,940 [105]. A recent study, performed by our group, showed an interesting results pattern in rats performing the Morris Water Maze task under two stress conditions: a more stressful condition due to exposure to colder water (19 °C) and a less stressful condition due to the exposure to warmer water (26 °C) [106]. Our results showed that the injection of WIN55,212-2 and JZL184 (a MAGL enzyme inhibitor which elevates endogenous 2-AG levels) into the hippocampus impaired the recall of the platform location position in rats trained under the higher stressful condition only [106]. Systemic THC administration prior to retrieval, impaired rats performance in a radial maze task in two different studies [103,107] and the cannabinoid antagonist rimonabant reverted those effects [103,107]. In addition, intra-hippocampal administration of CP-55,940 induced a deficit in radial maze retrieval reverted by pretreatment with the antagonist rimonabant [107]. A deficit in radial maze retrieval was also observed when the CB1/CB2 agonist WIN55,212-2 was injected systemically or into the dorsal hippocampus [108]. The same compound also induced impaired retention of contextual fear conditioning when infused into hippocampal CA1 (an effect reverted by prior hippocampal β-adrenoceptors blockade) [109] and when infused into ventral subiculum [110]. Moreover, intracerebroventricular administration [111] or intra-CA1 injection [75,76,112] of WIN55,212-2 also impaired retrieval of step-down Inhibitory Avoidance. Systemic WIN55,212-2 was also able to impair retrieval of an object recognition task and of a radial water maze test, and both the effects were blocked through pre-treatment with rimonabant [113]. In another study that evaluated the effects of WIN55,212-2 micro-infusions in different brain regions in the fear-potentiated startle paradigm, the drug was found to impair the retrieval of the task when infused into basolateral amygdala and medial prefrontal cortex [84].

### 5.2. Human studies

Studies investigating cannabinoids effects on memory retrieval are scarce and clinical experimental trials on psychiatric patients are, at least to our knowledge, completely absent in literature. In addition, results from studies examining human retrieval performance in long-term learning task with administered THC or marijuana are mixed, in striking contrast to the well known impairing retrieval effects in short-term/working memory tasks [114]. However, when interpreting experimental data in humans, it must be considered that the test material in memory tasks is usually composed by lists of words/digits, prose material, visuo-spatial items, semantic knowledge, knowledge of common fact, which all share really few features in common with traumatic events in PTSD, especially regarding the stress and emotional arousal levels involved. In a study by Miller and co-workers (1977), smoking marijuana before a retrieval test for prose material learned 24 h before and under drug-free conditions, significantly reduced the performance of the task [115]. Moreover, in a study which assessed college student's ability to recall a series of common facts from long-term memory, acute administration of marijuana (calibrated to 0.3 mg/kg of THC) did impair the performance [116]. When examining marijuana effects on semantic memory retrieval of simple category items, Block and Wittenborn (1984) reported only an increase in reaction times but no effects on error rates in treated subjects in comparison to placebo-treated ones [117]. In a similar study, where subject were asked to retrieve as many instances of a certain category as they could in 2 min, the same authors found that marijuana did not alter subjects' performance but only produced a shift of the responses towards more uncommon instances [118]. Another study examined subjects' performance on a series of cognitive tasks at different time points after acute THC administration. In relation to semantic retrieval, measured by means of a verbal fluency task, 6 h after THC administration the subjects receiving the higher dose of THC (15 mg) produced significantly more words than subjects receiving the lower dose (7.5 mg) but no differences were observed in comparison to placebo [119]. In conclusion, more data on cannabinoids effects on human memory retrieval need to be collected, and preferably from clinical trials, in order to consider them as of potential benefit for PTSD treatment.

## 6. Potentiating the efficacy of exposure therapy through cannabinoid-mediated enhancement of extinction

The pharmacological enhancement of extinction learning is one of the most prolific fields in the study of preclinical models of stress and fear-related disorders for a two-fold reason. First, the cognitive-behavioral exposure-based therapy engages extinction mechanisms [12] and extinction enhancer compounds can either increase the efficacy itself and/or reduce the duration of psychological intervention. Secondly, extinction has to be considered not as an erasure of the original traumatic memory, rather as a new inhibitory learning able to reduce the conditioned anxiety/fear responses elicited by the exposure to trauma-related reminders [120–122]. The possibility to retain the memory for the trauma,

but without the negative devastating consequences of an established PTSD, is of great advantage in comparison to the complete erasure of the trauma traumatic memory. Indeed, in this case, a subject can use previously learned experience to afford analogue future situations (e.g. soldiers in war).

Many are the extinction enhancer compounds under investigation in PTSD field (see Refs. [6,123–126] for review). In the present review we will focus on cannabinoid compounds.

### 6.1. Animal studies

#### 6.1.1. Agonists

Systemic administration of the non-selective agonist WIN55,212-2 or the indirect agonist AM404 was found to enhance extinction of contextual fear conditioning for both recent (24 h old) and remote (30 days old) memory [127]. The same treatments also facilitated contextual fear conditioning extinction with a single extended extinction session of 30 min [128]. AM404, the phytocannabinoid cannabidiol and WIN55,212-2 enhanced contextual fear conditioning extinction when intracereboventricularly infused [129,130]. Cannabidiol promoted contextual fear conditioning extinction also when infused into the infra-limbic region of medial prefrontal cortex, an effect blocked by systemic administration of rimonabant [131]. In addition, WIN55,212-2 and AM404 facilitated extinction of Inhibitory Avoidance when micro-infused into CA1 region of the hippocampus [132]. Systemic AM404 also enhanced extinction of fear-potentiated startle, an effect that was blocked by co-administration of the CB1 antagonist rimonabant [133], as well as micro-infusion of WIN55,212-2 into infra-limbic cortex [134]. Another study showed that the FAAH inhibitor URB597 facilitated short-term (but not long-term) extinction of contextual fear conditioning in mice. However, when mice where additionally stressed with a repeated social defeat procedure, URB597 also enhanced long-term contextual fear conditioning extinction [135]. Systemic URB597 enhanced extinction of auditory fear conditioning as well [136]. Moreover, the FAAH inhibitor AM3506 enhanced auditory fear conditioning extinction when systemically or intra-amygdala administered; the effect was mediated by anandamide activation of cannabinoid receptors [137]. Intra-CA1 injection of anandamide enhanced extinction of contextual fear conditioning, but co-administration with a non-altering dose of the CB1 antagonist AM251 blocked the enhancing effects thus again demonstrating the important role of cannabinoid receptor activation in facilitating memory extinction [91]. Finally, the FAAH inhibitor OL-135 showed extinction enhancing properties when systemically administered in a Morris Water Maze task, an effect blocked by administration of the cannabinoid receptor antagonist rimonabant [138].

#### 6.1.2. Antagonists

Regarding cannabinoid antagonists and extinction of memory for emotional events, different studies showed that systemic administrations of the CB1 antagonists rimonabant and AM251 impaired extinction of cued fear conditioning [136,139–142] as well as contextual fear conditioning [127,128,143,144]. Systemic antagonism of CB1 receptors also impaired extinction of fear-potentiated startle [133,145] and the same effect was observed when CB1 were blocked selectively into prefrontal cortex [84,134]. Also in the paradigm of Inhibitory Avoidance, CB1 antagonists produced an impairment in extinction learning when given either systemically [146], into the basolateral amygdala [147] or into the CA1 region of the hippocampus [132]. In addition, intra-CA1 infusion of AM251 also impaired extinction of contextual fear conditioning [91]. Systemic administration of rimonabant also produced an impairment of extinction in the Morris Water Maze task [148]. All these studies seem to point out to a strong enhancing effect of cannabinoid agonists on extinction processes which appears to be mediated by CB1 receptors, however evidence for the ameliorating effects on preclinical PTSD models are still lacking.

### 6.2. Human studies

Regarding extinction processes few more data are available on cannabinoid effects in comparison with retrieval evidence, thus also indicating the great success that this field of study has been receiving. For instance, Rabinak and colleagues (2013) conditioned healthy volunteers to a sound burst after the presentation of 2 different visual conditioned stimuli on a monitor [149]. They recorded the skin conductance responses, a physiological index of emotional reactivity, immediately after the conditioned stimuli onset. On the subsequent day, one of the two conditioned stimuli was extinguished with an extinction procedure carried 120 min after subjects' ingestion of 7.5 mg of THC or placebo [149]. On the following day, participants were subjected to an extinction memory recall test. Results showed that, even if no differences on skin conductance responses were found during the acquisition phase, on the recall test THC-treated group showed significantly lower skin conductance responses at the presentation of the extinguished CS in comparison to the unextinguished one, differently from the placebo-treated group. As a result, a difference between THC and placebo-treated subjects was also found in the mean difference of skin conductance responses on extinguished minus unextinguished CS trials [149]. The same group extended these results by replicating the experiment during functional magnetic resonance (fMRI) imaging scanning [150]. The authors found that subjects who received THC prior to extinction, exhibited greater ventromedial prefrontal cortex and hippocampal activation to the extinguished CS presentation during recall, when compared to placebo-treated subjects [150]. Another study involved a human version of fear conditioning using brief electric shocks as unconditioned stimuli [151]. In this study 32 mg of cannabidiol were administered by inhalation prior or immediately after the CS extinction procedure in order to target the acquisition or the consolidation of extinction respectively. While no differences were observed in skin conductance responses during extinction, the authors found a reduction of subjective shock expectancy ratings at the presentation of extinguished CS in the recall test carried 48 h after extinction in the group treated with cannabidiol after extinction but not in the other groups [151]. Moreover, when they reinstated the extinguished association through the presentation of another brief shock, they found a lower increase of the skin conductance responses on both groups that had received cannabidiol in comparison to the placebo group, thus showing that the learned extinction on these groups was more resistant to reinstatement [151]. Conversely, another human study involving a fear conditioning plus fear-potentiated startle procedure reported only a transient reduction of skin conductance responses during extinction training on THC-treated subjects compared to placebo-treated ones [152]. Indeed, this effect was not retained during the recall test conducted 48 h later and no effects of THC were observed in the fear-potentiated startle [152]. An interesting study investigated if a genetic variation at the level of regions of the genome encoding for CB1 receptors, could impact on extinction performance in human healthy volunteers. To this aim, the authors genotyped 150 subjects that underwent a procedure of fear-potentiated startle in a virtual reality environment [153]. They found that subjects homozygotes for a particular polymorphism located within the promoter region of the CB1 receptor gene, failed to extinguish fear thus displaying significantly higher levels of fear-potentiated startle at the end of extinction training, when compared to other groups [153].

To summarize, preclinical evidence points to cannabinoid agonists as potential candidates for extinction enhancement during

exposure therapy, thus soliciting more research on human subjects. As an example, clinical effects of cannabinoid agonists might be tested in PTSD patients with drugs given immediately after a series of exposure therapy sessions, with a placebo-controlled design. Scores to standardized tools for the assessment of PTSD symptomatology (e.g. CAPS) could then be compared in each patient with measures taken before the treatment, right after the treatment and after a defined follow-up interval (e.g. 3 or 6 months). In addition, for each treatment group, a direct comparison between each interval could be also performed.

## 7. Ameliorative effects of cannabinoid drugs on PTSD symptomatology

Although this is a recent area of research, some studied reporting beneficial effects of cannabinoid drugs in PTSD patients are appearing in the literature. Passie and co-workers (2012) reported a case of a 19-year-old male patient with a severe abuse-related PTSD symptomatology also including dissociative states and self-mutilation behaviors triggered by flashbacks [154]. When found positive to THC in toxicological testing, he declared to clinicians that he discovered that smoking cannabis when he first felt reactivation and intensification of the traumatic memories could prevent him to enter in the dissociative state increasing his ability to maintain cognitive control on the situation [154]. In addition, he also experienced a reduced need for self-mutilation. The improvement in self-control and stability was also noted by his therapist, not aware of the use of cannabis as self-medication [154]. Interestingly, it has been also recently published a study reporting the results of an open label clinical trial with the synthetic cannabinoid agonist nabilone given orally (0.5 mg per die, 1 h before bedtime) to 47 PTSD patients [155]. Thirty-four of the treated patients (representing the 72% of the sample) experienced the total cessation of nightmares or lessening of their severity and in some cases an improvement of daytime flashbacks as well [155]. Another study examined a cohort of 101 patients from a hybrid mental health and correctional institute with various psychiatric conditions, who received off-label nabilone for 4–5 years based on its known effectiveness in chronic pain reduction and on its potential effects on PTSD insomnia and nightmare amelioration [156]. The results showed: i) a significant increase in the average numbers of hours slept, ii) a significant reduction in the number of nightmare experiences, iii) a significant increase in global functioning as assessed by the Global Assessment of Functioning (GAF), and iv) most importantly (on the subgroup of patients (n = 58) with diagnosed PTSD) a significant decrease of average PTSD symptoms severity as assessed by the Post traumatic Checklist-Civilian version (PCL-C) [156]. A reduction of PTSD symptom severity was also reported in another study that compared pre-treatment and post-treatment CAPS scores of 80 PTSD patients who began to take medical cannabis in New Mexico in 2009, when cannabis use for PTSD was approved [157]. In particular, the symptom severity reduction was statistically significant for all the different symptom clusters examined by the CAPS: total score, criterion B (re-experiencing symptoms), criterion C (numbing and avoidance) and criterion D (hyperarousal) [157]. Other studies reported that the association between PTSD and cannabis use is usually motivated by the search for its sleep-promoting effects and a general help in coping and managing the symptomatology [158,159]. Last but not least, worth of note is a study investigating the effects of nabilone specifically on PTSD-associated nightmares, in a double-blind placebo-controlled cross-over design on 10 PTSD patients [160]. Nabilone was administered daily 1 h before bedtime, for 7 consecutive weeks which were followed by 2 weeks of wash-out before the start of the other treatment period (7 weeks long). 70% of the subjects reported symptom improvement after nabilone treatment, while only a 22% of subjects reported improvement in the placebo treated group [160]. The primary improvement in the nabilone treated group was registered for the CAPS Recurring and Distressing Dream Scores which were significantly reduced on both frequency and intensity. Other improvements were observed on the Clinical Global Impression of Change (CGI-C) and the General Well Being Questionnaire [160]. In addition, at the end of the nabilone treatment period, 44% of subjects reported no distressing dreams in the last week of treatment compared to the 0% of the placebo group. Conversely, none of the subjects in the nabilone treatment period reported daily distressing dreams, while the 50% of subjects in the placebo treatment period experienced distressing dreams [160].

Taken together, these studies seem to indicate that cannabinoids could exert positive effects on an already established PTSD syndrome. Even though the design of these studies does not allow to clearly identify the nature of the cannabinoid-mediated improvements of the symptomatology, the reduction of nightmares and the general sleep quality promotion is frequently reported by PTSD patients who began either to consume or to be treated with cannabis derivatives. It is worth noting that it is now widely accepted that consolidation and reorganization of different kinds of memory occur during sleep [161–163]. It is tentative to speculate that cannabinoid stimulation during sleep may affect the reorganization of the traumatic memory, reducing trauma-related nightmares and possibly gradually reducing the distressing impact that traumatic memory exerts on behavior and mood. If future research will confirm this hypothesis, it will be possible that the administration of cannabinoids in PTSD patients, by enhancing the extinction and/or attenuating the retrieval of traumatic memories, could not only reduce post-traumatic symptomatology but could also lead the patient towards a complete recovery from the disease.

## 8. Conclusions

In the present paper we reviewed data from both animal and human studies showing the modulatory effects of cannabinoids on different memory phases. Even though the most of the presented data come from animal studies, and therefore conclusions on their translational value need to be taken with a word of caution, we evaluated these results in the view of a future application of cannabinoid drugs in the treatment of PTSD. Indeed, by targeting a particular stage of the traumatic memory processing at the right time, the intensity of the post-traumatic symptomatology could be drastically reduced and the efficacy of the available exposure-based psychotherapies improved. Among the memory phases taken into account, cannabinoid treatments targeting the consolidation stage of the trauma, might be the less promising in terms of efficacy. Moreover, administrating a drug in the immediate aftermath of a trauma might not be always easily achievable in the clinical practice and is not devoid of ethic concerns. Targeting the retrieval of the traumatic memory with cannabinoid agonists might exert more promising effects by reducing the vividness and persistence of the memory trace and consequently the occurrence of related symptoms. However, to date only few preclinical studies investigated cannabinoids effects on retrieval, and human studies involving fear-related tasks or clinical trials are practically absent in literature. Finally, the enhancement of extinction learning is, above the others, the most promising effect that could find a recent future application in the treatment of PTSD and other stress-related disorders. Indeed, by potentiating extinction learning processes, cannabinoid agonists could reduce the conditioned fear and anxiety responses triggered by trauma reminders, increasing patients general ability to actively cope with the trauma without affecting the original memory trace. Moreover, the use of

cannabinoids in conjunction with exposure therapy could increase its efficacy and reduce the duration of the psychological intervention. In the last section, we reviewed data on PTSD patients who already benefited or are still benefiting from treatments with medical cannabinoids thus showing how cannabinoids efficacy in PTSD treatment is far from being a mere speculation derived from animal studies. Still, more studies are needed to better characterize the quality of cannabinoid-mediated improvements and the exact way in which they could be safely used.

## Conflict of interest

The authors declare no conflict of interest.

## References


[1] Association, A. P, "Diagnostic and Statistical Manual of Mental Disorders DSM-5 Fifth Edition", American Psychiatric Publishing, Washington, DC, 2013.
[2] S.A. Moore, Cognitive abnormalities in post traumatic stress disorder, Curr. Opin. Psychiatry 22 (2009) 19–24.
[3] C.R. Brewin, The nature and significance of memory disturbance in post traumatic stress disorder, Annu. Rev. Clin. Psychol. 7 (2011) 203–227.
[4] R.G. Parsons, K.J. Ressler, Implications of memory modulation for post-traumatic stress and fear disorders, Nat. Neurosci. 16 (2013) 146–153.
[5] V. Trezza, P. Campolongo, The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD), Front. Behav. Neurosci. 7 (2013) (pp. 100).
[6] N. Singewald, C. Schmuckermair, N. Whittle, A. Holmes, K.J. Ressler, Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders, Pharmacol. Ther. 149 (2015) 150–190.
[7] A. Holmes, N. Singewald, Individual differences in recovery from traumatic fear, Trends Neurosci. 36 (2013) 23–31.
[8] A. Catarino, C.S. Küpper, A. Werner-Seidler, T. Dalgleish, M.C. Anderson, Failing to forget: inhibitory-control deficits compromise memory suppression in post traumatic stress disorder, Psychol. Sci. 26 (2015) 604–616.
[9] E. Kong, F.J. Monje, J. Hirsch, D.D. Pollak, Learning not to fear: neural correlates of learned safety, Neuropsychopharmacology 39 (2014) 515–527.
[10] D.J.-F. de Quervain, D. Bentz, T. Michael, O.C. Bolt, B.K. Wiederhold, J. Margraf, F.H. Wilhelm, Glucocorticoids enhance extinction-based psychotherapy, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 6621–6625.
[11] D.D. Mendes, M.F. Mello, P. Ventura, C.D.M. Passareta, J.D.J. Mari, A systematic review on the effectiveness of cognitive behavioral therapy for post traumatic stress disorder, Int. J. Psychiatry Med. 38 (2008) 241–259.
[12] J.I. Bisson, N.P. Roberts, M. Andrew, R. Cooper, C. Lewis, Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults, Cochrane Database Syst. Rev. 12 (2013), pp. CD003388.
[13] S.M. Kehle-Forbes, L.A. Meis, M.R. Spoont, M.A. Polusny, Treatment initiation and dropout from prolonged exposure and cognitive processing therapy in a VA outpatient clinic, Psychol. Trauma. 8 (2015) 107–114.
[14] L.M. Najavits, The problem of dropout from gold standard PTSD therapies, F1000Prime Rep. 7 (2015), pp. 43.
[15] M. Morena, P. Campolongo, The endocannabinoid system: an emotional buffer in the modulation of memory function, Neurobiol. Learn. Mem. 112 (2014) 30–43.
[16] M.P. Viveros, E.M. Marco, S.E. File, Endocannabinoid system and stress and anxiety responses, Pharmacol. Biochem. Behav. 81 (2005) 331–342.
[17] L.A. Batista, P.H. Gobira, T.G. Viana, D.C. Aguiar, F.A. Moreira, Inhibition of endocannabinoid neuronal uptake and hydrolysis as strategies for developing anxiolytic drugs, Behav. Pharmacol. 25 (2014) 425–433.
[18] D. Hauer, G. Schelling, H. Gola, P. Campolongo, J. Morath, B. Roozendaal, G. Hamuni, A. Karabatsiakis, P. Atsak, M. Vogeser, L.-T. Kolassa, Plasma concentrations of endocannabinoids and related primary fatty acid amides in patients with post-traumatic stress disorder, PLoS One 8 (2013) e62741.
[19] M.N. Hill, L.M. Bierer, I. Makotkine, J.A. Golier, S. Galea, B.S. McEwen, C.J. Hillard, R. Yehuda, Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks, Psychoneuroendocrinology 38 (2013) 2952–2961.
[20] A. Neumeister, M.D. Normandin, R.H. Pietrzak, D. Piomelli, M.Q. Zheng, A. Gujarro-Anton, M.N. Potenza, C.R. Bailey, S.F. Lin, S. Najafzadeh, J. Ropchan, S. Henry, S. Corsi-Travali, R.E. Carson, Y. Huang, Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study, Mol. Psychiatry 18 (2013) 1034–1040.
[21] A. Neumeister, J. Seidel, B.J. Ragen, R.H. Pietrzak, Translational evidence for a role of endocannabinoids in the etiology and treatment of post traumatic stress disorder, Psychoneuroendocrinology 51 (2015) 577–584.
[22] M. Morena, S. Patel, J.S. Bains, M.N. Hill, Neurobiological interactions between stress and the endocannabinoid system, Neuropsychopharmacology 41 (2016) 80–102.
[23] J.L. McGaugh, Memory—a century of consolidation, Science 287 (2000) 248–251.
[24] J.L. McGaugh, Make mild moments memorable: add a little arousal, Trends Cogn. Sci. 10 (2006) 345–347.
[25] Y. Dudai, The restless engram: consolidations never end, Annu. Rev. Neurosci. 35 (2012) 227–247.
[26] E. Vermetten, J. Zhohar, H.J. Krugers, Pharmacotherapy in the aftermath of trauma: opportunities in the 'golden hours', Curr. Psychiatry Rep. 16 (2014) (pp. 455).
[27] K. Sakai, Reactivation of memory: role of medial temporal lobe and prefrontal cortex, Rev. Neurosci. 14 (2003) 241–252.
[28] K. Nader, G.E. Schafe, J.E.L. Doux, Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval, Nature 406 (2000) 722–726.
[29] L. Schwabe, K. Nader, J.C. Pruessner, Reconsolidation of human memory: brain mechanisms and clinical relevance, Biol. Psychiatry 76 (2014) 274–280.
[30] G.J. Quirk, D. Paré, R. Richardson, C. Herry, M.H. Monfils, D. Schiller, A. Vicentic, Erasing fear memories with extinction training, J. Neurosci. 30 (2010) 14993–14997.
[31] D.S. Charney, Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress, Am. J. Psychiatry 161 (2004) 195–216.
[32] J.F. McGuire, A.B. Lewin, E.A. Storch, Enhancing exposure therapy for anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder, Expert Rev. Neurother. 14 (2014) 893–910.
[33] Y. Gaoni, R. Mechoulam, "Isolation, structure, and partial synthesis of an active constituent of hashish", J. Am. Chem. Soc. 86 (1964) 1646–1647.
[34] V. Di Marzo, The endocannabinoid system: its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation, Pharmacol. Res. 60 (2009) 77–84.
[35] L.A. Matsuda, S.J. Lolait, M.J. Brownstein, A.C. Young, T.I. Bonner, Structure of a cannabinoid receptor and functional expression of the cloned cDNA, Nature 346 (1990) 561–564.
[36] S. Munro, K.L. Thomas, M. Abu-Shaar, Molecular characterization of a peripheral receptor for cannabinoids, Nature 365 (1993) 61–65.
[37] W.A. Devane, L. Hanus, A. Breuer, R.G. Pertwee, L.A. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger, R. Mechoulam, Isolation and structure of a brain constituent that binds to the cannabinoid receptor, Science 258 (1992) 1946–1949.
[38] R.G. Pertwee, Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists, Curr. Med. Chem. 17 (2010) 1360–1381.
[39] T. Sugiura, S. Kondo, A. Sukagawa, S. Nakane, A. Shinoda, K. Itoh, A. Yamashita, K. Waku, 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain, Biochem. Biophys. Res. Commun. 215 (1995) 89–97.
[40] N. Stella, P. Schweitzer, D. Piomelli, A second endogenous cannabinoid that modulates long-term potentiation, Nature 388 (1997) 773–778.
[41] V. Di Marzo, A. Fontana, H. Cadas, S. Schinelli, G. Cimino, J.C. Schwartz, D. Piomelli, Formation and inactivation of endogenous cannabinoid anandamide in central neurons, Nature 372 (1994) 686–691.
[42] V. Di Marzo, Biosynthesis and inactivation of endocannabinoids: relevance to their proposed role as neuromodulators, Life Sci. 65 (1999) 645–655.
[43] V. Di Marzo, T. Bisogno, L. De Petrocellis, D. Melck, P. Orlando, J.A. Wagner, G. Kunos, Biosynthesis and inactivation of the endocannabinoid 2-arachidonoylglycerol in circulating and tumoral macrophages, Eur. J. Biochem. 264 (1999) 258–267.
[44] M. Kano, T. Ohno-Shosaku, Y. Hashimotodani, M. Uchigashima, M. Watanabe, Endocannabinoid-mediated control of synaptic transmission, Physiol. Rev. 89 (2009) 309–380.
[45] A. Ligresti, E. Morera, M. Van Der Stelt, K. Monory, B. Lutz, G. Ortar, V. Di Marzo, Further evidence for the existence of a specific process for the membrane transport of anandamide, Biochem. J 380 (2004) 265–272.
[46] C.J. Hillard, L. Shi, V.R. Tuniki, J.R. Falck, W.B. Campbell, Studies of anandamide accumulation inhibitors in cerebellar granule neurons: comparison to inhibition of fatty acid amide hydrolase, J. Mol. Neurosci. 33 (2007) 18–24.
[47] J. Fu, G. Bottegoni, O. Sasso, R. Bertorelli, W. Rocchia, M. Masetti, A. Guijarro, A. Lodola, A. Armirotti, G. Garau, T. Bandiera, A. Reggiani, M. Mor, A. Cavalli, D. Piomelli, A catalytically silent FAAH-1 variant drives anandamide transport in neurons, Nat. Neurosci. 15 (2012) 64–69.
[48] B.F. Cravatt, D.K. Giang, S.P. Mayfield, D.L. Boger, R.A. Lerner, N.B. Gilula, Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides, Nature 384 (1996) 83–87.
[49] M. Karlsson, J.A. Contreras, U. Hellman, H. Tornqvist, C. Holm, cDNA cloning, tissue distribution, and identification of the catalytic triad of monoglyceride lipase evolutionary relationship to esterases, lysophospholipases, and haloperoxidases, J. Biol. Chem. 272 (1997) 27218–27223.
[50] T.P. Dinh, D. Carpenter, F.M. Leslie, T.F. Freund, I. Katona, S.L. Sensi, S. Kathuria, D. Piomelli, Brain monoglyceride lipase participating in endocannabinoid inactivation, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 10819–10824.
[51] M. Herkenham, A.B. Lynn, M.D. Little, M.R. Johnson, L.S. Melvin, B.R. de Costa, K.C. Rice, Cannabinoid receptor localization in brain, Proc. Natl. Acad. Sci. U. S. A. 87 (1990) 1932–1936.

[52] J.M. McPartland, M. Glass, R.G. Pertwee, Meta-analysis of cannabinoid ligand binding affinity and receptor distribution: interspecies differences, Br. J. Pharmacol. 152 (2007) 583–593.
[53] J.-P. Gong, E.S. Onaivi, H. Ishiguro, Q.-R. Liu, P.A. Tagliaferro, A. Brusco, G.R. Uhl, Cannabinoid CB2 receptors: immunohistochemical localization in rat brain, Brain Res. 1071 (2006) 10–23.
[54] A.C. Howlett, Pharmacology of cannabinoid receptors, Annu. Rev. Pharmacol. Toxicol. 35 (1995) 607–634.
[55] A.C. Howlett, Cannabinoid receptor signaling, Handb. Exp. Pharmacol. 168 (2005) 53–79.
[56] S.C. Azad, Jö. Kurz, G. Marsicano, B. Lutz, W. Zieglgänsberger, G. Rammes, Activation of CB1 specifically located on GABAergic interneurons inhibits LTD in the lateral amygdala, Learn. Mem. 15 (2008) 143–152.
[57] Y. Kawamura, M. Fukaya, T. Maejima, T. Yoshida, E. Miura, M. Watanabe, T. Ohno-Shosaku, M. Kano, The CB1 cannabinoid receptor is the major cannabinoid receptor at excitatory presynaptic sites in the hippocampus and cerebellum, J. Neurosci. 26 (2006) 2991–3001.
[58] H. Hermann, G. Marsicano, B. Lutz, Coexpression of the cannabinoid receptor type 1 with dopamine and serotonin receptors in distinct neuronal subpopulations of the adult mouse forebrain, Neuroscience 109 (2002) 451–460.
[59] M. Häring, G. Marsicano, B. Lutz, K. Monory, Identification of the cannabinoid receptor type 1 in serotonergic cells of raphe nuclei in mice, Neuroscience 146 (2007) 1212–1219.
[60] V.C. Oropeza, K. Mackie, E.J. Van Bockstaele, Cannabinoid receptors are localized to noradrenergic axon terminals in the rat frontal cortex, Brain Res. 1127 (2007) 36–44.
[61] J.M. Wehner, R.A. Radcliffe, Cued and contextual fear conditioning in mice, Curr. Protoc. Neurosci. (2004), vol. Chapter 8, pp. Unit 8.5C.
[62] C. Furini, J. Myskiw, I. Izquierdo, The learning of fear extinction, Neurosci. Biobehav. Rev. 47 (2014) 670–683.
[63] M.E. Bouton, Context and behavioral processes in extinction, Learn. Mem. 11 (2004) 485–494.
[64] J.L. McGaugh, C.K. McIntyre, A.E. Power, Amygdala modulation of memory consolidation: interaction with other brain systems, Neurobiol. Learn. Mem. 78 (2002) 539–552.
[65] L.A. Izquierdo, D.M. Barros, M.R.M. Vianna, A. Coitinho, T. deDavid e Silva, H. Choi, B. Moletta, J.H. Medina, I. Izquierdo, Molecular pharmacological dissection of short- and long-term memory, Cell. Mol. Neurobiol. 22 (2002) 269–287.
[66] M. Davis, Fear-potentiated startle in rats, Curr. Protoc. Neurosci. (2001), vol. Chapter 8, pp. Unit 8.11A.
[67] R. Stam, PTSD and stress sensitisation: a tale of brain and body Part 1: human studies, Neurosci. Biobehav. Rev. 31 (2007) 530–557.
[68] L.M. McTeague, P.J. Lang, The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress, Depress. Anxiety 29 (2012) 264–281.
[69] C.V. Vorhees, M.T. Williams, Morris water maze: procedures for assessing spatial and related forms of learning and memory, Nat. Protoc. 1 (2006) 848–858.
[70] R.A. Bevins, J. Besheer, Object recognition in rats and mice: a one-trial non-matching-to-sample learning task to study 'recognition memory', Nat. Protoc. 1 (2006) 1306–1311.
[71] G.L. Wenk, Assessment of spatial memory using the radial arm maze and Morris water maze, Curr. Protoc. Neurosci. (2004), vol. Chapter 8, pp. Unit 8.5A.
[72] M. Mačkowiak, A. Chocyk, D. Dudys, K. Wedzony, Activation of CB1 cannabinoid receptors impairs memory consolidation and hippocampal polysialylated neural cell adhesion molecule expression in contextual fear conditioning, Neuroscience 158 (2009) 1708–1716.
[73] M. Nasehi, M. Sahebgharani, A. Haeri-Rohani, M.R. Zarrindast, Effects of cannabinoids infused into the dorsal hippocampus upon memory formation in 3-days apomorphine-treated rats, Neurobiol. Learn. Mem. 92 (2009) 391–399.
[74] M.R. Zarrindast, M. Dorrani, R. Lachinani, A. Rezayof, Blockade of dorsal hippocampal dopamine receptors inhibits state-dependent learning induced by cannabinoid receptor agonist in mice, Neurosci. Res. 67 (2010) 25–32.
[75] N. Jamali-Raeufy, M. Nasehi, M.R. Zarrindast, Influence of N-methyl D-aspartate receptor mechanism on WIN55,212-2-induced amnesia in rat dorsal hippocampus, Behav. Pharmacol. 22 (2011) 645–654.
[76] A. Moshfegh, P. Babaei, S. Oryan, B. Soltani, M.-R. Zarrindast, Involvement of dorsal hippocampal $1-adrenergic receptors in the effect of WIN55,212-2 on memory retrieval in inhibitory avoidance task, Neurosci. Lett. 489 (2011) 69–73.
[77] M.R. Zarrindast, M. Ghiasvand, A. Rezayof, S. Ahmadi, The amnesic effect of intra-central amygdala administration of a cannabinoid CB1 receptor agonist WIN55,212-2, is mediated by a $-1 noradrenergic system in rat, Neuroscience 212 (2012) 77–85.
[78] M. Ghiasvand, A. Rezayof, S. Ahmadi, M.-R. Zarrindast, $1-noradrenergic system of the central amygdala is involved in state-dependent memory induced by a cannabinoid agonist WIN55,212-2, in rat, Behav. Brain Res. 225 (2011) 1–6.
[79] P. Campolongo, B. Roozendaal, V. Trezza, D. Hauer, G. Schelling, J.L. McGaugh, V. Cuomo, Endocannabinoids in the rat basolateral amygdala enhance memory consolidation and enable glucocorticoid modulation of memory, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 4888–4893.
[80] L. De Oliveira Alvares, B.P. Genro, F. Diehl, J.A. Quillfeldt, Differential role of the hippocampal endocannabinoid system in the memory consolidation and retrieval mechanisms, Neurobiol. Learn. Mem. 90 (2008) 1–9.
[81] C. Castellano, S. Cabib, A. Palmisano, V. Di Marzo, S. Puglisi-Allegra, The effects of anandamide on memory consolidation in mice involve both D1 and D2 dopamine receptors, Behav. Pharmacol. 8 (1997) 707–712.
[82] C. Castellano, R. Ventura, S. Cabib, S. Puglisi-Allegra, Strain-dependent effects of anandamide on memory consolidation in mice are antagonized by naltrexone, Behav. Pharmacol. 10 (1999) 453–457.
[83] M. Costanzi, M. Battaglia, C. Rossi-Arnaud, V. Cestari, C. Castellano, Effects of anandamide and morphine combinations on memory consolidation in cd1 mice: involvement of dopaminergic mechanisms, Neurobiol. Learn. Mem. 81 (2004) 144–149.
[84] S. Kuhnert, C. Meyer, M. Koch, Involvement of cannabinoid receptors in the amygdala and prefrontal cortex of rats in fear learning, consolidation, retrieval and extinction, Behav. Brain Res. 250 (2013) 274–284.
[85] P. Campolongo, M. Morena, S. Scaccianoce, V. Trezza, F. Chiarotti, G. Schelling, V. Cuomo, B. Roozendaal, Novelty-induced emotional arousal modulates cannabinoid effects on recognition memory and adrenocortical activity, Neuropsychopharmacology 38 (2013) 1276–1286.
[86] S. Kathuria, S. Gaetani, D. Fegley, F. Valiño, A. Duranti, A. Tontini, M. Mor, G. Tarzia, G. La Rana, A. Calignano, A. Giustino, M. Tattoli, M. Palmery, V. Cuomo, D. Piomelli, Modulation of anxiety through blockade of anandamide hydrolysis, Nat. Med. 9 (2003) 76–81.
[87] M. Morena, B. Roozendaal, V. Trezza, P. Ratano, A. Peloso, D. Hauer, P. Atsak, L. Trabace, V. Cuomo, J.L. McGaugh, G. Schelling, P. Campolongo, Endogenous cannabinoid release within prefrontal-limbic pathways affects memory consolidation of emotional training, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 18333–18338.
[88] G.M.S. Yip, Z.-W. Chen, C.J. Edge, E.H. Smith, R. Dickinson, E. Hohenester, R.R. Townsend, K. Fuchs, W. Sieghart, A.S. Evers, N.P. Franks, A propofol binding site on mammalian GABAA receptors identified by photolabeling, Nat. Chem. Biol. 9 (2013) 715–720.
[89] S. Patel, E.R. Wohlfeil, D.J. Rademacher, E.J. Carrier, L.J. Perry, A. Kundu, J.R. Falck, K. Nithipatikom, W.B. Campbell, C.J. Hillard, The general anesthetic propofol increases brain N-arachidonylethanolamine (anandamide) content and inhibits fatty acid amide hydrolase, Br. J. Pharmacol. 139 (2003) 1005–1013.
[90] D. Hauer, P. Ratano, M. Morena, S. Scaccianoce, I. Briegel, M. Palmery, V. Cuomo, B. Roozendaal, G. Schelling, P. Campolongo, Propofol enhances memory formation via an interaction with the endocannabinoid system, Anesthesiology 114 (2011) 1380–1388.
[91] L. de Oliveira Alvares, B.P. Genro, F. Diehl, V.A. Molina, J.A. Quillfeldt, Opposite action of hippocampal CB1 receptors in memory reconsolidation and extinction, Neuroscience 154 (2008) 1648–1655.
[92] C. Bucherelli, E. Baldi, C. Mariottini, M.B. Passani, P. Blandina, Aversive memory reactivation engages in the amygdala only some neurotransmitters involved in consolidation, Learn. Mem. 13 (2006) 426–430.
[93] S. Yamamoto, S. Morinobu, S. Takei, M. Fuchikami, A. Matsuki, S. Yamawaki, I. Liberzon, Single prolonged stress: toward an animal model of post traumatic stress disorder, Depress. Anxiety 26 (2009) 1110–1117.
[94] E. Ganon-Elazar, I. Akirav, Cannabinoids prevent the development of behavioral and endocrine alterations in a rat model of intense stress, Neuropsychopharmacology 37 (2012) 456–466.
[95] E. Ganon-Elazar, I. Akirav, Cannabinoids and traumatic stress modulation of contextual fear extinction and GR expression in the amygdala-hippocampal-prefrontal circuit, Psychoneuroendocrinology 38 (2013) 1675–1687.
[96] N. Korem, I. Akirav, Cannabinoids prevent the effects of a footshock followed by situational reminders on emotional processing, Neuropsychopharmacology 39 (2014) 2709–2722.
[97] T.A. Mayer, M.A. Matar, Z. Kaplan, J. Zohar, H. Cohen, Blunting of the HPA-axis underlies the lack of preventive efficacy of early post-stressor single-dose Delta-9-tetrahydrocannabinol (THC), Pharmacol. Biochem. Behav. 122 (2014) 307–318.
[98] M. Badia-Castelló, J. Trujillano-Cabello, L. Serviá-Goixart, J. March-Llanes, A. Rodrguez-Pozo, [Recall and memory after intensive care unit stay. Development of post traumatic stress disorder], Med. Clin. (Barc.) 126 (2006) 561–566.
[99] M. Usuki, Y. Matsuoka, D. Nishi, N. Yonemoto, K. Matsumura, Y. Otomo, Y. Kim, S. Kanba, Potential impact of propofol immediately after motor vehicle accident on later symptoms of post traumatic stress disorder at 6-month follow up: a retrospective cohort study, Crit. Care 16 (2012) R196.
[100] H.C. Hemmings Jr., K. Mackie, The rivers of Lethe and Mnemosyne converge: propofol and memory consolidation, Anesthesiology 114 (2011) 1277–1279.
[101] T. Agren, Human reconsolidation: a reactivation and update, Brain Res. Bull. 105 (2014) 70–82.
[102] L.M. Soravia, M. Heinrichs, A. Aerni, C. Maroni, G. Schelling, U. Ehlert, B. Roozendaal, D.J.-F. de Quervain, Glucocorticoids reduce phobic fear in humans, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 5585–5590.
[103] K. Mishima, N. Egashira, N. Hirosawa, M. Fujii, Y. Matsumoto, K. Iwasaki, M. Fujiwara, Characteristics of learning and memory impairment induced by delta9-tetrahydrocannabinol in rats, Jpn. J. Pharmacol. 87 (2001) 297–308.
[104] F. Niyuhire, S.A. Varvel, B.R. Martin, A.H. Lichtman, Exposure to marijuana smoke impairs memory retrieval in mice, J. Pharmacol. Exp. Ther. 322 (2007) 1067–1075.

[105] I. Bialuk, K. Dobosz, B. Potrzebowski, M.M. Winnicka, CP55,940 attenuates spatial memory retrieval in mice, Pharmacol. Rep. 66 (2014) 931–936.
[106] M. Morena, V. De Castro, J.M. Gray, M. Palmery, V. Trezza, B. Roozendaal, M.N. Hill, P. Campolongo, Training-associated emotional arousal shapes endocannabinoid modulation of spatial memory retrieval in rats, J. Neurosci. 35 (2015) 13962–13974.
[107] L.E. Wise, A.J. Thorpe, A.H. Lichtman, Hippocampal CB(1) receptors mediate the memory impairing effects of Delta(9)-tetrahydrocannabinol, Neuropsychopharmacology 34 (2009) 2072–2080.
[108] N. Wegener, S. Kuhnert, A. Thüns, R. Roese, M. Koch, Effects of acute systemic and intra-cerebral stimulation of cannabinoid receptors on sensorimotor gating, locomotion and spatial memory in rats, Psychopharmacology (Berl) 198 (2008) 375–385.
[109] P. Atsak, D. Hauer, P. Campolongo, G. Schelling, J.L. McGaugh, B. Roozendaal, Glucocorticoids interact with the hippocampal endocannabinoid system in impairing retrieval of contextual fear memory, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 3504–3509.
[110] A. Segev, I. Akirav, Differential effects of cannabinoid receptor agonist on social discrimination and contextual fear in amygdala and hippocampus, Learn. Mem. 18 (2011) 254–259.
[111] M.-R. Zarrindast, K. Kangarlu-Haghighi, A. Khalilzadeh, S. Fazli-Tabaei, Influence of intracerebroventricular administration of cannabinergic drugs on morphine state-dependent memory in the step-down passive avoidance test, Behav. Pharmacol. 17 (2006) 231–237.
[112] M. Piri, M.-R. Zarrindast, Modulation of WIN55,212-2 state-dependent memory by $2-adrenergic receptors of the dorsal hippocampus, Arch. Iran. Med. 14 (2011) 389–395.
[113] A. Galanopoulos, A. Polissidis, G. Georgiadou, Z. Papadopoulou-Daifoti, G.G. Nomikos, N. Pitsikas, K. Antoniou, WIN55,212-2 impairs non-associative recognition and spatial memory in rats via CB1 receptor stimulation, Pharmacol. Biochem. Behav. 124 (2014) 58–66.
[114] M. Ranganathan, D.C. D'Souza, The acute effects of cannabinoids on memory in humans: a review, Psychopharmacology (Berl) 188 (2006) 425–444.
[115] L.L. Miller, T.L. Cornett, D.R. Brightwell, D.J. McFarland, W.G. Drew, A. Wikler, Marijuana: effects on storage and retrieval of prose material, Psychopharmacology (Berl) 51 (1977) 311–316.
[116] C.F. Darley, J.R. Tinklenberg, W.T. Roth, S. Vernon, B.S. Kopell, Marijuana effects on long-term memory assessment and retrieval, Psychopharmacology (Berl) 52 (1977) 239–241.
[117] R.I. Block, J.R. Wittenborn, Marijuana effects on semantic memory: verification of common and uncommon category members, Psychol. Rep. 55 (1984) 503–512.
[118] R.I. Block, J.R. Wittenborn, Marijuana effects on associative processes, Psychopharmacology (Berl) 85 (1985) 426–430.
[119] H.V. Curran, C. Brignell, S. Fletcher, P. Middleton, J. Henry, Cognitive and subjective dose-response effects of acute oral Delta 9-tetrahydrocannabinol (THC) in infrequent cannabis users, Psychopharmacology (Berl) 164 (2002) 61–70.
[120] S.G. Hofmann, Cognitive processes during fear acquisition and extinction in animals and humans: implications for exposure therapy of anxiety disorders, Clin. Psychol. Rev. 28 (2008) 199–210.
[121] J.S. Abramowitz, The practice of exposure therapy: relevance of cognitive-behavioral theory and extinction theory, Behav. Ther. 44 (2013) 548–558.
[122] F.G. Morrison, K.J. Ressler, From the neurobiology of extinction to improved clinical treatments, Depress. Anxiety 31 (2014) 279–290.
[123] S.G. Hofmann, Enhancing exposure-based therapy from a translational research perspective, Behav. Res. Ther. 45 (2007) 1987–2001.
[124] D.C. Choi, B.O. Rothbaum, M. Gerardi, K.J. Ressler, Pharmacological enhancement of behavioral therapy: focus on post traumatic stress disorder, Curr. Top. Behav. Neurosci. 2 (2010) 279–299.
[125] J.C. Myskiw, I. Izquierdo, C.R.G. Furini, Modulation of the extinction of fear learning, Brain Res. Bull. 105 (2014) 61–69.
[126] M.E. Bowers, K.J. Ressler, An overview of translationally informed treatments for PTSD: animal models of Pavlovian fear conditioning to human clinical trials, Biol. Psychiatry 78 (2016) E15–27.
[127] F.A. Pamplona, R.D.S. Prediger, P. Pandolfo, R.N. Takahashi, The cannabinoid receptor agonist WIN 55 Takahashi, 212-2 facilitates the extinction of contextual fear memory and spatial memory in rats, Psychopharmacology (Berl) 188 (2006) 641–649.
[128] F.A. Pamplona, R.M. Bitencourt, R.N. Takahashi, Short- and long-term effects of cannabinoids on the extinction of contextual fear memory in rats, Neurobiol. Learn Mem. 90 (2008) 290–293.
[129] R.M. Bitencourt, F.A. Pamplona, R.N. Takahashi, Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats, Eur. Neuropsychopharmacol. 18 (2008) 849–859.
[130] R.M. Bitencourt, F.A. Pamplona, R.N. Takahashi, Corticosteroid-endocannabinoid loop supports decrease of fear-conditioned response in rats, Eur. Neuropsychopharmacol. 24 (2014) 1091–1102.
[131] F.H. Do Monte, R.R. Souza, R.M. Bitencourt, J.A. Kroon, R.N. Takahashi, Infusion of cannabidiol into infralimbic cortex facilitates fear extinction via CB1 receptors, Behav. Brain Res. 250 (2013) 23–27.
[132] H. Abush, I. Akirav, Cannabinoids modulate hippocampal memory and plasticity, Hippocampus 20 (2010) 1126–1138.
[133] J.P. Chhatwal, M. Davis, K.A. Maguschak, K.J. Ressler, Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear, Neuropsychopharmacology 30 (2005) 516–524.
[134] H.-C. Lin, S.-C. Mao, C.-L. Su, P.-W. Gean, The role of prefrontal cortex CB1 receptors in the modulation of fear memory, Cereb. Cortex 19 (2009) 165–175.
[135] D. Laricchiuta, D. Centonze, L. Petrosini, Effects of endocannabinoid and endovanilloid systems on aversive memory extinction, Behav. Brain Res. 256 (2013) 101–107.
[136] M.E. Bowers, K.J. Ressler, Interaction between the cholecystokinin and endogenous cannabinoid systems in cued fear expression and extinction retention, Neuropsychopharmacology 40 (2015) 688–700.
[137] O. Gunduz-Cinar, K.P. MacPherson, R. Cinar, J. Gamble-George, K. Sugden, B. Williams, G. Godlewski, T.S. Ramikie, A.X. Gorka, S.O. Alapafuja, S.P. Nikas, A. Makriyannis, R. Poulton, S. Patel, A.R. Hariri, A. Caspi, T.E. Moffitt, G. Kunos, A. Holmes, Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity, Mol. Psychiatry 18 (2013) 813–823.
[138] S.A. Varvel, L.E. Wise, F. Niyuhire, B.F. Cravatt, A.H. Lichtman, Inhibition of fatty-acid amide hydrolase accelerates acquisition and extinction rates in a spatial memory task, Neuropsychopharmacology 32 (2007) 1032–1041.
[139] G. Marsicano, C.T. Wotjak, S.C. Azad, T. Bisogno, G. Rammes, M.G. Cascio, H. Hermann, J. Tang, C. Hofmann, W. Zieglgänsberger, V. Di Marzo, B. Lutz, The endogenous cannabinoid system controls extinction of aversive memories, Nature 418 (2002) 530–534.
[140] W. Plendl, C.T. Wotjak, Dissociation of within- and between-session extinction of conditioned fear, J. Neurosci. 30 (2010) 4990–4998.
[141] S. Dubreucq, I. Matias, P. Cardinal, M. Häring, B. Lutz, G. Marsicano, F. Chaouloff, Genetic dissection of the role of cannabinoid type-1 receptors in the emotional consequences of repeated social stress in mice, Neuropsychopharmacology 37 (2012) 1885–1900.
[142] C.L. Pickens, F.R. Theberge, Blockade of CB1 receptors prevents retention of extinction but does not increase low preincubated conditioned fear in the fear incubation procedure, Behav. Pharmacol. 25 (2014) 23–31.
[143] A. Suzuki, S.A. Josselyn, P.W. Frankland, S. Masushige, A.J. Silva, S. Kida, Memory reconsolidation and extinction have distinct temporal and biochemical signatures, J. Neurosci. 24 (2004) 4787–4795.
[144] C.G. Reich, M.H. Mohammadi, B.E. Alger, Endocannabinoid modulation of fear responses: learning and state-dependent performance effects, J. Psychopharmacol. 22 (2008) 769–777.
[145] J.P. Chhatwal, A.R. Gutman, K.A. Maguschak, M.E. Bowser, Y. Yang, M. Davis, K.J. Ressler, Functional interactions between endocannabinoid and CCK neurotransmitter systems may be critical for extinction learning, Neuropsychopharmacology 34 (2009) 509–521.
[146] F. Niyuhire, S.A. Varvel, A.J. Thorpe, R.J. Stokes, J.L. Wiley, A.H. Lichtman, The disruptive effects of the CB1 receptor antagonist rimonabant on extinction learning in mice are task-specific, Psychopharmacology (Berl) 191 (2007) 223–231.
[147] E. Ganon-Elazar, I. Akirav, Cannabinoid receptor activation in the basolateral amygdala blocks the effects of stress on the conditioning and extinction of inhibitory avoidance, J. Neurosci. 29 (2009) 11078–11088.
[148] S.A. Varvel, E.A. Anum, A.H. Lichtman, Disruption of CB(1) receptor signaling impairs extinction of spatial memory in mice, Psychopharmacology (Berl) 179 (2005) 863–872.
[149] C.A. Rabinak, M. Angstadt, C.S. Sripada, J.L. Abelson, I. Liberzon, M.R. Milad, K.L. Phan, Cannabinoid facilitation of fear extinction memory recall in humans, Neuropharmacology 64 (2013) 396–402.
[150] C.A. Rabinak, K.L. Phan, Cannabinoid modulation of fear extinction brain circuits: a novel target to advance anxiety treatment, Curr. Pharm. Des. 20 (2014) 2212–2217.
[151] R.K. Das, S.K. Kamboj, M. Ramadas, K. Yogan, V. Gupta, E. Redman, H.V. Curran, C.J.A. Morgan, Cannabidiol enhances consolidation of explicit fear extinction in humans, Psychopharmacology (Berl) 226 (2013) 781–792.
[152] F. Klumpers, D. Denys, J.L. Kenemans, C. Grillon, J. van der Aart, J.M.P. Baas, Testing the effects of $9-THC and D-cycloserine on extinction of conditioned fear in humans, J. Psychopharmacol. 26 (2012) 471–478.
[153] I. Heitland, F. Klumpers, R.S. Oosting, D.J.J. Evers, J. Leon Kenemans, J.M.P. Baas, Failure to extinguish fear and genetic variability in the human cannabinoid receptor 1, Transl. Psychiatry 2 (2012) e162.
[154] T. Passie, H.M. Emrich, M. Karst, S.D. Brandt, J.H. Halpern, Mitigation of post-traumatic stress symptoms by Cannabis resin: a review of the clinical and neurobiological evidence, Drug Test Anal. 4 (2012) 649–659.
[155] G.A. Fraser, The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in post traumatic stress disorder (PTSD), CNS Neurosci. Ther. 15 (2009) 84–88.
[156] C. Cameron, D. Watson, J. Robinson, Use of a synthetic cannabinoid in a correctional population for post traumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: a retrospective evaluation, J. Clin. Psychopharmacol. 34 (2014) 559–564.
[157] G.R. Greer, C.S. Grob, A.L. Halberstadt, PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program, J. Psychoact. Drugs 46 (2014) 73–77.
[158] M.O. Bonn-Miller, K.A. Babson, R. Vandrey, Using cannabis to help you sleep: heightened frequency of medical cannabis use among those with PTSD, Drug Alcohol Depend. 136 (2014) 162–165.

[159] K. Betthauser, J. Pilz, L.E. Vollmer, Use and effects of cannabinoids in military veterans with post traumatic stress disorder, Am. J. Health. Syst. Pharm. 72 (2015) 1279–1284.
[160] R. Jetly, A. Heber, G. Fraser, D. Boisvert, The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study, Psychoneuroendocrinology 51 (2015) 585–588.
[161] S. Diekelmann, I. Wilhelm, J. Born, The whats and whens of sleep-dependent memory consolidation, Sleep Med. Rev. 13 (2009) 309–321.
[162] N. Landmann, M. Kuhn, H. Piosczyk, B. Feige, C. Baglioni, K. Spiegelhalder, L. Frase, D. Riemann, A. Sterr, C. Nissen, The reorganization of memory during sleep, Sleep Med. Rev. 18 (2014) 531–541.
[163] N. Landmann, M. Kuhn, J.-G. Maier, K. Spiegelhalder, C. Baglioni, L. Frase, D. Riemann, A. Sterr, C. Nissen, REM sleep and memory reorganization: potential relevance for psychiatry and psychotherapy, Neurobiol. Learn Mem. 122 (2015) 28–40.