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Medical use of cannabis and psychedelics in treating symptoms of mental disorders among military and veteran populations: A systematic review

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Abstract. Military personnel and veterans experience distinct trauma exposures, resulting in totally different mental disorder prevalence, comorbidities, and treatment responses compared to the general population. The medical use of psychoactive substances as novel strategies for specific mental health conditions within military contexts is being investigated, while their therapeutic efficacy and safety remain uncertain. This systematic review aims to summarize the available evidence for the medical use of these substances, mainly cannabis and psychedelics, in treating symptoms of mental disorders in military populations. A systematic search was conducted in Medline, PubMed, and Web of Science databases from inception until May 16th, 2023, following PRISMA guidelines. References of relevant papers and high-quality reviews were also hand-searched. The included studies were randomized controlled trials, self-controlled trials, and case reports that explored the use of cannabis or psychedelics for the treatment of mental disorders in military and veteran populations. Two independent reviewers screened all studies and performed data extraction. Eight studies were included, with five focused on cannabis and three on psychedelics. Most of the studies reported positive results, but detailed information on side effects and long-term follow-up was limited. In conclusion, the potential benefits yet the lack of high-quality RCTs underscore the need for more rigorous research in this field.

Keywords: military personnel and veterans, cannabis, psychedelics, mental disorders

1. Introduction

Military and veteran population are considered vulnerable to several mental disorders, the managements of which have long been a challenging task [1]. Despite the advances in conventional treatments including psychotherapies and pharmacotherapies, this unique population often exhibits distinctive symptoms presentation and comorbidities compared to the general population[2], resulting in suboptimal treatment response [3].Considering these challenges, researchers are exploring alternative treatment options, including psychoactive drugs. Psychoactive drugs have been historically used for recreational purposes and portrayed as extremely dangerous drugs for decades due to their ability to alter perception and mood[4]. However, in recent years, an increasing number of studies have investigated their medicinal value. Although still in early stages of research, these drugs show promise as novel and effective treatment options for mental disorders [5]. Considering these factors, evidence of

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medical use of these drugs for military and veteran populations is warranted. Cannabis and psychedelics are the two most used psychoactive substances.

1.1. Evidence of effectiveness of cannabis and psychedelics for mental disorders

Cannabis, targeting the ECB system [6], may have therapeutic potential for mental disorders, such as depression, anxiety, and PTSD, by reducing symptoms and improving cognitive performance [7]. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most well-known and studied components of cannabis [8]. THC is the primary psychoactive component of cannabis and exerts its effects by binding to CB-1 and CB-2 receptors in the ECB system[9]. Unlike THC, CBD does not have psychoactive properties[10], making it a popular choice for those seeking the potential benefits of cannabis without the "high risk" associated with THC. The properties of CBD seem to depend on several cannabinoid-dependent and independent mechanisms, including interacting with a number of different receptors, such as the CB1 and CB2 receptors, the GPR55 receptor, the TRPV1 receptor, the 5-HT1A receptor[11] and FAAH inhibition[12]. Besides THC and CBD, some synthetic cannabinoids have emerged in recent years, of which nabilone is the most explored one. Nabilone, a synthetic CB1 receptor agonist chemically similar to THC [13], has been shown to be safe and well-tolerated with little evidence of abuse or tolerance development[14]. It has also been used to relieve pain[15] and alleviate PTSD-related insomnia and nightmares [16].

Psychedelics, including substances such as 3,4-methylenedioxymethamphetamine (MDMA), psilocybin, lysergic acid diethylamide (LSD), 5-methoxytryptamine (5-MeO-DMT), and ibogaine, were first explored as therapeutic drugs during the 1960s. These psychedelics act primarily through activating serotonin receptors (e.g., 5-HT1A/2A/C)[17] and can produce substantial changes in sensory perception, mood, cognition, and behavior [18]. Recently, several studies have explored the use of psychedelics as adjunctive therapies in psychotherapy and have shown promising results in reducing symptoms of anxiety, depression, PTSD and substance abuse disorder [19-22].

1.2. Cannabis and psychedelics for military and veteran populations

The specific nature of the profession often exposes military service members to various traumatic events and high levels of stress, making them vulnerable to mental health disorders [23]. Moreover, military members often face unique challenges such as adapting to military culture, separation from loved ones during deployments, and reintegrating into civilian life after service. In the military context, prevalence of traumatic brain injury (TBI) is relatively high, which may result in a range of physical, cognitive, and emotional symptoms [24]. Additionally, somatization symptoms such as musculoskeletal conditions, chronic pain, and insomnia due to rigorous combat experiences and deployment history further affect their mental health [25]. Stigma is common among the military personnel [26]. Taken together, military and veteran populations exhibit considerable distinctions in illness development, symptom presentation and comorbidities, and is often less responsive to traditional mental health treatments compared to general population [27]. While studies have supported the potential therapeutic effects of cannabis and psychedelics for mental disorders among the general population, the extent to which they may be appropriate for military and veteran populations remain unclear. We haven't found any review focusing on military population.

There has been growing interest in the potential therapeutic benefits of cannabis and psychedelics for mental disorders. Several systematic reviews have been conducted and the results are mainly positive [28-36]. However, relatively rare studies focus on military and veteran populations. Considering the high incidence and distinctive features of mental disorders in this unique population, the medical use profile of cannabis and classical psychedelic for them requires further exploration. Our goal is to collect evidence regarding the medical use of cannabis and psychedelics in treating mental health symptoms in military personnel and veterans.

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2. Methods

The present systematic review was documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [37]. In 2 November 2023, Medline, PubMed and Web of science online databases were searched from their inception up to October 2023 . In addition, to be as comprehensive as possible, we manually searched through reference listings of included papers and high-related reviews for further studies. Only papers written in English were included. The full search strategies are shown in supplemental annex A; no protocol was registered. Table 1 shows the eligibility criteria. Due to the possible limited numbers of included studies, the assumed large heterogeneity in the type of designs and outcome measurements, a descriptive review was completed.

Two reviewers independently extracted the data on authors, date of publication, sample characteristics, interventions, psychedelics or cannabis details, study designs, control group, outcomes measures and main findings, and consensus were reached by discussion. Data were collected using a specifically designed table finally. For bias assessment, the Cochrane Risk of Bias (Rob) tool was used. Results and analysis are provided in supplemental annex C.

Table 1. PICOS table of eligibility criteria

Items	Details
Population	Military personnel and veterans (two studies including several policemen and firefighters were also included considering their similar working experience and the relatively small sample sizes) with symptoms of mental disorders, including PTSD, SUD, depression or anxiety disorders, to some extent
Intervention	Using cannabis (including THC, CBD, Nabilone) or classical psychedelics (including MDMA, psilocybin, LSD, 5-MeO-DMT, ibogaine) as monotherapies or adjunctive to conventional therapies
Comparator	Placebo or none
Outcome	Reported change of symptoms of mental disorders
Study design	Study design (S): randomized controlled trails (RCTs), self-control trails and case reports. Narrative and systematic reviews, meta-analyses editorial and book chapters were excluded.

PICOS, population, intervention, comparator, outcome, study design

3. Results

Figure 1 shows the PRISMA flow diagram of included and excluded studies. In total, 8 studies were included in this systematic review. Of these, 5 were about cannabis (1 about nabilone, 4 about THC and/or CBD), and 3 were about psychedelics (2 about ibogaine and 5-MeO-DMT, 1 about MDMA). All the included studies in this systematic review were published between 2014 and 2020. Among these studies, three were RCTs [38-40], two were retrospective studies [41, 42], one was a case-matched controlled cross-sectional study [43], one was a self-control study [44], and one was a case study[45]. Four studies were conducted in the United States[17, 40, 43, 45], three studies in Canada[38, 39, 41], and the other in New Mexico [42]. Most of the studies focused on military personnel and veterans with PTSD, who often had comorbidities such as AUD and mood disorders. Of the eight studies, seven included only veterans, while one chose currently serving soldiers. Three RCTs had a small sample size of 10 to 80 participants, with only 6 to 20 participants in each arm. The other four open-label studies had larger sample sizes of 80 to 700 participants. Given the diversity in study designs, medications implicated, and outcome measures, we briefly introduced each study and reached conclusions at the end of the review. The main characteristics of the 8 studies are reported in table 2. Details of the 8 included studies are shown in supplemental annex B.

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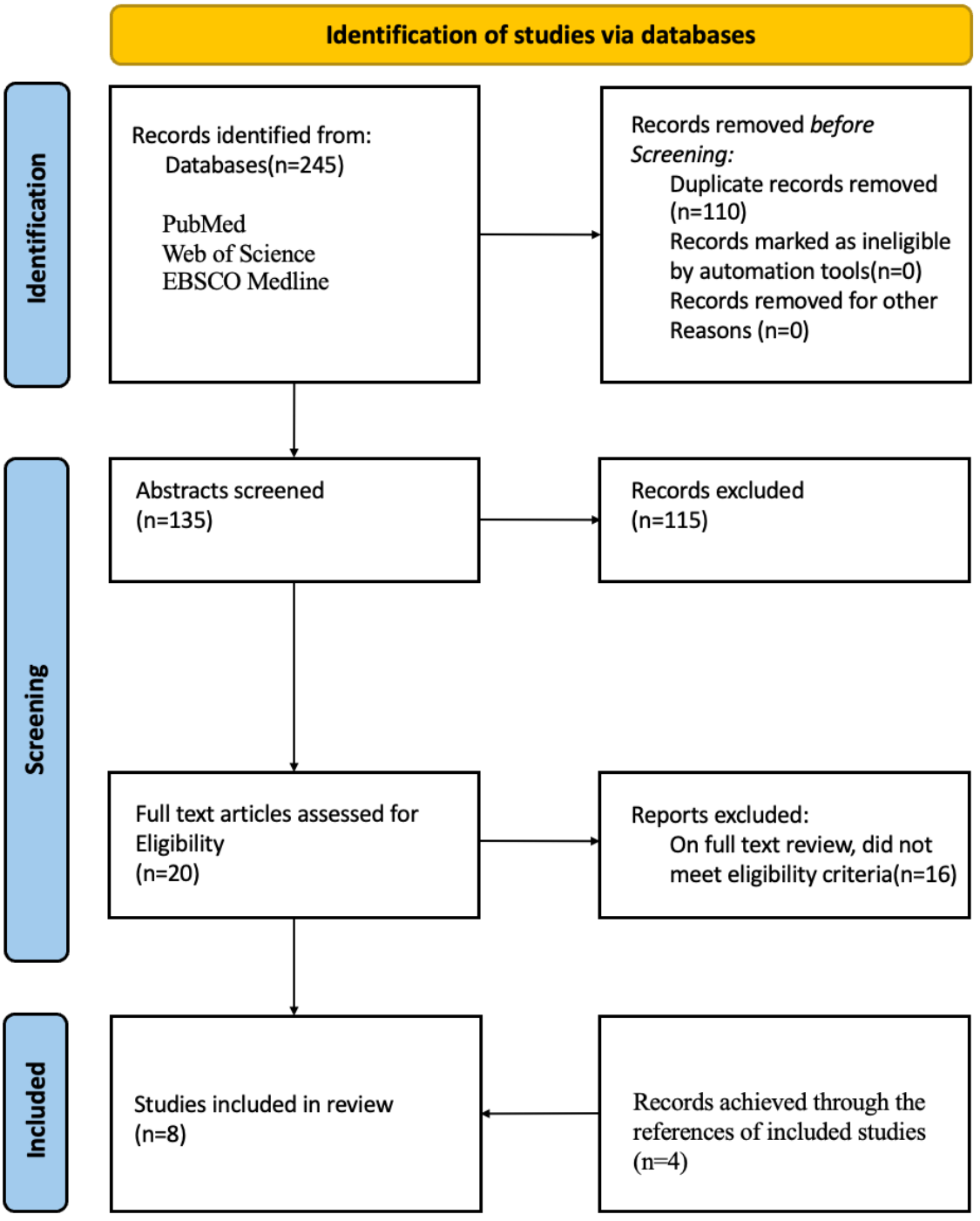

Figure 1. PRISMA flow diagram detailing the study selection process

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Table 2. Summary of retrieved papers

Authors (country)	Study Design	Population	Intervention/ Comparator	Dose (s) and Duration of Medication	ROA	Out-comes	Adverse effects	Follow-up	Main Findings
Jetly et al. 2014 (Canada)	RCT, crossover	10 currently serving male soldiers with PTSD	NAB/ Placebo	The average dose achieved in each group was: NAB: 1.95 ± 0.9 mg. PBO: 2.78 ± 0.7mg.; 7 weeks	OS	CAPS CGI-C WBQ	Most common were mouth and headache and no patient dropped out because of adverse effects.	n.d.	NAB induced significant relief for military personnel with PTSD and reductions in symptoms of nightmares.
Greer et al. 2014 (New Mexico)	A retrospective self-control study	80 veterans with PTSD	Cannabis (THC+ CBD)/ None	n.d.; n.d.	Smoked	CAPS	n.d.	n.d.	Reductions in PTSD symptoms in some patients.
Smith et al. 2017 (Canada)	A retrospective self-control study	100 veterans with PTSD	Cannabis (THC+ CBD)/ None	9.4 grams/day on average; n.d.	Smoked	A scale of 0 to 10 including various symptoms	n.d.	The time of follow-up ranged from less than 3 months to 18 months and improve-ment were significant betwee	Significant improvements across all PTSD symptoms, as well as social and family impact out-comes and pain severity.

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								n baseline and follow-up.	
Bonn-Miller et al. 2020 (Canada)	RCT, crossover	80 veterans with PTSD	Cannabis (THC+CBD)/ None	Ad libitum use up to 1.8 grams/day; 3 weeks	Smoked	CAPS-5 PCL-5 IDAS IPF ISI	Cardiac disorders; eye disorders; gastrointestinal disorders; general disorders; in-fections; injuries; nervous system disorders and psychiatric disorders; etc.	n.d.	All treatment groups, including placebo, showed good tolerability and significant improvements in PTSD symptoms during three weeks of treatment, but no active treatment statistically outperformed placebo in this brief, preliminary trial.
Johnson et al. 2016 (United States)	A case-matched controlled cross-sectional study	700 veterans with PTSD	Cannabis / Not using cannabis	n.d.; n.d.	Smoked	PCL-C PHQ-9 PQSI A BOMC TLFB ASSIST	n.d.	n.d.	No association between PTSD scores and frequency of cannabis use.

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Davis et al. 2020 (United States)	A self-control study	51 Veterans with PTSD	Ibogaine and 5-MeO-DMT/ None	A single dose(10 mg/kg) of ibogaine on day 1 and day 3 to 50mg 5-MeO-DMT on day 3;3days.	OS and inhaled	PCL-5 PHQ-2 GAD 2-item DSISS MOS-CF subscale AAQ-II	n.d.	n.d.	Significant and large reductions in PTSD, depression and anxiety symptoms, suicidal ideations and cognitive impairment; increased psychological flexibility.
Barsuglia 2018 (United States)	A case study	A veteran with PTSD and AUD and non-specified mood disorder	Ibogaine and 5-MeO-DMT/ None	1550mg ibogaine HCl on day1 and 5–7mg 5-MeO-DMT on day3; 3days	Intravenous administrated and inhaled	SPECT examina-tions Self-report	Ataxia; vomiting; acute panic; hallucination.	The therapeutic effects for alcohol abuse disorder were sustained at 1month, with a partial return to mild alcohol use at 2 months.	Acute remission of alcohol use, reduced cravings for alcohol and improvements in cognition, mood, and interpersonal functioning; reduced orbitofrontal, temporal, occipital and cerebellar

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									perfusion and increased perfusion in bilateral caudate nuclei, left putamen as well as in temporal, occipital and cerebellar regions.
Mithoefer et al. 2018 (United States)	RCT, crossover	26 veterans with PTSD	MDMA/ Active control	30 mg, 75 mg, or 125 mg MDMA; n.d.	OS	CAPS-IV BDI-II PSQI PTGI NEO-PI-R DES-II GAF	85 adverse events were reported and the most frequently included anxiety, headache, fatigue, and muscle tension. Most adverse reactions were mild to moderate in severity.	Scores on all secondary measures at 12-month follow-up showed improve-ment compared with baseline.	Active doses (75 mg and 125 mg) of MDMA with adjunctive psychotherapy in a controlled setting were effective and well tolerated in reducing PTSD, depression symptoms and improved sleep quality.

Abbreviations: ROA: route of administration; n.d.: not documented; PTSD: post-traumatic stress disorder; Nabilone: NAB; CBD: cannabidiol; THC: tetrahydrocannabinol; 5-MeO-DMT:5-methoxy-

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N,N-dimethyltryptamine; MDMA:3,4-methylenedioxymethamphetamine; OS: oral administrated; PCL-C: PTSD Checklist-Civilian Version; PCL-5: patient-completed PTSD Checklist for the DSM-5; PHQ-2: Patient Health Questionnaire-2; GAD: Generalized Anxiety Disorder; DSISS: Depressive Symptom Index Suicidality Subscale; MOS-CF: Medical Outcomes Study—Cognitive Functioning; AAQ-II: Acceptance and Action Questionnaire II; AUD: alcohol use disorder; IPF: Inventory of Psychosocial Functioning; CMMQ: Comprehensive Marijuana Motives Questionnaire; IDAS: Inventory of Depression and Anxiety Scale; GAF: Global Assessment of Functioning; PCL-M: Post-Traumatic Stress Disorder Checklist-Military Version; CES: Combat Exposure Scale; PSQI: Pittsburgh Sleep Quality Index; NFQ: Nightmare Frequency Questionnaire- Revised; NES: Nightmare effects survey; CAPS: Clinical Administered PTSD Scale; CGI-C: Clinical Global Impression of Change; WBQ: General Well Being Questionnaire; n.d.: not documented; PHQ-9: Patient Health Questionnaire; PQSIA: Paykel questionnaire for suicidal ideations and attempts; BOMC: Blessed Orientation-Memory-Concentration Test; BDI-II: Beck Depression Inventory-II; PSQI: Pittsburgh Sleep Quality Index; PTGI: Post-Traumatic Growth Inventory; DES-II: Dissociative Experiences Scale II; NEO-PI-R: NEO Personality Inventory; TLFB: Timeline Followback; ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test.

3.1. Cannabis

Five studies evaluated the effectiveness of cannabis for psychological issues in military personnel and veterans. A double-blind, placebo-controlled crossover study was conducted by Jetly et al.[82] to investigate the efficacy of NAB in reducing the frequency and intensity of nightmares in male Canadian military personnel with PTSD who experience trauma-related nightmares despite standard treatment. The study suggests that synthetic endocannabinoids, like nabilone, may have potential as a medication for PTSD-related nightmares in the military population, but further studies with larger cohorts are needed to validate these findings. In a study by Greer et al.[42], psychometric data on PTSD symptoms were analyzed in 80 military veterans applying to the New Mexico Medical Cannabis Program from 2009 to 2011. Patients in this sample reported over 75% reduction in all three clusters of PTSD symptoms while using cannabis[42], adding support to the conclusion that reasonable cannabis use may be conducive to PTSD symptom relief in some military veterans. However, details of medication, including dose and duration, were not mentioned, and adverse effects during the medication were not reported. To evaluate the outcomes of medical cannabis for military and police veterans with PTSD, Smith et al.[41] conducted a retrospective study among 100 patients from January 2014 to January 2016. The study concluded that cannabis use resulted in improvements in all PTSD symptoms, social and family outcomes, and pain severity, making it an effective therapy for military veterans with PTSD. However, no data about the side effects of cannabis were collected. Aimed to collect preliminary data on the safety and potential efficacy of three different active concentrations of smoked cannabis (i.e., High THC = approximately 12% THC and < 0.05% CBD; High CBD = 11% CBD and 0.50% THC; THC+CBD = approximately 7.9% THC and 8.1% CBD) compared to placebo (< 0.03% THC and < 0.01% CBD) in the treatment of PTSD among military veterans, Bonn-Miller et al. [38]conducted a randomized, double-blind, placebo-controlled, cross-over design study, assigning 80 participants to 4 groups. This study provided preliminary evidence supporting the potential therapeutic effect and safety of medical cannabis among military personnel, with generally mild and transient side effects reported. Although the above studies reported positive findings on the therapeutic effects of cannabis, including THC, CBD, and nabilone, for symptoms of mental disorders among military and veteran samples, one study reported inconsistent conclusions. Johnson et al.[43]conducted a case-controlled cohort study among a large clinical population of veterans with probable PTSD and concluded that PTSD symptomatology was not associated with the frequency of cannabis use.

3.2. Psychedelics

The efficacy of psychedelic medicine in the treatment of psychological problems among military personnel was examined in three studies. Davis et al. [44] conducted a retrospective cohort study to

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examine the efficacy of psychedelic treatment with ibogaine and 5-MeO-DMT for trauma-related psychological and cognitive impairment among 65 U.S. Special Operations Forces Veterans. Given the repeated trauma exposure and nature of such exposure experienced by Special Operations Forces, this population may have unique treatment needs. The study suggested that psychedelic-assisted therapy may hold unique promise for this population but did not report follow-up and adverse effects data. Barsuglia [45] presented a case report on the potential therapeutic effects of ibogaine and 5-MeO-DMT in a 31-year-old male military veteran with comorbidity of AUD and PTSD and suggested a short-term therapeutic effect of ibogaine and 5-MeO-DMT.To investigate the efficacy and safety of MDMA-assisted psychotherapy for chronic PTSD, A randomized, double-blind, dose-response, phase 2 trial with 26 participants diagnosed with PTSD investigated the efficacy and safety of MDMA-assisted psychotherapy[40]. The study supported the safety and potential efficacy of MDMA for PTSD and indicated that the efficacy was closely related to the doses. An active dose (75 mg and 125 mg) of MDMA combined with psychotherapy was effective and well-tolerated in alleviating symptoms of PTSD.

4. Discussion

The current article aimed to review the medical applications of cannabis and psychedelics in the context of military and veteran personnel. To our knowledge, this is the first systematic review investigating the available evidence for these psychoactive drugs in treating symptoms of mental disorders among this unique population. Summarizing the existing studies, we found that the conclusion both positive and negative. According to our systematic review, cannabis and psychedelics may offer an innovative, rapid-acting, well-tolerated, and potentially cost-effective intervention for the military population suffering from mental problems. Nevertheless, there are still many disputes and disagreements regarding the application of these drugs.

4.1. Positive

1. Rapid-acting: Cannabis and psychedelics have a unique advantage in their ability to produce quick effects. Patients may experience noticeable improvements in symptoms after taking them for a short period of time or just a few times. Of the five studies included in our review that used cannabis, two reported the duration of medication [38, 39]. One study found that seven weeks of nabilone use provided significant relief for symptoms of nightmares[39], and another found that three weeks of cannabis use showed significant improvements in PTSD symptoms[38]. Psychedelic medicine, on the other hand, does not require daily use for months or years, but rather can be used on one or a few occasions during psychotherapy sessions. Conventional pharmacological treatment and psychotherapy are often time-consuming and result in low patient compliance. Additionally, studies have found that psychedelics can increase patients' psychological flexibility more rapidly than traditional psychotherapy[46]. Therefore, many patients are willing to adhere to medication and view the treatment process as a positive life experience.

2.Cost-effective. Smith et al. found that during the use of medicinal cannabis, most patients were able to reduce the dosage of other PTSD-related drugs, with some even stopping all drugs during follow-up [41]. A pharmacoeconomic evaluation found that this resulted in an average savings of $2,300 to $3,800 per patient per year. Another longitudinal study found reductions in the use of prescribed psychiatric medication three months after initiation of cannabis[47]. Therefore, if cannabis and psychedelics could replace other expensive conventional pharmacotherapies to some extent among military personnel, the treatment-related costs and financial burden could be considerably reduced.

3. Well-tolerated. Although some side effects were reported in a few studies using cannabis and psychedelics, most were mild or moderate in severity and did not lead to discontinuation[40]. In contrast, traditional therapies, especially pharmacotherapy, are often discontinued due to intolerable side effects such as decreased libido, extreme changes in weight and metabolic function, sleep disruption, anorgasmia, and orgasmic delay[48, 49].

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4.2. Negative

1. Limited high-quality evidence. Although interest in using cannabis and psychedelics as adjunctive or alternative treatments for mental health problems has grown dramatically in recent years, there is a notable lack of high-quality evidence regarding their efficacy and safety, especially their long-term effects and delayed or residual side effects. Furthermore, given the documented problems associated with these drugs, such as addiction[38], and the strict regulation of these drugs in many countries, research on their application to treat psychological problems progresses slowly, especially among the military population. Although only a few studies have briefly reported the side effects in our systematic review, indicating they were relatively mild or moderate in severity[38-40, 43], few studies have investigated the long-term effects of these drugs. In terms of available literature, it is not easy to draw a definitive conclusion on the safety of these drugs based on current limited evidence.

2. Lack of standardized protocols. One of the major challenges in using cannabis and psychedelics lies in the diversity of psychoactive ingredients and protocols of administration, none of which has been standardized. For example, cannabis can be found in many different natural plants and synthetic products, and the exact content of psychoactive ingredients can vary significantly. Even though heterogeneity can be minimized under extremely strict conditions, it is rather difficult to set standards of potency and purity[50]. Additionally, different preparations also have different routes of administration, such as smoking, swallowing, absorption sublingually, or topical application[51]. Previous research has shown that the route of administration can directly affect the therapeutic potential and risk of problematic use [52]. There's no doubt that dose is a direct factor affecting the efficacy and safety of drugs. Although some studies have explored the relationship between dose and efficacy, no standard prescribed dose has been specified.

The systematic review provides valuable insights into the medical use of cannabis and psychedelics among military and veteran populations, but the landscape is complex with mixed results. Currently, there is a severe lack of definitive evidence-based medical guidance on the use of these drugs. Therefore, larger randomized controlled trials with high methodological quality are urgently needed to provide more conclusive evidence on the efficacy and safety of these drugs compared to placebos and conventional therapies. Longitudinal studies are also necessary to evaluate the long-term effects and potential side effects. Additionally, standardized protocols for administration, including specific doses, routes of administration, and treatment duration, need to be developed to allow for uniformity and comparability across studies. Evidence-based medicine is critical for developing clinical guidelines on the medical use of these drugs for mental health issues among military personnel.

5. Conclusions

The relatively high prevalence and unique features of mental disorders among the military and veteran population highlight the need for novel and effective strategies, and some researchers are exploring the potential of psychoactive drugs. The current systematic review focused on collecting evidence on the medical use of two of these drugs--cannabis and psychedelics. The existing evidence is promising but limited, and further research is necessary to provide more robust evidence on the efficacy, safety, and clinical utility of these interventions. Addressing methodological and practical challenges associated with their implementation is also critical. If proven effective and safe, cannabis and classic psychedelics have the potential to improve the lives of military personnel, veterans, and others struggling with mental health disorders who often face unique challenges and barriers to accessing conventional mental health care. The systematic review also has several limitations, including small sample sizes, a limited number of available studies, heterogeneity in experimental design and medication details. The small sample sizes may lead to exaggerated effects of psychoactive drugs and limit the generalizability of conclusions. Additionally, only three out of the eight included studies were randomized controlled trials, while the rest were cohort or self-control studies, including one case report, which may limit the persuasiveness of the results. Most studies did not investigate participants' past use of psychoactive drugs, which could have affected their response. Finally, most studies relied on self-reported experimental results, which may be subject to bias and reduce the reliability of the studies.

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