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To  
Patients of Ukraine Foundation  
by e-mail

Dear Sir or Madam,

I am sending you a detailed analysis of the effectiveness of cannabis and cannabinoids in post-traumatic stress disorder. I understand that this plays a big role in these difficult times that the population of Ukraine is going through.

I have many patients in my practice that I treat very successfully with cannabis for post-traumatic stress disorder. Sleep is improved, nightmares are reduced or disappear completely. Cannabis is perceived by these patients as a great blessing in overcoming their problems.

Yours sincerely

A handwritten signature in black ink that reads 'Franjo Grotenhermen'. The signature is written in a cursive, flowing style.

Dr. Franjo Grotenhermen  
Exekutive Director

# **Cannabis and PTSD: the current scientific knowledge**

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## **Basic research**

The cannabis active ingredient THC binds to the cannabinoid-1 receptor, which is found primarily in the central nervous system. Together with the body's own cannabinoids, the so-called endocannabinoids, and enzymes for the formation and degradation of endocannabinoids, cannabinoid receptors form the endocannabinoid system. This is found in all organs of the human body and has multiple functions in the organism, including in particular the regulation of stress and thus better stress management. The best researched endocannabinoids are anandamide (arachidonoyl ethanolamide) and 2-AG (arachidonoylglycerol). However, about 200 endocannabinoid-like substances have been detected in the human organism so far.

As early as 2003, a research group led by Professor Zieglgänsberger at the Max Planck Institute of Psychiatry in Munich was able to demonstrate, according to a highly regarded article in the journal *Nature*, that the endogenous cannabinoid system plays a central role in the erasure of unpleasant memories (Marsiano et al. 2003).

Transgenic mice lacking brain cannabinoid receptors (CB1) and mice treated with a CB1 receptor antagonist showed significantly impaired fear extinction in experiments. The animals, which had been conditioned to associate a musical tone with an electrical shock, produced a fear response and continued to respond in this manner when the tone was no longer followed by a shock. Normal mice quickly stopped responding to the tone when it was no longer associated with a shock, but the treated mice took much longer to forget the fear. The team found that the amygdala, a region of the brain important for storing memory and fear, was flooded with endocannabinoids when the mice gradually forgot the learned response to the shock.

Pankaj Sah, a noted neuroscientist at the Australian National University in Canberra, Australia, said in an accompanying commentary that the recent findings could explain why

some people with psychiatric problems would try to find relief with marijuana. He suggested that people with certain psychiatric problems might self-medicate in an attempt to help their brains erase some painful and traumatic memories and thoughts.

Recent research shows that the endocannabinoid system is disrupted in people with post-traumatic stress disorder.

For example, a study at the Department of Kinesiology at the University of Wisconsin-Madison (USA) involving 20 patients with PTSD and healthy controls demonstrated that blood levels of the endocannabinoids anandamide, 2-AG, and oleylethanolamide were reduced after physical exertion and psychosocial stress (Crombie et al. 2019). Only healthy controls showed a significant increase in 2-AG levels after physical exertion and psychosocial stress. The researchers wrote that these data provide preliminary evidence that the endocannabinoid system "is hypoactive in PTSD after exposure to physical and psychosocial stressors." This means that individuals with PTSD do not cope as well with stress.

A study of 85 adult women with PTSD at the University of Texas at Austin, Department of Psychiatry and Behavioral Sciences (USA) found that a genetic variation in the gene encoding the enzyme FAAH (fatty acid amide hydrolase), which is responsible for the degradation of anandamide, "influences physiological, cognitive, and neural signatures of fear learning in women with PTSD" (Crombie et al. 2021).

According to a study at the University of California at Irvine (USA), raising endocannabinoid levels by reducing their degradation had anxiety-relieving effects in stressed rats (Danandeh et al. 2018). The authors wrote that "anandamide-mediated signaling to CB1 receptors has an important regulatory function in the response to stress," and that inhibiting endocannabinoid degradation "may offer a potential therapeutic strategy against post-traumatic stress disorder."

It is well known that exercise leads to increased release of endocannabinoids. In a study of 35 women who completed moderate-intensity aerobic exercise, blood levels of the endocannabinoid anandamide increased and anxiety decreased (Crombie et al. 2021). The study was conducted by researchers from several institutions in the United States. Participants completed a three-day anxiety acquisition (day 1), extinction (day 2), and extinction recall (day 3) protocol in which they were randomized to either moderate-intensity aerobic exercise or a low-intensity control condition after extinction training (day 2). It was found that circulating concentrations of anandamide and brain-derived neurotrophic factor (BDNF) mediated the association between moderate-intensity aerobic training and lower threat expectancy ratings after exercise resumption. The authors concluded that exercise-induced increases in these two substances "appear to play a role in the consolidation of fear extinction learning, leading to reduced threat expectancy in women with PTSD after reinstatement."

## **Relationship between cannabis use and PTSD**

According to a March 22, 2016, story on Military.com, a U.S. website, an increasing number of U.S. states are considering whether to legalize cannabis for the treatment of post-traumatic stress disorder. But for many war veterans, the discussion is already over, it said. They are

using cannabis at an increasing rate, even though it remains illegal in most states and is not approved by the Department of Veterans Affairs because large studies have yet to show whether it is effective against PTSD. While research is conflicting and limited, many former members of the military say cannabis helps them manage their anxiety, insomnia and nightmares. Some say prescribed medications were not effective or made them feel like a zombie. "I moved from a state of anxious disarray to numbing myself with pills they gave me," explained Mike White, a 39-year-old former Marine who lives in Philadelphia, where cannabis is illegal. "Cannabis helped me get out of the hole I was in. I started talking to people and overcame my social anxiety." Others, however, get little benefit from the drug.

According to analysis of a large database of approximately 46,000 U.S. war veterans by staff at the VA South Central Mental Illness Research, Education and Clinical Center (MIRECC) in Houston, USA, there was an association between post-traumatic stress disorder and cannabis use disorder (Bryan et al. 2017). Veterans with cannabis use disorder also had higher levels of depression, panic disorder, alcohol use, insomnia, and opioid use disorder.

## **Clinical studies**

Some clinical studies show that the use of THC or cannabis provides significant relief for at least some patients with post-traumatic stress disorder. A selection of the studies is briefly presented here, without claiming to be exhaustive.

THC causes significant improvement in PTSD. This is the result of an open study with 10 patients by researchers from the Hebrew University in Jerusalem (Israel) (Roitmann et al 2014). The study assessed the tolerability and safety of oral THC in chronic PTSD. 10 patients on stable medication received 5 mg of oral THC twice daily as an adjunctive treatment. There were mild side effects in 3 patients, none of which led to treatment discontinuation. Treatment caused statistically significant improvement in overall symptom severity, sleep quality, frequency of nightmares, and symptoms of increased nervous arousal.

According to a study of 150 patients suffering from PTSD, cannabis use was associated with a reduction in symptoms after one year compared to non-users (Bonn-Miller et al. 2020). The study was conducted by researchers at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, USA, and published online in *Cannabis and Cannabinoid Research*. This prospective study examined PTSD symptoms and functioning in two samples of participants diagnosed with PTSD: (1) individuals with PTSD who used cannabis from a dispensary and (2) individuals with PTSD who did not use cannabis. Over the course of one year, cannabis users reported greater decreases in PTSD symptom severity compared to controls. Participants who used cannabis were 2.6 times more likely to no longer meet DSM 5 illness criteria for PTSD at the end of the study observation period than participants who did not use cannabis. The authors concluded that their "study provides evidence that the types of cannabis available at recreational and medical cannabis dispensaries may hold promise as an alternative treatment for PTSD."

According to a placebo-controlled study with 71 participants, THC decreased amygdala reactivity (Rabinak et al. 2020). The amygdala is a brain structure that plays an important role

in processing emotional responses such as fear, anxiety, and aggression. The study was conducted by researchers at Wayne State University in Detroit, USA, and published in the journal *Psychopharmacology*. 3 groups of adults were formed: (1) 25 non-trauma-exposed healthy controls (2) 27 trauma-exposed adults without PTSD and (3) 19 trauma-exposed adults with PTSD. They received either THC or placebo and completed a well-established threat processing paradigm during a functional magnetic resonance imaging examination. In adults with PTSD, THC lowered threat-related amygdala reactivity and showed other functional signs of threat resistance in brain activity. The authors concluded that these "preliminary data suggest that THC modulates threat-related processing in trauma-exposed individuals with PTSD, which may prove beneficial as a pharmacological approach to treating stress- and trauma-related psychopathology."

According to 404 medical cannabis users from the United States who self-identified as having post-traumatic stress disorder, cannabis effectively reduced symptoms by more than 50% (LaFrance et al. 2020). The data came from a medical cannabis app that patients use to track changes in symptoms as a function of different cannabis strains and doses over time. Participants used the app 11,797 times over a 31-month period to assess symptoms (intrusive thoughts, flashbacks, irritability, and/or anxiety) immediately before and after cannabis inhalation. All symptoms were reduced by more than 50% immediately after cannabis inhalation. Over time, greater reductions in intrusive thoughts and irritability were predicted, with later cannabis use sessions predicting greater symptom relief than earlier sessions. Higher doses of cannabis predicted greater decreases in intrusions and anxiety, not previously reported. Christian baseline severity of all symptoms remained constant over time.

Researchers from the University of British Columbia in Vancouver and other Canadian universities used data from the 2012 Canadian Community Health Survey-Mental Health to examine the association between PTSD posttraumatic stress disorder and some health outcomes (Lake et al. 2020). Among 24,089 eligible respondents, 420 reported a current clinical diagnosis of PTSD. Overall, 28% of those with PTSD reported past-year cannabis use. Among nonusers, PTSD was significantly associated with recent marked depressive episodes and suicidal ideation. Among cannabis users, PTSD was not significantly associated with these outcomes. The authors wrote that this "study provides preliminary epidemiologic evidence that cannabis use may help reduce the association between posttraumatic stress disorder and major depressive and suicidal states."

Bonn-Miller and colleagues at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, USA, who had already conducted a study of 150 people cited above, published the first placebo-controlled study of 80 military veterans suffering from PTSD in March 2021 (Bonn-Miller et al. 2021). Given the lack of efficacy of existing pharmacologic treatments, they wrote, "There is an urgent need for the development of new pharmacologic agents for the treatment of posttraumatic stress disorder (PTSD)." They compared the safety and efficacy of three smoked cannabis strains with a placebo cannabis cigarette. The 3 active strains contained (1) bohren THC content (about 12% THC) and hardly any CBD, (2) high CBD content (about 11% CBD) and hardly any THC, or about equal levels of THC and CBD (about 8% THC and about 8% CBD). The researchers used a cross-over design in which participants, randomly divided into 4 groups of 20, received either one of the active cannabis treatments or a placebo for 3 weeks in the 1st phase and, after a 2-week break, received one of the 3 other active treatments for 3 weeks in the 2nd phase. No differences

were found between the active cannabis treatments and placebo at the end of phase 1. Their conclusion states, "All treatment groups, including placebo, showed good tolerability and significant improvements in PTSD symptoms during the 3-week treatment, but no active treatment was statistically superior to placebo in this short, preliminary study." For example, the THC-rich cannabis resulted in a slightly greater 15.2-point improvement in PTSD on a standardized scale and the placebo resulted in a 13.1-point improvement. The authors noted that these improvements were "much greater than effect sizes for symptom change reported for other psychopharmacological studies for PTSD." Or, to put it another way, the placebo (dummy drug) used in this study worked better against symptoms of PTSD than standard PTSD medications in other studies.

The authors cited various reasons for the lack of differences between placebo and cannabis, including, for example, the fact that all participants had previous cannabis experience and, because of the experience, the expectation of the efficacy of the therapy may have been strongly influenced. This may have had an impact on the unusually strong placebo effect. In addition, it could be that the cannabis dose used was too low to achieve a sufficiently therapeutic effect.

Thus, in conclusion, the authors wrote, "The fact that the treatment groups did not differ from the placebo groups is probably due to the higher than average treatment response in the placebo condition and to the shorter than average treatment duration. Studies with higher efficacy trying to mitigate the effect of the pronounced placebo seem warranted."

## **Conclusion**

The current scientific data on the efficacy of cannabis-based medications and PTSD shows the following:

1. the body's endocannabinoid system of specific binding sites (cannabinoid receptors) and endogenous cannabinoids (endocannabinoids) plays an important role in forgetting and erasing unpleasant memories.
2. the endocannabinoid system is hypoactive in PTSD. This decreased activity results in individuals with PTSD being less stress resistant.
3. raising endocannabinoid levels had an anxiety-relieving effect in stressed rats in animal experiments.
4. people with PTSD are more likely than healthy people to use cannabis. Most of the cannabis users with PTSD report that cannabis has a positive effect on their symptoms. However, some also report negative effects. This differential effect is also known from most other medications.
5. initial studies show that therapy with cannabis can alleviate symptoms of PTSD, at least in some cases.
6. the first placebo-controlled study shows that there is a pronounced kind of placebo effect in

the treatment of PTSD when the study is very short, because in this study even treatment with a placebo showed a stronger efficacy than was the case with other drugs for PTSD in previous studies. By no means did study show that cannabis is not effective for PTSD.

The current scientific evidence base is fully sufficient to meet the requirements of § 31 (6) SGB V for a "not entirely remote prospect" of noticeable relief of PTSD symptoms through cannabis-based medications. This applies both to explanatory models of their efficacy from basic research and to the clinical studies conducted to date.

As far as I know, THC is the first pharmacological substance that can causally influence the symptomatology of PTSD by helping patients to largely erase unpleasant experiences from their minds through effects on specific brain regions, so that nightmares and flashbacks diminish. So far, no other drug has been able to do this.

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