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Cannabis and cannabinoids in the treatment of post-traumatic stress disorder: a literature review and analysis of the content of websites of Polish clinics specializing in medical marijuana treatment[1]

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Summary

The latest scientific literature shows that the incidence of post-traumatic stress disorder (PTSD) in Poland has increased significantly. The rise in the number of people affected by PTSD translates into a growing demand for specialist support and treatment of this disease entity. Polish clinics specializing in therapy with the so-called medical marijuana (MM) describe it as a raw material with potential for the treatment of PTSD and an alternative to conventional treatment methods. The paper presents the basic medicines used in PTSD treatment. The authors carried out a review of the literature evaluating the efficacy and safety of cannabis and cannabinoids in the treatment of PTSD. In addition, the article refers to papers highlighting the negative mental health consequences of marijuana use, with particular emphasis on its impact on the course of PTSD. Previously published studies relating the attitudes of psychiatrists towards the use of MM are also discussed. The manner of presenting the potential of Cannabis sp. and their products in the treatment of PTSD on the websites of Polish medical marijuana clinics was analyzed, discussed and critically evaluated. Currently, there is no sufficient solid evidence to recommend MM or cannabinoids to treat PTSD, but people struggling with this disorder reach for Cannabis sp. products for their anxiolytic, sedative, hypnotic, and antipsychotic effects. In anticipation of new data from randomized, large-scale,

[1] Polish law does not contain a definition of medical marijuana. However, the Act on Counteracting Drug Addiction distinguishes between the following concepts: cannabis, fiber hemp, and non-fiber hemp. Since the term "medical marijuana" is a MeSH indexing term (defined as "a product of the CANNABIS plant, CANNABINOIDS, or synthetic derivatives thereof, used in the treatment of a wide range of clinical symptoms"), it is therefore used in the rest of the paper for the sake of simplicity.

controlled trials, it is advisable to develop available sources of information and appropriate oversight to counteract harmful marketing of medical marijuana.

Key words: post-traumatic stress disorder, medical marijuana, cannabis, advertising

Introduction

The concept of post-traumatic stress disorder (PTSD) appeared in medical terminology in 1980, although it had already been observed and described much earlier, during World War I or the Civil War. Post-traumatic stress disorder is a common and debilitating mental disorder triggered by violent and stressful events such as accidents, natural disasters, the sudden death of a loved one, terrorist attacks, or wars [1]. This disorder significantly impairs personal, family, social, educational, and professional life [2].

Most of the people in the world (up to 90%) experience traumatic events, but only some of them (5–10%) develop PTSD [3, 4]. In a recent paper, Rzeszutek et al. [5] indicated that PTSD may affect as many as 18.8% of Polish citizens. It is believed that the number of people struggling with stress disorders after experiencing trauma will continue to rise, which may be linked to the effects of both the COVID-19 pandemic and the war in Ukraine. This situation may become a challenge for health care systems and result in an increased demand for specialized support and treatment of PTSD [6].

Pharmacotherapy for PTSD

Most studies on PTSD treatment indicate that psychological therapies are more effective than pharmacological treatment [7, 8]. Moreover, psychological interventions have a lower dropout rate [9].

According to the 2018 guidelines of the National Institute of Health and Care Excellence (NICE) in the United Kingdom, psychotherapeutic interventions, not pharmacotherapy, should be the option of first choice in the treatment of post-traumatic disorders. Psychotherapy-based treatment may be departed from in case of a direct threat to the patient's life, lack of consent to psychotherapy, its unavailability, or a threat of suicide. In clinical practice, pharmacological treatment (especially benzodiazepines) is often initiated shortly after exposure to trauma, which is why the guidelines underline that pharmacological treatment should not be used to prevent the development of PTSD [10].

Also, the latest VA/DoD (Department of Defense and U.S. Army Department of Veterans Affairs) guidelines published in 2023 indicate that while psychotherapy and pharmacotherapy are effective in treating PTSD, when both methods are available, it

is recommended to opt for the former. According to these guidelines, pharmacotherapy of PTSD should consider the use of paroxetine, sertraline, or venlafaxine. Treatment with these medicinal products should be initiated at the recommended starting dose which is to be increased according to clinical response and tolerance. The duration of the trial should be 8–12 weeks. However, there is insufficient evidence for or against the efficacy of amitriptyline, bupropion, buspirone, citalopram, duloxetine, escitalopram, eszopiclone, fluoxetine, mirtazapine, lamotrigine, olanzapine, pregabalin, rivastigmine, topiramate, or quetiapine in the treatment of PTSD. The Working Group does not recommend the use of sodium divalproate, ketamine, risperidone, tiagabine, or vortioxetine, and strongly advocates against the use of benzodiazepines to treat the disorder [11].

Currently, there is no uniform approach to the pharmacotherapy of PTSD. Suggestions of medicines used in the treatment of the disorder are presented in Table 1. SSRIs (selective serotonin reuptake inhibitors) and one representative of SNRIs (serotonin and norepinephrine reuptake inhibitors), namely, venlafaxine, are considered first-line drugs. The FDA (U.S. Food and Drug Administration) has approved only two SSRIs for the treatment of PTSD: paroxetine and sertraline. Antidepressants, however, cause numerous side effects, including intensification of suicidal ideation. The use of benzodiazepines should be limited, as there are reports suggesting that they may even increase the risk of PTSD [12].

Table 1. **Preferred medications in PTSD therapy. Compiled on the basis of [13], including additional data from sources: [10, 11, 14]**

Symptoms	Drug group	Drug	Dosage (given in milligrams/day; split dosing not considered)	Comments
Intrusion (criterion A in DSM-5)	Benzodiazepines	Alprazolam	0.5-6 [according to 13] Standard release: 0.75-1.5; elderly or debilitated: 0.5–0.75 SR: 1; elderly or debilitated: 0.5-1 If necessary, the dose may be increased to max. 4 mg/d [according to 11]	Only in the initial stage of treatment. The treatment time should be as short as possible, max. 2–4 weeks, as it can lead to addiction! Risk of depression, insomnia, withdrawal syndrome, and even paradoxical anxiety. Treatment not recommended by VA/DoD (or NICE – for PTSD prevention).
	Beta-blockers	Propranolol	40–160	Blood pressure and heart rate should be monitored (risk of bradycardia). It can cause sleep disorders and nightmares. Risk of bronchospasm in patients with asthma.

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Intrusion (criterion A in DSM-5)	SSRI	Fluoxetine	20–60	Common adverse side effects of SSRIs and SNRIs: sleep disorders (insomnia, somnolence, nightmares), gastrointestinal dysfunction (nausea, diarrhea, vomiting, constipation), headache and dizziness, anxiety/fear, sexual dysfunction, irritability. Hyponatremia or SIADH may occur; the risk is higher in elderly patients. Serotonin syndrome may occur, especially when drugs with serotonergic effects are used concomitantly. Increased risk of suicidal behavior in patients under 25. Only sertraline and paroxetine have been approved by the FDA for the treatment of PTSD. VA/DoD recommends the use of sertraline, paroxetine, and venlafaxine in the pharmacotherapy of PTSD. Venlafaxine may raise blood pressure; caution is advised in patients with hypertension.
		Paroxetine	20–50	
		Sertraline	50-200	
		Citalopram	20-60	
		Fluvoxamine	50-300	
	SNRI	Venlafaxine	SR: 75-300	
	TCA	Amitriptyline	150-300	Cholinolytic side effects. Very common adverse side effects: orthostatic hypotension, aggression, headache, dizziness, muscle tremors, somnolence, speech disorders, gastrointestinal disorders, cardiac arrhythmias, dry mouth, excessive sweating. VA/DoD highlights the lack of sufficient evidence for or against the efficacy of amitriptyline in the treatment of PTSD.
Intrusion (criterion A in DSM-5)	α2-adrenergic agonists	Clonidine	0.2-0.6	Attempts to use clonidine in PTSD to reduce hyperactivity and increased tension have been unsuccessful. Risk of worsening depression. Common side effects: orthostatic hypotension, nervousness, insomnia, cardiac arrhythmias.
	Second-generation antipsychotics	Risperidone	4-16	Discontinue once symptoms have resolved. Risperidone, olanzapine, or quetiapine are not recommended by VA/DoD in the pharmacotherapy of PTSD. Possibility of extrapyramidal symptoms. Sleep disorders, orthostatic hypotension, dry mouth, increased prolactin, triglycerides, cholesterol, increased appetite, digestive system disorders, and increased blood glucose levels may occur.
		Olanzapine	5-20	
		Quetiapine	50-750	

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Intrusion (criterion A in DSM-5)	Anticonvulsants	Carbamazepine	400–1600	Very common and common adverse side effects: hematopoietic disorders, dizziness, ataxia, somnolence, gastrointestinal dysfunction, visual disturbances, urticaria, allergic dermatitis, fatigue, increased activity and γ-glutamyltransferase, edema, fluid retention, hyponatremia.
		Valproic acid	50-1750	Very common and common adverse side effects: confusion, aggression, agitation, attention disorders, hallucinations, tremor, dizziness, extrapyramidal disorders, convulsions, somnolence, stupor, memory impairment, headache, nystagmus, hearing loss (transient or permanent), gastrointestinal dysfunction, hemorrhage, liver damage, alopecia, nail and nail bed disorders, urinary incontinence, hematopoietic disorders.
Avoidance (criterion B in DSM-5)	SSRI	Fluoxetine	20-60	Common adverse side effects of SSRIs and SNRIs: sleep disorders (insomnia, somnolence, nightmares), gastrointestinal dysfunction (nausea, diarrhea, vomiting, constipation), headache and dizziness, anxiety/fear, sexual dysfunction, irritability. Hyponatremia or SIADH may occur; the risk is higher in elderly patients. Serotonin syndrome may occur, especially when drugs with serotonergic effects are used concomitantly. Increased risk of suicidal behavior in patients under 25. Only sertraline and paroxetine have been approved by the FDA for the treatment of PTSD. VA/DoD recommends the use of sertraline, paroxetine, and venlafaxine in the pharmacotherapy of PTSD. Venlafaxine may raise blood pressure; caution is advised in patients with hypertension.
		Paroxetine	20-50	
		Sertraline	50-200	
		Citalopram	20-60	
		Fluvoxamine	50-300	
	SNRI	Venlafaxine	XR: 75-300	
	TCA	Amitriptyline	150-300	Cholinolytic side effects. Very common adverse side effects: orthostatic hypotension, aggression, headache, dizziness, muscle tremors, somnolence, speech disorders, gastrointestinal disorders, cardiac arrhythmias, dry mouth, excessive sweating.
	SARI	Trazodone	200-400	Do not combine with drugs that increase serotonin levels (increased risk of serotonin syndrome). According to VA/DoD, there is insufficient evidence for or against the effectiveness of the drug in the treatment of PTSD.

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Hyperactivity (criterion E in DSM-5)	SSRI	Paroxetine	20-50	Common adverse side effects of SSRIs: sleep disorders (insomnia, somnolence, nightmares), gastrointestinal dysfunction (nausea, diarrhea, vomiting, constipation), headache and dizziness, anxiety/fear, sexual dysfunction, irritability. Hyponatremia or SIADH may occur; the risk is higher in elderly patients. Serotonin syndrome may occur, especially when medications that affect serotonin levels are used concomitantly. Increased risk of suicidal behavior in patients under 25. Only sertraline and paroxetine have been approved by the FDA for the treatment of PTSD. No beneficial therapeutic effects of fluvoxamine and citalopram have been found.
		Sertraline	50-200	
		Citalopram	20-60	
		Fluvoxamine	50-300	
	Beta-blockers	Propranolol	40-160	Blood pressure and heart rate should be monitored (risk of bradycardia). It can cause sleep disorders and nightmares. Risk of bronchospasm in patients with asthma.
Hyperactivity (criterion E in DSM-5)	Anticonvulsants	Carbamazepine	400-1600	Very common and common adverse side effects: hematopoietic disorders, dizziness, ataxia, somnolence, gastrointestinal dysfunction, visual disturbances, urticaria, allergic dermatitis, fatigue, increased activity and γ-glutamyltransferase, edema, fluid retention, hyponatremia.
		Valproic acid	50-1750	Very common and common adverse side effects: confusion, aggression, agitation, attention disorders, hallucinations, tremor, dizziness, extrapyramidal disorders, convulsions, somnolence, stupor, memory impairment, headache, nystagmus, hearing loss (transient or permanent), gastrointestinal dysfunction, hemorrhage, liver damage, alopecia, nail and nail bed disorders, urinary incontinence, hematopoietic disorders.

DSM – *Diagnostic and Statistical Manual of Mental Disorders* (classification of mental disorders of the American Psychiatric Association); FDA – Food and Drug Administration; NICE – National Institute for Health and Clinical Excellence; PTSD – post-traumatic stress disorder; SARI – serotonin antagonist and reuptake inhibitor; SIADH – syndrome of inappropriate antidiuretic hormone; SNRI – serotonin/norepinephrine reuptake inhibitor; SR – sustained-release; SSRI – selective serotonin reuptake inhibitor; TCA – tricyclic antidepressant; VA/DoD – Department of Veterans Affairs/U.S. Department of Defense; XR – extended release

Cannabis sp. products and cannabinoids as potential agents in the treatment of PTSD

A growing body of evidence suggests the involvement of the endocannabinoid system (eCB) in the etiology and pathophysiology of PTSD [15–19]. Hill et al. [20] indicated that endocannabinoid deficiency may result in increased susceptibility to stress conducive to the development of trauma-related psychopathology.

Studies on animal models have shown that cannabinoids can prevent the impact of stress on emotional function and memory processes, facilitate fear extinction, and provide an anxiolytic effect [16]. They can also influence inflammatory processes in the central nervous system [21]. Moreover, cannabinoids administered shortly after exposure to a traumatic event have been found to prevent the development of a PTSD-like phenotype [16]. Correcting endocannabinoid deficiency in mice with genetic deletion of cannabinoid receptor 1 (CB1), exposed to a traumatizing event, was shown to enable the extinguishing of stress-inducing memories by inhibiting γ-aminobutyric acid pathways in the amygdala [22]. The same mechanism is also believed to explain human responses to cannabinoids [23]. The phytocannabinoids delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) also increased the extinction of aversive memory in laboratory animals [24, 25].

Drugs that increase the activity of the eCB system in the brain can alleviate the effects of traumatic experiences [25]. This may explain the popularity of self-medication with cannabinoid-containing preparations among patients with PTSD [16, 26, 27].

Psychiatrists' attitudes towards the use of MM in the treatment of PTSD

We found three papers on psychiatrists' attitudes toward the use of medical marijuana (MM) and/or cannabinoid-containing drugs to treat a variety of conditions, including PTSD. In 2017, Custodia et al. [28] conducted such a study among 83 psychiatrists from the state of Michigan, USA. The majority of the respondents did not support the use of MM in PTSD treatment. Most of them also pointed to the lack of research and sufficient scientific evidence confirming the legitimacy of the use of MM in the treatment of PTSD. On the other hand, according to the study of Jacobs et al. [29] (2019) conducted among Australian psychiatrists, 57.1% perceived the use of CBD in the treatment of anxiety/PTSD as a therapy with scientific efficacy corroborated by scientific evidence, and 39.5% believed there was evidence supporting the effectiveness of the use of THC (tetrahydrocannabinol) to treat such conditions. In 2021, Orjuela-Rojas et al. [30] conducted a similar study on a group of 150 Colombian psychiatrists, 145 of whom completed the entire survey. 15.9% declared their support for the use of MM in PTSD, while 39.3% did not endorse it. The rest (44.8%) remained neutral. Access to MM and the legal framework for prescribing it varies from country to country, but

conducting such analyses can provide the data needed to develop health policies in different countries. The papers reported the need for further research and education on the use of MM/cannabinoid-containing drugs.

Medical marijuana in the treatment of PTSD according to "medical marijuana clinics" in Poland and around the world

The websites of Polish medical treatment centers specializing in medical marijuana therapy often point to the potential of phytocannabinoids in the treatment of post-traumatic stress disorder and present it as an alternative to conventional treatment methods. In order to verify how many of them mention PTSD as an indication for therapy and to review the evidence they cite to support this indication, between 10 and 24 January 2024, the websites of clinics providing MM therapy were searched for and analyzed. In order to find suitable services, Google search engine was used. The clinics listed on the following websites were selected:

- https://www.canndo.pl/kliniki/
- https://faktykonopne.pl/kliniki-konopne/
- https://hemplo.pl/kliniki-i-przychodnie/

As a result, websites of 42 entities declaring the provision of treatment with the use of cannabis (prescribing a prescription drug containing the so-called medical marijuana) were found. For further analysis, 40 of them were taken into account, as the website of one was under reconstruction and another was excluded due to the closure of operations. Of these, 29 (72.5%) listed cannabis and cannabinoid therapy as an indication for PTSD treatment or mentioned the medicinal properties of medical marijuana in this regard. However, only 5 of the analyzed websites referred to scientific publications confirming this indication (12.5%). Usually, these references were not accurate, there were no bibliographic footnotes, and they were replaced by general descriptions of the study, e.g., "literature analysis presented by a research team from the UK and Italy in 2019," or only the author's name and date of publication were cited, making it difficult or impossible to identify relevant articles. A total of 14 individual papers on the use of medical marijuana in the treatment of PTSD were cited on the reviewed websites. One of the papers could not be identified (it was described as a questionnaire study involving American war veterans, conducted in 2016 by a research group led by Prof. Mechoulam). Statistics on the type of the remaining 13 indicated or selected studies are illustrated in Table 2.

Table 2. **Studies on the medicinal use of cannabis and cannabinoids in the treatment of PTSD, as indicated by Polish medical marijuana clinics**

Type of study	Number of studies, *n* (%)
Review	2 (15.38)
Observational cohort study (prospective and retrospective)	3 (23.08)
Systematic review	2 (15.38)
Basic scientific study; Pilot study	3 (23.08)
Randomized controlled trial (RCT)	2 (15.38)
Qualitative research	1 (7.69)
Case series	1 (7.69)

The studies referred to on the clinics' websites were highly heterogeneous in terms of type, methodology, objectives, study populations, cannabinoids used, and routes of administration.

In 2023, O'Neill et al. [31] published a paper aimed at evaluating the evidence supporting medical marijuana claims posted on clinic websites in Ontario, Canada. They noted that the evidence presented on those websites to support the effectiveness of cannabis in treating various health problems was of poor quality. Despite this, clinics that offer MM therapy "advertise" the remedy by referring to these studies. Moreover, these studies are sometimes presented on the websites of clinics as rigorous and accurate. For example, in a post titled *The Role of Medical Cannabis in Managing PTSD Symptoms*, Aphria, Inc. (currently Tilray Brand, Inc.), the world largest producer of medical marijuana, referred to an imaging study conducted among 25 participants to state that "cannabinoid studies suggest a link between endocannabinoid deficiencies and maladaptive changes in the brain after trauma exposure" [32]. We noticed a similar trend when analyzing the websites of Polish clinics specializing in cannabis therapy. One of them reads: "Medical marijuana patients see a reduction in PTSD symptoms of up to 75%" [33]. This statement was based on data from a study that analyzed psychometric data on PTSD symptoms collected during psychiatric evaluations of eighty patients applying to the Medical Cannabis Treatment Program in the State of New Mexico between 2009 and 2011 [34]. It should be noted, however, that the website in question indicated psychotherapy as the main treatment for PTSD. On another website, we read: "Studies have also shown that THC (alone or in combination with CBD) can reduce or block the brain's ability to consolidate and retain memories of fear" [35]. However, no information is given about the type of study. Meanwhile, these are the conclusions of a preclinical experiment conducted on male rats [36].

As Caputi points out [37], a fundamental principle of modern medical regulations is the need for rigorous justification of health claims before they are disseminated among patients. Health decisions should be based on high-quality scientific evidence. However, marketing research has made it possible for MM companies to circumvent these laws. For example, one of the world's largest MM manufacturers (Aurora), published a blog post citing a cross-sectional survey it funded to reach the following conclusion: "Medical marijuana patients report using CBD for a number of reasons, including to reduce PTSD symptoms, anxiety, and pain" [37].

In summary, the content on the use of medical marijuana in the treatment of PTSD presented on the websites of the evaluated clinics coincides with the assessment of the databases on the effectiveness of cannabis in the treatment of various ailments. In a review of systematic reviews, Allan et al. [38] noted that high-quality scientific evidence on cannabinoid use is available for only three indications: neuropathic pain, chemotherapy-related nausea and vomiting, and multiple sclerosis-related spasticity. There is a need for further high-quality research to consolidate the reports on the efficacy of cannabinoids for other medical issues, including PTSD.

Literature review: medical marijuana as a treatment for PTSD

According to the literature, medical marijuana is used to treat post-traumatic stress – most commonly to improve sleep. In addition, it is used to reduce anxiety/fear and unwanted memories, as well as increase concentration [39, 40]. People suffering from PTSD turn to cannabis and cannabinoids for their anxiolytic, sedative, hypnotic, and antipsychotic effects [17, 34, 41–45]. War veterans experiencing PTSD use cannabis to alleviate nightmares [46–50].

In 2017, O'Neil et al. [51] published the first systematic review of studies evaluating the potential of plant-based cannabis preparations to treat PTSD in adults. The evidence, however, was insufficient to draw conclusions about the benefits and harms of using those preparations in patients suffering from the disorder. A systematic review by Orsolini et al. [52] suggested that cannabis and synthetic cannabinoids may have potential applications in the treatment of PTSD and its symptoms, e.g., by reducing anxiety, improving sleep, and modulating memory-related processes, but the evidence substantiating their safety and efficacy is limited. In another review, Black et al. [53] also confirmed the insufficiency of evidence to formulate appropriate recommendations for the use of MM in the treatment of mental disorders, including PTSD. The systematic review of cannabinoid use in the treatment of PTSD published by Hindocha et al. [54] in 2020 concluded that cannabinoids may help reduce PTSD symptoms, sleep disorders, and nightmares; however, high-quality evidence supporting their efficacy is lacking, which rules out any clinical recommendations for

their use in routine clinical practice. Another systematic review was carried out by Stanciu et al. [55]. They analyzed eight studies conducted on small groups of patients and did not find adequate evidence for the effectiveness of CBD and THC in treating affective disorders, anxiety disorders, or PTSD. Similar conclusions can be drawn from a systematic review and meta-analysis of randomized controlled trials (RCTs) conducted by McKee et al. [56]. The study evaluated the potential therapeutic benefits of using cannabinoid-containing products in the treatment of various psychiatric disorders in adults. The authors identified 2,397 articles of which 31 met the criteria for inclusion in the analysis. The analyzed RCTs focused on the use of cannabis and cannabinoids in the treatment of: cannabis use disorder (10 papers), schizophrenia (6 papers), opioid/tobacco use disorder (5), anxiety disorder (3), Tourette syndrome (2), anorexia nervosa (2), attention deficit disorder/attention deficit hyperactivity disorder (1), obsessive-compulsive disorder (1), and post-traumatic stress disorder (1). Evidence of the efficacy of cannabinoids in the acute treatment of psychiatric symptoms is limited, and no study has corroborated the medium – and long-term effectiveness of any cannabinoid or cannabinoid-containing product in this regard. None of the studies have confirmed that cannabis flower is an efficacious treatment option for any mental disorder. The only study on PTSD included in this review evaluated the effectiveness of nabilone (synthetic cannabinoid which mimics the effects of THC) in treating nightmares associated with this disorder. The study involved ten Canadian military personnel suffering from PTSD-related nightmares despite following standard drug treatment. Participants received nabilone or placebo for 7 weeks. Then, after a 2-week break, they received the second agent for 7 weeks. The initial dose of 0.5 mg was increased to an effective or a maximum dose of 3.0 mg. The mean reduction in nightmares as measured by the CAPS *Recurring and Distressing Dream* score was – 3.6 ± 2.4 for nabilone and – 1.0 ± 2.1 for placebo ($p = 0.03$). The average overall improvement as measured by the *Clinical Global Impression of Change* scale (CGI-C) was 1.9 ± 1.1 (i.e., significant improvement) and 3.2 ± 1.2 (i.e., minimal improvement) in the nabilone group and the placebo group, respectively ($p = 0.05$). Nabilone provided relief to military personnel suffering from PTSD nightmares, but the study was conducted on a small group, so further research is required to confirm the effect of nabilone (and likely other synthetic cannabinoids) on this and other PTSD symptoms [50].

Despite the lack of solid evidence for the efficacy of MM in treating PTSD, research suggests that a growing number of people are reaching for cannabis to alleviate symptoms of the disorder [57]. Based on a study of 150 participants, Bonn-Miller et al. [58] found that PTSD sufferers reported a greater reduction in symptoms when using MM compared with the control group. Moreover, in comparison with the control group, the participants using MM were 2.57 times more likely to no longer meet the

DSM-5 criteria for PTSD at the end of the study period. A study by Pillai et al. [59] assessed changes in health-related quality of life (HRQoL) and adverse events in 162 patients from the UK Medical Cannabis Registry who were treated for PTSD with cannabis-based medicinal products. At 1, 3, and 6 months after starting therapy, they showed an improvement in HRQoL. There were significant improvements in terms of PTSD symptoms, sleep, and anxiety. 20.37% of the participants reported adverse side effects. They were, however, usually mild to moderate. The most common were insomnia and fatigue.

It has been observed that the use of MM has increased among American veterans. Many of them claim that it helps treat a range of symptoms related to mental and physical conditions, which translates into the overall better quality of life. There were approximately 19 million veterans living in the U.S. in 2020, one fourth of whom suffered from PTSD [60]. According to Metrik et al. [61], among U.S. veterans deployed after September 11, 2001, the most common indications for MM use were anxiety/stress, PTSD, pain, depression, and insomnia.

In the United States, grassroots initiatives have sprung up to provide free cannabis and cannabinoid-containing preparations to veterans with so-called medical marijuana cards, as Veteran Affairs healthcare providers are not allowed to offer advice to patients in this respect, and cannabis is not refunded [62, 63]. VA/DoD guidelines do not recommend the use of cannabis and its derivatives in the treatment of PTSD due to the lack of well-designed RCTs to assess their effectiveness in large trials, as well as because of the serious side effects associated with their use [11]. The medical marijuana refund program for veterans has been in place in Canada since 2007. Since 2016, the refund covers up to 3 g of dried cannabis flower (or equivalent) at a rate of 8.50 Canadian dollars per gram [64].

In 2019, McNabb et al. [60] conducted a survey among 510 U.S. veterans. The participants reported various medical conditions and cannabis use. 26% (n = 131) of the respondents reported suffering from PTSD. 67% (n = 343) of the respondents admitted to using cannabis on a daily basis. 463 veterans (91% of the respondents) stated that MM allowed them to have a better quality of life, and 105 (21%) declared they decreased their use of opioids as a result of using MM [60].

Literature review: negative mental health consequences of marijuana use

Most of the published studies on the use of cannabis by veterans have focused on the negative effects of the agent. In their systematic review, Turna and MacKillop [65] identified 86 studies evaluating the correlates and consequences of cannabis use among veterans. Most studies have linked marijuana use to negative health effects, such as substance abuse, intensification of mental disorders, self-harm, and

suicidal tendencies. Few studies have examined its therapeutic effects [65]. This is largely due to the fact that the largest funder of cannabis research, the U.S. National Institute on Drug Abuse (NIDA), has allocated grants primarily to endeavors focusing on its harmfulness. According to an analysis of grants awarded by 50 public agencies and charity founders, in 2018, about twice as much funding was allocated to research on the potential harmfulness of cannabis as to research on its therapeutic effects [60, 66].

For example, in a U.S. government-backed study of 1,126 veterans of the Gulf War, Grove et al. [67] examined the association between cannabis use in the past year and (a) suicidal ideation in the year before and (b) the overall risk of suicidal behavior. Logistic regression models showed that marijuana use was associated with suicidal ideation and an increased risk of suicidal behavior. The results suggested that cannabis use was a risk factor for suicide among veterans. The study by Dillon et al. [68] established an association between cannabis use disorders and aggressive behavior and violence among Iraq and Afghanistan veterans. Wilkinson et al. [69] demonstrated the link between cannabis use and increased aggression in veterans treated for PTSD.

Steenkamp et al. [70] indicated that marijuana use was associated with adverse psychiatric effects, such as depression, anxiety, psychosis, and substance abuse, conditions commonly associated with PTSD. In their systematic review of the use of MM in psychiatric indications, Wilkinson et al. [71] reported that chronic exposure to cannabinoids could lead to the development of tolerance, addiction, and withdrawal syndrome. Marijuana impairs cognitive functions, including the ability to drive, and early and heavy marijuana use has been linked to the onset of psychosis.

Johnson et al. [72] published a cross-sectional case-control study on psychiatric and sociocultural factors associated with cannabis use in veterans likely to suffer from PTSD. The study involved 350 veteran cannabis users and 350 non-cannabis control subjects. It was observed that, compared with the control group, cannabis users were more likely to be non-Caucasian, financially unstable, and unmarried. There were no significant differences between the cannabis and control groups in terms of the severity of PTSD or depressive symptoms. Cannabis users were significantly more likely to experience suicidal thoughts and reported significantly higher alcohol consumption compared with the control group (an average of about 6 alcoholic beverages per week compared with about 3 beverages per week in the control sample).

Kansagara et al. [73] published a systematic review of the benefits and harms of marijuana use for chronic pain or PTSD. They pointed out that although most of the adverse side effects observed in the studies were mild, serious adverse side effects such as suicide attempts, paranoia, and agitation, were possible. Although the authors

found no studies evaluating the effects of cannabis use on suicide risk in patients with PTSD, a review and meta-analysis of 4 epidemiological studies conducted in general populations found a significantly increased risk of suicide death (pooled OR 2.56; 95% CI: 1.25–5.27) for cannabis use [73].

There are also indications that marijuana users may be less sensitive to PTSD treatment, even after they stop using cannabis. In 2013, Bonn-Miller et al. [74] published a survey conducted among veterans with PTSD. Heavy marijuana use prior to the 15-day abstinence required in the therapeutic program was associated with poorer outcomes of treating PTSD symptoms (hyperactivity and avoidance/numbness) compared with non-cannabis users.

In addition to the potential mental health effects of marijuana, it is worth noting that it can also cause physical health harm, such as respiratory diseases, weight gain, cardiovascular disease, and liver dysfunction. Driving a vehicle under the influence of marijuana increases the risk of traffic accidents [70].

Recapitulation

Currently, there is no sufficient evidence to support the recommendation to use MM or cannabinoids in the treatment of PTSD. Nevertheless, people struggling with this disorder turn to cannabis and cannabinoids for their anxiolytic, sedative, hypnotic, and antipsychotic effects. Numerous studies report improved sleep quality, alleviation of nightmares, and overall better quality of life. When it comes to the use of marijuana by war veterans, most of the studies published so far have focused on the negative effects of its use.

Websites of Polish cannabis clinics generally list PTSD as a treatment option, but they usually do not provide any scientific evidence to support their claims, and if they do, it is of low-quality, and the conclusions of the studies are biased. By relying on poor quality research, medical marijuana clinics can mislead patients. Such marketing may potentially diminish the value of rigorous scientific research and undermine patients' confidence in its integrity.

A significant limitation in assessing the efficacy of cannabis and cannabinoids based on existing data is their heterogeneity in terms of the type of tested agent, dosage, method of administration, as well as chemotype when using the whole plant. Studies on the effectiveness of the whole cannabis plant and individual cannabinoids for PTSD syndrome are limited and methodologically not very rigorous, which precludes conclusions about their potential therapeutic effects [70].

There is a need for further high-quality research on the medical use of cannabis in the treatment of post-traumatic stress disorder. Telch et al. [19] described the design of a phase II randomized clinical trial evaluating the use of CBD oil in the treatment

of PTSD. The completion date was estimated for May 2025, however, the study is currently suspended, as the Institutional Review Board at the University of Texas at Austin has determined that CBD oil, according to the FDA's definition, is a drug. Therefore, according to FDA regulations, an appropriate application must be submitted for a new drug in the preclinical phase under the so-called IND (Investigational New Drug) procedure.

In anticipation of new data from randomized, large-scale, controlled trials, it is advisable to develop available sources of information and appropriate oversight to counteract harmful marketing of medical marijuana.

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