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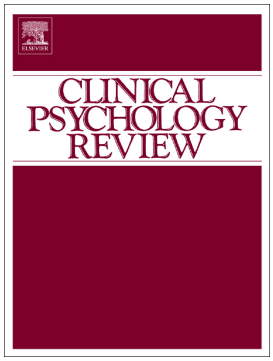

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CANNABIS USE AMONG MILITARY VETERANS: A GREAT DEAL TO GAIN OR LOSE?

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ABSTRACT

Policy changes have resulted in dramatic increases in access to cannabis for medical purposes. Veterans are disproportionately affected by conditions for which medical cannabis is often pursued, making an evidence-based perspective on risks versus benefits of high priority. The current review sought to examine the state of the evidence on consequences and correlates of cannabis use among veterans. Using a comprehensive search strategy, 501 articles were identified and 86 studies met criteria for inclusion. The literature was predominated by cross-sectional studies (67%) of male veterans (71.4%-100% male) from the United States (93.0%). Three overarching themes emerged comprising cannabis associations with other substance use, mental health, and physical health outcomes. The balance of the evidence associated cannabis use with negative health outcomes, with consistent positive associations with other substance use, psychiatric disorders, and self-harm/suicidality. Few studies examined the therapeutic effects of cannabis, thus limiting the potential to evaluate evidence of efficacy. Priority areas for future research are studies using designs that can examine the directionality of links between cannabis and health in veterans more conclusively, and studies directly examining therapeutic efficacy of cannabis-based therapies in veterans. Methodologically rigorous design will be essential to inform clinical recommendations and practices guidelines in an era of burgeoning access to cannabis.

Keywords: veterans, cannabis, marijuana, post-traumatic stress, pain

INTRODUCTION

Cannabis has been long used for a variety of purported therapeutic effects; however, the evidence supporting such use is often scant, methodologically poor, or inconsistent (National Academies of Sciences, 2017; Turna, Patterson, & Van Ameringen, 2017; Whiting et al., 2015). Indeed, the dearth of literature has been a leading criticism for the medical use of cannabis. Yet medical use of cannabis, be it prescription or self-medication, is on the rise. In Canada, for example, medical cannabis has been legal since 2001, but legislative changes in 2014 and 2017 substantially increased access. This resulted in nationwide medical authorizations increasing from approximately 3,000 in 2014 to over 340,000 in 2018, immediately prior to federal legalization of recreational cannabis (Health Canada, n.d.). Similarly, in the U.S., there has been a surge in the number of states to have legalized medical cannabis in some form, with two-thirds (33 states) now permitting medical cannabis.

Veterans are a group disproportionately affected by conditions for which medical cannabis treatment is often pursued. For instance, veterans experience greater disability from chronic pain (Thompson et al., 2015) and rates of post-traumatic stress disorder (PTSD) are five- to ten-fold higher than in the general population (Thompson et al., 2016). In Canada, 1 of every 5 medical reimbursements to Veterans from the federal government is for medical cannabis (Sterniczuk & Whelan, 2016). Reimbursements for medical cannabis for veterans in Canada have ballooned from approximately $100,000 in the first year of the program to almost $75,000,000 (CAD) in the fiscal year 2018-2019 (Veterans Affairs Canada, 2019). This reflects reimbursements for nearly 9,000,000 grams of medical cannabis (Veterans Affairs Canada, 2019). Beyond medical use, cannabis is also one of the most common illicit substances used by veterans (Teeters, Lancaster, Brown, & Back, 2017) and the legal status of non-medical (recreational) cannabis use is changing quickly worldwide. Given that cannabis use has been associated with numerous physical and mental health problems, is becoming more widely

available and that the therapeutic benefits are unclear, the goal of the current review is to broadly appraise the evidence of risks/harms versus benefits from cannabis (medical and non-medical) for veterans. Specifically, the goal of the review is to systematically examine the empirical literature on the consequences (bad and good) and correlates of cannabis use in veterans. Finally, the review will discuss implications of the evidence for treatment and policy and offer recommendations to inform future research in this area.

METHODS

The reporting of this review is compliant with all relevant components of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)(Moher et al., 2009).

Search Strategy

Relevant articles on cannabis use among Veteran populations were identified using the Boolean search terms “cannabis” or “CBD” or “THC” or “marijuana” or “cannabinoid” and “Veteran”. The search was specific to Veteran populations, individuals who at one point served in the active Military, Army, Naval, or Air Force and have since returned to civilian life. As such, studies of only active service members were excluded. The search was conducted using PubMed/MEDLINE, EMBASE, and PsycINFO in December 2019, and the initial searches were downloaded to shared drives. Titles and abstracts resulting from the initial search were screened by 2 reviewers for suitability for full-text review and final inclusion. To be included, an article was required to meet the following criteria: (i) an original empirical research article published in a peer-reviewed journal since 1990; (ii) written in (or available in) English; (iii) study design must include cannabis involvement as an independent or dependent variable; and (iv) at least a subsample of the population must be made up of Veterans.

Insert Fig 1 here

RESULTS

Characteristics of the Literature

Overall, 86 studies were identified for full-text inclusion (Figure 1). A wide variety of themes were present and are described in the following sections, from largest literatures to the smallest. Notable overlap was present among studies, so individual studies are included in the subsections most consistent with the design and findings. In terms of study designs, 66.8% used cross-sectional designs, with only 27.4% of studies using longitudinal designs and 5.8% of studies using were randomized controlled trial designs. In terms of study populations, the vast majority (93.0%) of the literature was based on U.S. veterans, while only 3 studies were from Canada (3.4%), 1 from Israel (1.2%), 1 from South Africa (1.2%) and 1 from Nigeria (1.2%). Of U.S. Veterans, samples were predominantly those receiving treatment at a Veterans Affairs (VA) facility or participants in the Vietnam Era Twin (VET) Registry and Veterans Aging Cohort Study (VACS). Given that many of these studies analyzed subsets of existing datasets and some reports are a sub-analysis of a primary study, it is difficult accurately state how many unique samples make up this literature. We estimate that approximately 51 of studies meeting inclusion criteria utilized unique samples. Of the studies indicating the relevant conflict, Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND), Gulf War and Vietnam War veterans were most often represented (38.3%). Aside from one study exclusively focusing on female veterans, all other studies utilized predominantly male samples, ranging from 71.4-100% male.

Cannabis and other substance use among veterans

Numerous studies examined cannabis use and other substance use in veteran populations and are summarized in Table 1. Themes in these studies include levels of cannabis use/cannabis use disorder

(CUD), overlapping alcohol and cannabis use, and cannabis use in the transition from military to civilian life.

Cannabis use is elevated among veterans and may be associated with poorer outcomes

In general, veterans are a high substance using population, exceeding what has been reported in civilians (Boden & Hoggatt, 2018; Wagner et al., 2007). Typically, alcohol and tobacco use are most common; however, cannabis is increasingly ranked as one of the top three substances used and the most frequent illicit substance used by veterans in the U.S. (Teeters et al., 2017). For example, a recent survey of 812 young veterans revealed that 57% reported lifetime cannabis use, with 24% using in the past six-months (Pedersen, Marshall, & Kurz, 2017). Rates of lifetime cannabis (65.5%-70.3%) or problematic cannabis (9.7%-18.2%) use are also comparable between conflicts as demonstrated in a study of veterans (n=373) from the Vietnam era, post-Vietnam era and Persian Gulf/Mideast (Kline et al., 2009). Even female veterans, who are typically underrepresented in the literature, report past year cannabis use at rates higher than civilian women (11% vs. 6.4-6.9%)(Browne, Dolan, Simpson, Fortney, & Lehavot, 2018). The only non-U.S. study to emerge was a study from Israel which also illustrated that substance use, including cannabis, was elevated among veterans compared to their general population (past 30 days: 43.7% vs. 20.9%, p<.001)(Heingold, Zerach, & Levi-Belz, 2018).

Compared to non-using veterans, those who use cannabis report worse marital status (Bauer et al., 2005), poorer educational attainment (Grant et al., 2012) and poorer functioning on several physical and mental health domains (Boden & Hoggatt, 2018; Stewart, Farris, Jackson, Borsari, & Metrik, 2019). However, results of a co-twin study of the VET registry comparing heavy cannabis using and non-using co-twins revealed no significant differences on self-reported sociodemographic characteristics, current or lifetime substance use disorder (SUD), health-related quality of life or other

health outcomes (Eisen et al., 2002). More recently, though, further co-twin analysis revealed that early cannabis users were at greater risk than later/never-using co-twins for 8/9 substance-related comparisons, including using other illegal drugs (OR=2.71-4.09), having other illegal drug abuse/dependence (OR=2.02-2.13) and developing AUD (OR=2.36)(Grant et al., 2010). After familial influences on early cannabis use were controlled for (regardless of age cannabis initiated), cannabis use continued to confer greater risk for the aforementioned drug behaviours (Grant et al., 2010).

Alcohol and cannabis co-use

Alcohol-related problems, including heavy drinking and alcohol use disorder (AUD), are prominent among veterans who use cannabis. For instance, veterans who use cannabis are more likely to co-use alcohol at a heavy rather than moderate level (OR=2.34)(Metrik, Gunn, Jackson, Sokolovsky, & Borsari, 2018). Hazardous alcohol use has also been associated with past year cannabis use among HIV-infected veterans (Marshall et al., 2015) and among veterans in the VACS registry (Ruggles et al., 2017). Similarly, in a national survey sample of female veterans, past year regular cannabis use was also associated with current smoking, other substance use and screening positive for alcohol misuse (Browne et al., 2018). An Israeli study also revealed that the prevalence of alcohol and cannabis use is more than two times higher among veterans than the general population (Feingold et al., 2018). Further, in a sample of AUD veterans, those with a history of cannabis use (n=142, 23% of sample) reported earlier AUD onset than cannabis non-users (n=226, 36% of sample)(Tsuang et al. 1994). This is critical given that earlier onset of AUD has been associated with greater impulsivity, more severe and frequent withdrawal complications and dependence (Le Strat, Grant, Ramoz, & Gorwood, 2010).

The inverse relationship has also been observed where risk for past year cannabis use is elevated among hazardous use of other substances, particularly alcohol. Data from the VHA revealed that past

year cannabis use was predicted by presence of AUDs (AOR=2.31), past year drug use (AOR=5.40) and smoking status (AOR=1.50)(all p<.001; (Goldman et al., 2010). Similarly, recent data from the National Survey on Drug Use and Health (NSDUH) illustrated a similar picture with greater odds of past year cannabis use associated with heavy episodic drinking, AUD, nicotine dependence and greater functional disability among veterans (Davis, Lin, Ilgen, & Bohnert, 2018). This increased prevalence of co-use is critical as those engaging in hazardous alcohol and cannabis use were more likely to screen positive for mental health problems among a community sample than those only screening positive for hazardous cannabis use (Pedersen et al., 2017).

Interestingly, the link between cannabis and hazardous alcohol use lessens when veterans are using cannabis medically. One study indicated that veterans using medical cannabis were less likely to engage in heavy episodic drinking (45.4% vs. 19.3%) or meet AUD criteria (19.6% vs. 4.7%) compared to non-medical users (Davis et al., 2018). Similarly, veterans with PTSD who use medical cannabis to treat a variety of conditions reported fewer alcohol drinking days (d=0.28, 6.50±8.75 vs 9.55±10.24) compared to those using cannabis recreationally (Loflin, Earleywine, & Bonn-Miller, 2017). In another retrospective chart review (n=101), medical cannabis use was associated with fewer veterans consuming alcohol at follow-up (67.3%, 5.5 drinks/week) compared to baseline (81.2%, 8.1 drinks/week), though this difference was not statistically significant (Jin et al., 2017). This pattern of lower alcohol use among veterans who use cannabis medically, compared to those using recreationally, was confirmed by a longitudinal analysis of three semi-annual waves of timeline followback interview data (Gunn, Jackson, Borsari, & Metrik, 2019). Compared to medical users, recreational users reported more drinking days, heavy drinking days and were more likely to meet criteria for past year AUD (baseline and 1-year follow-up). Conversely, medical cannabis users revealed more cannabis use days, alcohol co-use days and were more likely to be diagnosed with CUD (baseline and 1-year follow-up). While mixed effect

multilevel modelling revealed that any cannabis use (recreational or medical) on a given day positively predicted the number of drinks on the same day (OR=1.45, p<.001), there was also a significant interaction of cannabis use and type of user (OR=4.10, p<.001). Specifically, there were greater odds of drinking more on cannabis use days vs. non-use days for recreational users compared to medicinal(Gunn et al., 2019).

Cannabis use disorder is elevated among veterans

Rates of CUD(previously called cannabis dependence or abuse) are on the rise among the general population, a trend attributed to dramatic changes in legislation (Grucza, Agrawal, & Bierut, 2016; Hasin et al., 2017; Wall, Keyes, Hasin, Galea, & Cerdá, 2011). However, rates of CUD may be increasing more rapidly among veterans. For instance, between 2002 and 2009, the prevalence of CUD diagnosis among U.S. veterans in the VHA increased 50% while prevalence in the general population remain unchanged (Bonn-Miller & Harris, 2012). Rates of other SUDs in veterans also remained unchanged (Bonn-Miller & Harris, 2012). Despite the drastic increase, these estimates may underreport the true prevalence as CUD diagnosis was 100% in a clinical sample of 82 consecutively recruited military veterans compared to the 22.8% of VHA records with CUD diagnosis (Bonn-Miller & Bucossi, 2012). Among post-9/11 veterans (n=323) with lifetime cannabis and alcohol use, 15% met criteria for CUD (Miller, Metrik, Borsari, & Jackson, 2019). However, a recent analysis of NESARC-III data indicated similar rates of CUD (and other illicit drug use) among self-identified veterans and non-veterans (Boden & Hoggatt, 2018). Data from the VET registry illustrates that the probability of transitioning from exposure to initiation of use was highest for cannabis compared to any other drug. Moreover, most who used cannabis continued use and became regular users, with one-third of regular users going on to develop cannabis abuse/dependence (Tsuang et al., 1999). Further, a latent class

analysis of the VET registry (n=2506 cannabis users) revealed that reported specific profiles of subjective effects of cannabis use were associated with cannabis dependence (Grant et al., 2005).

The potentially elevated rate of CUD among veterans is critical given that it may increase susceptibility of an already vulnerable group to other negative outcomes. For instance, CUD has been associated with greater odds of inpatient hospitalization among veterans with SUD and severe mental illness (Painter et al., 2018), having poly-SUDs (Bhalla, Stefanovics, & Rosenheck, 2017) and accidental overdose death (Cox hazard ratio=2.86, p<.001)(Bohnert et al., 2012). More specifically, CUD has been associated with accidental medication-related (Cox hazard ratio=2.39, p<.001) and alcohol/illegal drug-related accidental overdose (Cox hazard ratio=3.63, p<.001), exceeding the risk of any psychiatric disorders examined (Bohnert et al., 2012). A 2019 study also revealed that 80% of veterans with CUD also reported other mental health disorders as well (Ecker, Lang, Hogan, Cucciare, & Lindsay, 2020). These factors are critical given that veterans with poly-SUDs present with more numerous and serious medical and psychiatric comorbidities in addition to greater service utilization (Bhalla, Stefanovics, & Rosenheck, 2017; Ecker et al., 2020).

Factors that impede and promote cannabis cessation attempts among veterans

Within community-based substance use treatment programs it seems that non-veterans may be more likely to report cannabis as the primary problem substance (21% vs. 8%) whereas for veterans this is often alcohol (66% vs. 49%)(Yu, Hussain, & Appel, 2015). However, given rates of CUD, it is not surprising that a prominent cannabis-cessation literature exists.

Certain factors may serve as relevant impediments to cannabis cessation. For instance, higher levels of anxiety, depression and insomnia have been associated with less confidence in one's ability to change cannabis use (Morris et al., 2018). Among cannabis-dependent veterans specifically, those with

greater perceived distress tolerance may use less cannabis during self-guided quit attempts (Hasan, Babson, Banducci, & Bonn-Miller, 2015). Similarly, good perceived sleep quality was also associated with less cannabis use during a self-guided quit attempt while sleep efficiency and duration were unrelated (Babson, Boden, & Bonn-Miller, 2013). Poor pre-quit sleep quality, on the other hand, was associated with greater risk for lapse within the first two days following the quit attempt (Babson, Boden, Harris, Stickle, & Bonn-Miller, 2013). Fewer difficulties with emotion regulation were associated with a greater reduction in panic symptoms, it was unrelated to cannabis use outcomes in a sample of cannabis-dependent veterans following a quit attempt (Galang, Babson, Boden, & Bonn-Miller, 2015). Delayed discounting (an index of impulsivity) did not predict any cannabis-cessation outcomes (Heinz, Peters, Boden, & Bonn-Miller, 2013) despite impulsivity serving as an important risk factor associated with the stages of substance use. Higher impulsivity was however related to greater compulsive craving and previous failed quit attempts, among other factors (Heinz et al., 2013).

Physical activity may be predictive of success with a cannabis cessation attempt, and consequently may be an effective early intervention strategy among veterans who use cannabis (Irons et al., 2014). There may also be promise in using telephone-administered motivational interviewing to enhance mental health treatment in Iraq/Afghanistan veterans (Seal et al., 2012) as greater engagement in mental health treatment is associated with significant reductions in stigma and cannabis use at 8 weeks ($p<.05$)(Seal et al., 2012). Further, a randomized trial of motivational interviewing and CBT for physical aggression and substance use reduced physical aggression, partner injury , cannabis and other substance use (Chermack et al., 2019).

Interestingly, two barriers to CUD treatment in the VA include potential negative consequences of being diagnosed with CUD, and also a veteran's perception of cannabis having a positive influence

on their medical and psychological symptoms. However, formal assessment approaches for SUD may facilitate discussion of use and available treatment options (Bujarski et al., 2016).

Cannabis use changes during the military to civilian transition

Three studies discussed changes in cannabis use throughout the military career. The first focused on veterans returning to low-income, predominantly minority communities (n=249)(Golub & Bennett, 2014). In this sample, cannabis was the most common illegal drug used prior to entering the military (54.9%). Although use decreased while in the military (20.0%); it increased following return to civilian life (33.7% from 8.8% at the previous deployment, p<.01). Interestingly, heavy and binge-drinking decreased during this transition despite being the most commonly use substance (Golub & Bennett, 2014). A more recent study chose to focus on a smaller but more generalizable veteran sample (n=80)(Derefinko et al., 2018). Here, the active duty to post-separation transition revealed statistically significant increases in cannabis (3.7% to 26.2 %, p<.001) and other illicit drug use (4.9% to 11.4%, p<.013)(Derefinko et al., 2018). Whereas, alcohol, cigarette and prescription drug use were sustained (Derefinko et al., 2018). Increases in post-separation cannabis were related to cigarette (r=0.34, p<.001) and cannabis (r=0.31, p<.001) use during active duty (Derefinko et al., 2018). Finally, habitual cannabis use may be more common while in the military than in civilian life (23.1% vs. 10.3%) as indicated by a telephone follow-up of members of the Veterans Experience Study where they specified habitual use during military service and during civilian life (White, Mortensen, & Batty, 2012). These results suggest that cannabis use is a particularly dynamic behaviour among veterans.

Mental health among veterans who use cannabis

The second most common focus was mental health among veterans who use cannabis (Table 2).

Mental health problems, particularly PTSD and depression are common among veteran populations (Seal et al., 2009) and symptoms of these conditions are strongly related to cannabis use (Boden et al., 2013; Cheung et al., 2010). Veterans who reported cannabis misuse, and were discharged by means other than honourable, had higher rates of general anxiety, depression, history of traumatic brain injury and alcohol misuse (Brooks Holliday & Pedersen, 2017). Whether these associations speak to veterans pursuing cannabis to treat such symptoms or whether cannabis use exacerbates such symptoms is unclear (Black et al., 2019; Turna et al., 2017). Nonetheless, psychiatric disorders (e.g., PTSD) are common qualifying conditions for medical cannabis use in several U.S. states (Wilkinson, Radhakrishnan, & D'Souza, 2016). In Canada, any condition can be treated as long as it is supported by physician authorization, and psychiatric conditions lead the reasons for pursuing cannabis treatment in Canadians (Rotermann & Macdonald, 2018). Common themes in these studies included the overlap of PTSD, internalizing psychiatric disorders (depression and anxiety), self-harm, and sleep with cannabis use.

PTSD and cannabis use among veterans

The literature highlights the co-occurrence of CUD and PTSD among veteran samples. Almost 20% of individuals seeking PTSD treatment present with CUD (Calhoun et al., 2000), and this profile is associated with poorer treatment outcomes (Bonn-Miller et al., 2012) including lower levels of improvement (between treatment intake and discharge) in overall PTSD symptom severity and PTSD avoidance-numbing and hyperarousal symptom severity (all $p<.05$)(Bonn-Miller et al. 2013). The

majority of studies generally suggest that cannabis use is elevated among veterans with PTSD, associated with greater symptom severity and aggression.

This significant comorbidity between PTSD and cannabis misuse is critical to note as PTSD is often cited as reason for cannabis treatment, being an attractive option for those who have previously failed more conventional therapies (BonnMiller, Vujanovic, & Drescher, 2011). Among veterans, the therapeutic effect of cannabis on PTSD is limited to 1 retrospective chart review of 100 treatment-seeking Canadian police and military veterans with PTSD (Smith et al., 2017). During a treatment period which ranged between <3 months up to 18 months after baseline, significant reductions in PTSD symptomatology were noted (mean score of 7.0 to 2.9, 59% reduction), as per symptom rating on a scale of 0 to 10 (with 10 being the most severe or negative). Scored PSTD symptomology included symptoms of anger and irritability, anxiety, avoidance, depersonalization, among others. Patients were also asked to rate how PTSD affected their social and family life (marital/relationship harmony, personal beliefs, etc.). Similarly, suicidal thoughts (77% reduction), anxiety (59% reduction) and depression (60% reduction) also improved at follow-up (Smith et al., 2017). It is critical to note that the mean dose reported by participants was 9.4g/day of cannabis, where a ceiling dose of 10g/day was advised. For context, 0.5-1 g of cannabis is the equivalent of 1 joint (Freeman & Lorenzetti, 2019) as such these individuals were on a high daily dose. Further, cannabis expectancies may impact the reported "effectiveness" of this treatment as suggested by a study of 650 combat-exposed veterans, who used cannabis at least once a week. Here, veterans who used cannabis appeared to use more as the magnitude of PTSD symptoms and their expectations of cannabis-induced relief of those symptoms increased (Earlywine & Bolles, 2014). Further, veterans who do not show improvements in PTSD symptoms following intensive PTSD treatment are significantly more likely to either relapse (among prior users) or initiate (among naïve users) cannabis (BonnMiller, Vujanovic, & Drescher, 2011) suggesting a link

between the two. As such, it is critical that the objective efficacy and safety of cannabis for these conditions be evaluated.

The literature regarding PTSD and risk of relapse to cannabis is mixed. For instance, a prospective evaluation of a self-guided cannabis cessation attempt revealed that those with PTSD were more likely to use cannabis at a higher rate and take longer to reduce cannabis use at the beginning of the cessation period(Bonn-Miller et al., 2015). Another study also revealed that veterans who relapsed a month into their quit attempt had higher PTSD symptom severity (Carter et al., 2016). Finally, participation in a 12-step self-help group predicted more distal cannabis abstinence; however, presence of an Axis I psychiatric disorder at intake was associated with a lower likelihood of abstinence at 1-year (Bonn-Miller, Zvolensky, and Moos 2011). Empirical evidence also suggests that veterans with CUD who abstain from cannabis for the purpose of intensive PTSD treatment are less likely to receive PTSD treatment benefits than their non-CUD counterparts (Bonn-Miller, Boden, Vujanovic, & Drescher, 2013).

Finally, a recent study of male veterans (n=449) from the National Longitudinal Study of Adolescent to Adult Health (Waves I and IV; 1994-2008) utilized structural equation modelling to examine mental health and substance use among pre- and post-9/11 veterans (Cancio, 2019). Overall, this analysis revealed that among pre-9/11veterans, depression and anxiety predicted higher cocaine and prescription drug use; whereas, among post-9/11 veterans PTSD and depression predicted greater cannabis use in addition to methamphetamine and prescription drug use (Cancio, 2019). Not only do these results provide additional evidence for the relationship between mental health and cannabis use among veterans, but also suggest that post-9/11 (OIF/OEF/OND) veterans may be a group of particular interest when examining cannabis use.

Symptoms of depression and anxiety among veterans who use cannabis

In addition to PTSD, Pedersen et al. (2018) examined the relationship between cannabis problems and depression (Pedersen, Villarosa-Hurlocker, & Prince, 2018). While the number of days cannabis was used did not differ between depressed and non-depressed participants, those who screened positive for depression reported more cannabis use problems (2.76± 3.90 vs. 1.48±197, p<.02)(Pedersen et al., 2018). An earlier study also revealed similar results where a diagnosis of depression was significantly associated with greater number of cannabis problems (p<0.001) (Metrik et al., 2016). Cannabis quantity may also be associated with depression (r=0.21, p<.05) and positive (r=0.24, p<.05), but not negative cannabis expectancies (Farris, Zvolensky, Boden, & Bonn-Miller, 2014). There was a significant effect of depression on quantity of cannabis use (b=0.032, p=0.039), with greater depressive scores predicting greater quantity of cannabis use (Farris et al., 2014). However, whether these effects are cannabis-specific is unclear as VACS data revealed that current depression was associated with current use of all examined substances (cannabis, OR=1.33-1.38, p<.001), with the exception of unhealthy alcohol use (Ruggles et al., 2017).

Two studies have attempted to further clarify the mechanism surrounding cannabis use problems and depression, focusing specifically on impulsivity and motives for use. The first examined impulsivity among veterans (n=357) who used cannabis at least once in their lifetime (Gunn, Jackson, Borsari, & Metrik, 2018). Only negative urgency (characterized by rash action when experiencing emotional distress), but not other impulsivity traits, partially accounted for the relationship between depression and cannabis problems (Gunn et al., 2018). However, impulsivity was not predictive of cannabis use despite significant bivariate associations (Gunn et al., 2018). Another study evaluated the effect of cannabis use

motives (i.e. coping, situational anxiety and sleep) on the relationship between depression and cannabis use/problems among OEF/OIF/OND veterans (n=301)(Metrik et al., 2016). Mediation analyses revealed that all three motives partially accounted for the strong association between depression and cannabis use, related problems and CUD (Metrik et al., 2016).

Depression has also been shown to independently predict CUD (*OR*= 1.78, *p*<0.01)(Metrik et al., 2016). Further, a co-twin analysis of the VET registry (n=234 twin pairs) revealed that only a lifetime diagnosis of DSM-III-R major depression remained significantly associated with lifetime diagnoses of cannabis (AOR=2.3), amphetamine (AOR=5.8,) and sedative abuse/dependence (AOR=10.9)(all p<.0001) after controlling for familial factors (Lin et al., 1996).

Surprisingly, anxiety did not emerge as a prominent variable in this literature. One study reported that frequency of cannabis use was not associated with anxiety sensitivity (tendency to fear anxiety-related bodily sensations) among OIF/OEF veterans (n=138) (Stewart et al., 2019). However, there were main and interactive effects of cannabis use frequency and anxiety sensitivity on physical health and functioning (Stewart et al., 2019). Moreover, mediation analyses revealed that situational anxiety partly accounted for the relationship between PTSD and depression in cannabis use frequency, cannabis problems and CUD (Metrik et al., 2016).

Self-harm

Meta-analyses have suggested that heavy cannabis use may be associated with suicidal and non-suicidal self-injury (Borges, Bagge, & Orozco, 2016; Giletta, Scholte, Engels, Ciairano, & Prinstein, 2012). Such behaviours are major concerns among veterans, particularly due to the high rates of psychiatric disorders and other risk factors noted. In a sample of 292 Iraq/Afghanistan-era veterans, CUD was significantly associated with suicidal (OR=3.10, p=0.045) and non-suicidal self-injury (OR=5.12, p=.009) even after

adjusting for a wide variety of covariates including PTSD, depression and non-cannabis drug use disorders (Kimbrel, Meyer, DeBeer, Gulliver, & Morissette, 2018). Another study went on to reveal that CUD was also associated with current suicidal ideation (OR=1.68, p=0.008) and lifetime suicide attempts (OR=2.30, p<.0001) among 3233 Iraq/Afghanistan veterans even after relevant covariates like sex, history of childhood sexual abuse and combat exposure were considered (Kimbrel et al., 2017). Cannabis dependence was associated with post-deployment suicide attempts regardless of pre-deployment suicide attempts (*AOR*=7.96, *p*=.014) (Adkisson et al., 2016). One study, using national VHA records, revealed that CUD was associated with risk of completed suicide (unadjusted analysis)(Bohnert, Ilgen, Louzon, McCarthy, & Katz, 2017). However, after adjusting for other factors, most notably psychiatric disorders, the association of CUD and risk of completed suicide decreased markedly. The association remained significant for men, but not women once co-occurring psychiatric diagnoses were adjusted for (Bohnert et al., 2017)

Sleep

No studies have examined the therapeutic effects of cannabis on sleep in veterans. Preliminary work suggests that short-term cannabis use may have a therapeutic impact (specifically sleep onset latency and slow wave sleep), however, it may impair sleep in the long-term (Babson, Sottile, & Morabito, 2017). In a sample of cannabis -dependent veterans enrolled in a cannabis cessation study, poorer sleep quality was noted in those with lower distress tolerance (Short et al., 2016). Similarly, a pilot study explored changes in cannabis use and sleep following mobile-delivered CBT for insomnia during a cannabis cessation attempt. Based on a small sample of 4 (n=2 for CBT-I app vs. n=2 control mood app), patients using the app reported decreased cannabis use and improved sleep efficiency and one patient reported increased sleep quality (Babson, Ramo, Baldini, Vandrey, & Bonn-Miller, 2015). In

the control group, 1 participant withdrew and the other reported increased sleep quality but also increased cannabis use (Babson et al., 2015).

Other Conditions

Two studies examined antisocial personality disorder (ASPD) and cannabis use using VET registry data. Among 99 cannabis discordant twin pairs, those with a lifetime history of cannabis abuse/dependence (compared to those that never abused any drug) had more ASPD symptoms (Scherrer et al., 1996). Moreover, ASPD may also be associated with increased risk of CUD, major depression and AUD (Fu et al., 2002). Among veterans with Obsessive-Compulsive Disorder in VHA administrative data (N=38,157), 36.70% also had a SUD diagnosis (Ecker et al., 2019). The most common were AUD (36.70%), tobacco use disorder (26.20%), and CUD (5.53%), which, in the latter case, still exceeded rates of general population.

Physical health outcomes among veterans who use cannabis

In addition to psychiatric conditions, cannabis and cannabinoid-therapies are often sought to alleviate a variety of physical symptoms. Analgesia is one of the most frequently cited reasons for cannabis-based therapies (Nugent et al., 2017). Although the list of cannabis' purported therapeutic effects is vast, the literature describing this is severely lacking. Finally, only a small number of studies focused on physical symptoms, strictly pain and HIV (Table 3).

Pain

Older meta-analyses suggest moderate quality evidence for smoked THC and nabiximols (Whiting et al., 2015), however recent work proposes that the benefits of cannabis/cannabinoid therapies may in fact be outweighed by their harms (Mücke, Phillips, Radbruch, Petzke, & Häuser, 2018; Stockings et al., 2018).

Despite high levels of cannabis use for analgesic purposes among veterans, our search only returned one negative crossover RCT of 28-days of dronabinol (5-25mg/d) and diphenhydramine (25-75mg/d) (Rintala, Fiess, Tan, Holmes, & Bruel, 2010). In this sample of 7 veterans with spinal cord injury, dronabinol (mean change in pain rating: 0.20±0.837 vs. -1.80±2.490) was no more effective in alleviating neuropathic pain below level of injury (Rintala et al., 2010).

Risky substance use is also a concern among veterans using cannabis for pain. Rates of CUD among veterans with non-cancer pain receiving opioid medication have ranged from 1.98% to 3.92% (Hefner, Sofuoglu, & Rosenheck, 2015). Compared to those without CUD, those prescribed opioids who also had a CUD diagnosis were significantly younger, more likely to be homeless, have more mental health problems and utilize greater health services (Hefner et al., 2015). However, motivational interviewing may be able to reduce risky substance use in veterans with certain forms of pain. Specifically, veterans with musculoskeletal injuries that received a motivational interview-based intervention focusing on engagement in pain treatment and reducing risky substance use, were significantly less likely to use substances over time compared to those receiving treatment-as-usual or only the pain module (β=-0.13, =0.015). However, looking at individual substances, whether the findings are applicable to those engaging in risky cannabis use specifically was unclear (β=-0.12, *P*=0.269)(Rosen et al., 2019).

Human Immunodeficiency Virus

Research on substance use and HIV has yielded equivocal results and the body of literature among veterans is limited. Among 6351 HIV-infected and uninfected veterans from the VACS, a latent class analysis revealed 5 classes: non-users, past primarily cannabis users, past multidrug users, current high consequence multidrug user, and current low consequence primarily cannabis users (Green et al., 2010).

Non-users were most prevalent among uninfected individuals; whereas, HIV status was strongly represented by current high consequence multidrug users. HIV+ veterans were more likely than uninfected individuals to also be current low consequence cannabis users. Despite chronic cannabis use, the cannabis using groups did not reveal high rates of CUD (Green et al., 2010). Similarly, an analysis of VACS data of 3099 HIV-infected men revealed that compared to lower risk alcohol use, cannabis use ($\beta=-0.97$, $p=0.048$) was not associated with increased mortality whereas stimulant use was ($\beta=1.08$, $p=0.021$)(Adams et al., 2018).

DISCUSSION

Cannabis use is associated with a variety of risks and negative sequelae, and veterans may be a particularly vulnerable group to such effects. As a group with high rates of cannabis use, often for medical reasons, delineating the extent to which cannabis use is positive or negative is critical. Overall, the literature provides a number of insights into associations with cannabis use among veterans. First, some veterans who use cannabis report greater substance use behaviours, typically heavy or problematic alcohol consumption. Though there are other studies to suggest that there is no difference in substance use behaviours, unless the distinction between medical and recreational users is taken into consideration. Further, studies repeatedly show that veterans who use cannabis report either worse or the same levels of mental health problems as veterans who do not use cannabis. To date, only one retrospective analysis has suggested improvement in PTSD symptoms in veterans. However, whether the association with worse mental health symptoms is related to the fact that cannabis use leads to mental health problems or that many treat mental health problems with cannabis has yet to be elucidated. In terms of variables associated with physical health, the literature is quite scarce and consequently difficult to develop conclusions. Further, attempts to quit cannabis may be complicated by these variables associated with cannabis use, as suggested by cannabis cessation studies. However, the existing cannabis cessation literature is limited by several factors thus providing only a partial understanding.

The largest literature to emerge was cannabis and other substance use among veterans. Upon closer inspection this literature suggested that cannabis use may be associated with problematic use of other substances. Specifically, just using cannabis (non-problematic consumption) may increase susceptibility to problematic use of other substances. Of course, we are unable to preclude the possibility of individuals who use cannabis simply being more open to other substance use, especially legal substances like alcohol and nicotine. Veterans may also be at greater risk of CUD which requires critical

consideration given the high rates of cannabis use in this group. Despite increased uptake of cannabis among veterans, we do not have accurate representations of what prevalence rates actually are in this population. Further, the differences in substance use behaviours among veterans using medical versus recreational cannabis also highlights the importance in characterizing at-risk veteran groups.

On the topic of medical cannabis use, mental health conditions often lead lists describing reasons for pursuing therapeutic cannabis in Canada and the US (Rotermann & Macdonald, 2018). Given the high rates of mental illness among veterans and uptake of medical cannabis, one may anticipate a sizeable literature supporting this indication, yet the current review only found one study describing the therapeutic potential of cannabis for PTSD (Smith et al., 2017). Further, the quality of evidence of this retrospective study of treatment-seeking Canadian veterans and police officers is quite low highlighting the lack of evidence for a treatment that is widely sought by this vulnerable population. Although this is the first review of cannabis use among veterans, reviews have generally suggested that heavy cannabis use is associated with an increased risk of depressive disorders (Lev-Ran et al., 2014), psychotic disorders (Moore et al., 2007), SUDs (Hasin, Perez, & Ghose, 2017) and adverse mental health effects (Nugent et al., 2017) in the general population. Moreover, the current review identified a robust association with self-harm. A 2017 systematic review of the benefits and harms of cannabis for PTSD revealed that there was insufficient evidence to draw any conclusions (O'Neil et al., 2017). While the current review provides a similar conclusion for cannabis and PTSD in veterans, it is critical to note that the mixed literature here is one that suggests either no consequence or a negative association with cannabis use, rather than a positive one. This is especially important given that in this population cannabis is being used to treat PTSD. Moreover, the previous review did not describe co-occurrence rates of CUD and PTSD, meaning that a large part of the cannabis and PTSD story was not addressed. Other sections of the current review also provide compelling evidence regarding negative non-PTSD

related outcomes like self-harm, decreasing the overall support for cannabis as a PTSD treatment in veterans groups. Finally, PTSD symptomatology may not only impede cannabis cessation but cannabis use may impede PTSD treatment overall. Therefore, the insufficient literature regarding the therapeutic potential of cannabis for PTSD paired with work suggesting the possibility that the symptoms being treated may in fact complicate cessation suggests that cannabis used to treat PTSD among veterans specifically needs to be carefully evaluated.

Similar to psychiatric conditions, the literature addressing cannabis for physical symptoms is also limited. Despite analgesia often cited as a reason for medical cannabis use in veteran populations, this literature is severely limited, with only one small negative pilot RCT in veterans with neuropathic pain following spinal cord injury (Rintala et al., 2010). While it was long purported that the analgesic effects of cannabis are supported by scientific evidence, recent meta-analyses have brought to light the fact that the harms (adverse effects) likely outweigh the benefits for chronic non-cancer pain (number-needed-to-treat [NNT] < number-needed-to-harm [NNH])(Stockings et al., 2018), although this review did not focus on veteran populations. Given that some of the most anecdotally supported and frequently prescribed indications (e.g., PTSD and chronic pain) are severely lacking scientific merit and instead paired with exacerbations of the conditions they claim to treat, there is an alarming gap in the literature that needs to be addressed.

Beyond the lack of studies examining therapeutic efficacy, weaknesses in overall study design detract from the overall quality of the existing literature. For instance, an overwhelming majority of studies were cross-sectional in design. Although cross-sectional studies are critical to the research process, longitudinal and prospective studies are required to appropriately assess the extent to which veterans are impacted by cannabis use. Further, female veterans are severely underrepresented in the literature, with most veteran study samples being 70% or more male. Although veterans are

predominantly male, female veteran populations are growing with the expectation that the proportion of female veterans will grow to 15.9% by 2040 in the U.S (Aponte et al., 2017) and in Canada 14% of veterans are female at present (Veterans Affairs Canada, 2015). As such, not only does more work need to be done in veterans, but female veterans should also be recruited in a representative fashion. Further, literature from outside the U.S., specifically the VA, is scarce, highlighting the need for additional research. The few studies from other nations also support the notion of elevated cannabis use among veterans. At present, Veterans Affairs Canada will automatically reimburse to Canadian veterans up to 3g per day of dried cannabis (or its equivalent of fresh cannabis or cannabis oil) and up to 10g daily with a supplemental authorization (Veterans Affairs Canada, 2018.). In the 2018-19 fiscal year Veterans Affairs Canada reimbursed cannabis to 10,466 veterans amounting to over $74M. Given the lack of literature demonstrating therapeutic efficacy and the possibility for harm, perhaps such guidelines should be revisited.

It is also critical to note that several studies of veterans appear to be samples of convenience versus the population of interest. Specifically, a number of studies do not reference the study findings within a veteran's context and instead simply use the results to describe associations with substance or cannabis use. This can be problematic, particularly when discussing substance use and mental health, as the literature is clear that veterans are not representative of the general public. In particular, rates and trajectories of these conditions are more severe among veterans. Further, studies specifically focusing on cannabis were limited as many focused on SUD's in general with a minor comment on CUD or cannabis use behaviours.

Overall, the balance of the evidence implicates cannabis use with negative health outcomes in veteran populations. Although the study designs do not permit causal inference, the results at least suggest that cannabis use is a fellow traveler with a wide variety of health ills, psychiatric and physical.

As such, priority areas for future research should include studies using designs that can more conclusively examine the directionality of links between cannabis and health in veterans. For instance, studies directly examining efficacy of cannabis (or cannabinoids) in veteran populations would be of interest. In particular, Studies evaluating efficacy in PTSD and chronic pain are of utmost importance given the mixed literature and high interest of use for these purposes among veteran groups. No less, future clinical trials should systematically characterize potential harms including risk for problematic substance use, mental health or other functional outcomes. Legislative changes regarding medical cannabis and rate of prescription, particularly in veterans, have both already outpaced clinical tests of its effectiveness, but that is a case for more evidence, not abandoning the need for evidence. To the question of whether veterans have more to gain or lose from cannabis, the answer is that the lion's share of the evidence suggests greater risk of harm than benefit, although absence of evidence of therapeutic efficacy is not evidence of absence. Directly addressing these questions with methodologically rigorous design will be essential to inform clinical recommendations and practices guidelines in an era of burgeoning access to medical and recreational cannabis.

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ABSTRACT

Policy changes have resulted in dramatic increases in access to cannabis for medical purposes. Veterans are disproportionately affected by conditions for which medical cannabis is often pursued, making an evidence-based perspective on risks versus benefits of high priority. The current review sought to examine the state of the evidence on consequences and correlates of cannabis use among veterans. Using a comprehensive search strategy, 501 articles were identified and 86 studies met criteria for inclusion. The literature was predominated by cross-sectional studies (67%) of male veterans (71.4%-100% male) from the United States (93.0%). Three overarching themes emerged, comprising cannabis associations with other substance use, mental health, and physical health outcomes. The balance of the evidence associated cannabis use with negative health outcomes, with consistent positive associations with other substance use, psychiatric disorders, and self-harm/suicidality. Few studies examined the therapeutic effects of cannabis, thus limiting the potential to evaluate evidence of efficacy. Priority areas for future research are studies using designs that can examine the directionality of links between cannabis and health in veterans more conclusively, and studies directly examining therapeutic efficacy of cannabis-based therapies in veterans. Methodologically rigorous design will be essential to inform clinical recommendations and practices guidelines in an era of burgeoning access to cannabis.

Keywords: veterans, cannabis, marijuana, post-traumatic stress, pain

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Jasmine Turna and James MacKillop contributed equally to this article.

Conflict of Interest
James MacKillop is a principal in Beam Diagnostics Inc. Jasmine Turna has no conflicts of interest to declare.

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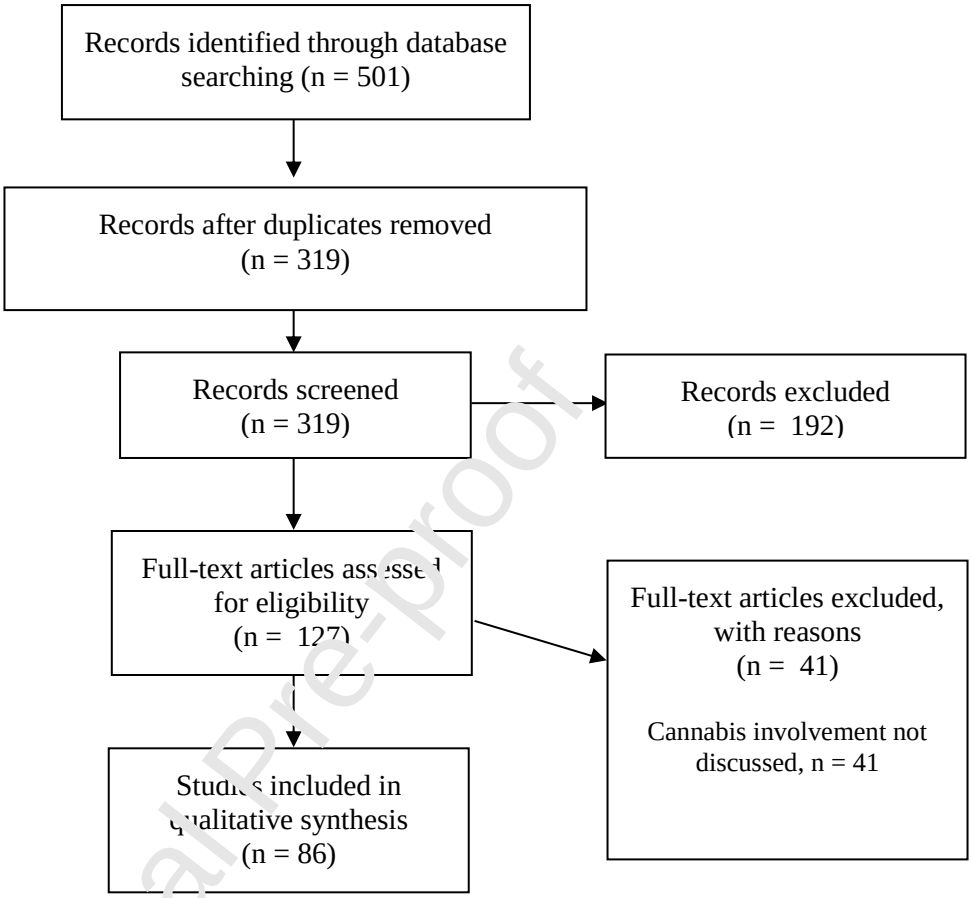

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) study flow diagram

Highlights

- First systematic review of the empirical literature on correlates and consequences of cannabis use in military veterans.

- The literature predominantly comprises cross-sectional studies; few studies have used longitudinal or RCT study designs.

- Cannabis use is associated with primarily negative outcomes, including other substance use, greater psychiatric severity, and self-harm/suicidality.

- Very few studies have examined the therapeutic efficacy of medical cannabis in veterans and those that have are of low quality methodologically.

Table 1. Studies investigating cannabis and other substance use.

Author	Year	Location	Sex Ratio (% male)	Sample Size	Conflict	Study De
RANDOMIZED CONTROLLED TRIALS						
Chermack et al.	2019	U.S.	92.0%	N=180 veteran in treatment for SUDs	- Not specified	Impact o interventi CBT+12- TAU) de aggressio
Seal et al.,	2012	U.S.	64.4%	N=73 VA enrolled veterans with mental illness	- OEF/OIF	Efficacy to enhanc
LONGITUDINAL OBSERVATIONAL STUDIES						
Gunn et al.	2019	U.S.	93.0%	N= 115 veterans reporting cannabis and alcohol co-use in past 18-months	- OEF/OIF	Drawn fr cannabis
Miller et al.	2019	U.S.	93.0%	N=325 veterans reporting lifetime EtOH use and CU	- OEF/OIF/OND	Sample c examinin behaviors
Painter et al.	2018	U.S.	94.8%	N= 470,548 VHA patients with SUD and/or SMI	- Portion of OIF/OEF veterans represented	Retrospe utilizatio sample o and one y
Ruggles et al.	2017	U.S.	95.9%	N=5479 veterans who reported EtOH intake and cigarette use	- Not specified	Data fron
Jin et al.	2017	Canada	96.0%	N=101 military and police veterans with PTSD	- Not specified	Retrospe baseline 8.25-mo
Carter et al.	2016	U.S.	81.0%	N=116 CUD+ veterans	- 59% Vietnam Era	Associati support c
Bonn-Miller et al.	2015	U.S.	95.2%	N=104 CUD+ veterans with quit intentions	- Not specified	Prospecti success f quit.
Galang et al.	2015	U.S.	Not reported	N=104 CUD+ veterans with quit intentions	- Not specified	No comp attempt.
Hasan et al.	2015	U.S.	95.0%	N=103 cannabis dependent veterans	- Not specified	No comp 5-mo pos
Marshall et al.	2015	U.S.	100%	N=1065 male HIV+ veterans	- Not specified	Subsamp
Irons et al.	2014	U.S.	96.4%	N=84 cannabis dependent veterans	- Not specified	No comp week of a
Golub & Bennett	2014	U.S.	85.1%	N=269 veterans discharged in past 2 years living in low-income areas	- OEF/OIF	Veterans specific t

Babson et al.	2013	U.S.	94.5%	N=55 cannabis dependent veterans	- Not specified	No comp week of a
Heinz et al.	2013	U.S.	95%	N=72 cannabis dependent veterans	- Not specified	No comp cannabis guided qu up.
Bohnert et al.	2012	U.S.	90.0%	N=3,291,181 VHA patients alive at FY 2000	- Not specified	Followed 2006.
Bonn-Miller et al.	2012	U.S.	2002: 96.3% 2008: 95.7% 2009: 95.3%	2002: n=289,904 2008: n=403,117 2009: n=448,669	-OEF/OIF	Retrospe patients r diagnosis
White et al.	2012	U.S.	100%	N=14,362	- Vietnam War	Analysis
Grant et al.	2010	U.S.	100%	N=293 monozygotic and dizygotic twin pairs discordant for early CU	- Vietnam Era	Co-twin VET Reg
Tsuang et al.	1994	U.S.	100%	N=630 inpatient AUD+ male veterans	- Not specified	Followed
CROSS-SECTIONAL STUDIES						
Ecker et al.	2020	U.S.	92.9%	N= 258,055	- Not specified	VHA pat of CUD b
Stewart et al.	2019	U.S.	93.5%	N=138	- OEF/OIF/OND	Part of a examinin related pr disorders
Boden & Hoggatt	2018	U.S.	Veteran group, 90.2%	n=3,119 veterans, N=36,301	- Not specified	Nationall survey, a identified
Browne et al.	2018	U.S.	0.0%	N=636 female veterans	- Not specified	Online su health.
Davis et al.	2018	U.S.	92.4%	N=2587 veterans from NSDUH	- Not specified	Data from
Derefinko et al.	2018	U.S.	90.1%	N=80	- Not specified	Retrospe last 6-mo civilian li
Feingold et al.	2018	Israel	95.4%	N=191 Israeli combat veterans	- Not specified	Online su
Metrik et al.	2018	U.S.	94%	N=127 veterans reporting >1 day of cannabis and EtOH co-use in past 180 d	- OEF/OIF/OND	Retrospe Drawn fr CU and a
Morris et al.	2018	U.S.	88.0%	N=278	- Not specified	Veterans use treatr
Bhalla et al.	2017	U.S.	95.4%	N=472,624 veterans ≥1 SUD diagnosis	- Not specified	Using na
Gentes et al.	2017	U.S.	100%	N=719 veterans in VA	73.2% Vietnam era	Prevalen

				PTSD clinic	10.6% Gulf War era 16.3% OEF/OIF	
Holliday & Pederson	2017	U.S.	87.6%	N=734 young adult veterans who received honorable, general or OTH discharge	- Most OEF/OIF/OND	Online sa aimed at behaviou
Loflin et al.	2017	U.S.	94.3%	N=1971 veterans who reported lifetime CU	- Not specified	Online as
Pedersen et al.	2017	U.S.	87.4%	N=812 young adult veterans	- Most OEF/OIF/OND	Online sa aimed at behaviou
Bujarski et al.	2016	U.S.	NA	N=39 treatment programs	- Not specified	Qualitati
Yu et al.	2015	U.S.	93.6%	N=81,471 veterans	- Vietnam era, Gulf War and OEF/OIF	Data fron with alco
Bonn-Miller et al.	2012	U.S.	96.4%	N=84 CUD+ veterans	- Not specified	Comparin retrospec
Grant et al.	2012	U.S.	100%	N=6,242 male twins (n=3,121 pairs)	- Vietnam era	Co-twin 1987 que diagnosti
Goldman et al.	2010	U.S.	91.7%	N=5492 VA patients	- Not specified	Reviewe Laborato
Kline et al.	2009	U.S.	Persian Gulf/Mideast: 96.7% Vietnam: 98.8% Post-Vietnam era: 95.7%	N=373 homeless veterans	- Vietnam era - Post-Vietnam era - Persian Gulf/Middle East era	Baseline between
Wagner et al.	2007	U.S.	Veteran group, 90.0%	n=12,072 veterans, N=184,339	- Not specified	Nationall analysis 2003 poo
Bauer et al.	2005	U.S.	Predominantly male (% not reported)	N=328 inpatient veterans with bipolar disorder	- Not specified	Acutely h from VA
Grant et al.	2005	U.S.	100%	N=2,506 veterans with lifetime CU	- Vietnam Era	Latent cl Registry.
Eisen et al.	2002	U.S.	100%	N=56 CU discordant monozygotic twin pairs	- Vietnam Era	Co-twin survey of
Tsuang et al.	1999	U.S.	100%	N=3,200 male-male twin pairs	- Vietnam Era	VET Reg

VHA = Veterans Health Administration; CUD = cannabis use disorder; SUD = substance use disorder; RCT = randomized Motivational interviewing and CBT; E-TAU = enhanced treatment as usual; OEF/OIF/OND = Operation Enduring Freedo Freedom/Operation New Dawn; EtOH = alcohol; CU = cannabis use; SMI= Serious mental illness; NSDUH = National Su PTSD = post-traumatic stress disorder; OTH = Other than honorable; VACS = Veteran Aging Cohort Study; HIV = human

VET = Vietnam Era Twin; SCID = structured clinical interview for DSM; VA = Veterans Affairs; AUD = alcohol use disc

Table 2. Studies investigating cannabis use and mental health outcomes.

Author	Year	Location	Sex Ratio (% male)	Sample Size	Conflict	Study Design
RANDOMIZED CONTROLLED TRIAL						
Babson et al.	2015	U.S.	100%	N= 4	- Not specified	Two-week intervention, receive either CBT-I Coach mobile app or placebo (mood tracking app)
LONGTUDINAL DESIGN						
Cancio	2019	U.S.	100%	N=449	Pre- and post-9/11 veterans	Analysis of Wave I and IV (1994 to 2008) from National Longitudinal Study of Adolescent to Adult Health.
Bohnert et al.	2017	U.S.	91.7%	n = 4,863,086 VHA users in FY2005 who were alive at FY 2006	- Not specified	Longitudinal design of suicide during 6 years of follow-up (FY2006-2011).
Smith et al.	2017	Canada	97.0%	N=100 military or police veterans	- Not specified	Retrospective chart review. Change in PTSD symptoms prior to medical cannabis initiation to first follow-up (av. 8.25 mo later).
Wilkinson et al.	2015	US	96.7%	N=2,276 veterans with PTSD	- Not specified	Patients of VA treatment program between 1992 -2011.
Bonn-Miller et al.	2013	U.S.	100%	N=260 combat-exposed veterans with PTSD	- Not specified	Analysis of veterans admitted to a VA residential rehabilitation program for PTSD between 2000 - 2008.
CROSS-SECTIONAL DESIGN						
Ecker et al.	2019	U.S.	82.2%	N=38,157 veterans with OCD	- Not specified	Co-occurrence of OCD and SUDs in VHA records from 2010 to 2016.
Loflin et al.	2019	U.S.	84.9%	N=93 veterans in Santa Cruz	- Not specified	Examining cannabis use among veterans with free access.

				Veterans' Alliance		
Stewart et al.	2019	U.S.	93.5%	N=138 veterans reporting past 6-mo CU	- OEF/OIF/OND	Baseline assessment of a longitudinal study of CU trajectories, CUD, related problems and concurrent affective disorders.
Adkisson et al.	2018	U.S.	81.8%	N=319	-OEF/OIF/OND	
Gunn et al.	2018	U.S.	94.0%	N=357 veterans reporting lifetime CU	- OEF/OIF/OND	VHA veterans based on self-reported lifetime cannabis use.
Kimbrel et al.	2018	U.S.	77.0%	N=292	-OEF/OIF/OND	
Metrik et al.	2018	US	94.0%	N=143 veterans who use cannabis	- OEF/OIF/OND	VHA veterans based on self-reported lifetime CU.
Pedersen et al.	2018	US	83.3%	N=180 young adult veterans reporting past 6-mo CU	- Not specified	Enrolled in RCT of brief online EtOH intervention study for young adult (18-34 years) veteran drinkers.
Buchholz et al.	2017	U.S.	93.3%	N=810 veterans entering VA mental health treatment	- Not specified	Analysis of baseline assessment from an RCT for SU and violence prevention intervention.
Kimbrel et al.	2017	U.S.	79.7%	N=3,233	-OEF/OIF/OND	
Davis et al.	2016	U.S.	94.0%	N=841 veterans receiving mental health or SUD treatment	- Vietnam Era, Post-Vietnam era, Persian Gulf Era and OEF/OIF/OND represented	Secondary analysis of screening data for an RCT of substance use and violence prevention.
Grant et al.	2016	US	87.7%	n = 790 young adult veterans (age 18-34)	- Targeted veterans of Iraq and Afghanistan conflicts	Pilot of data from larger online survey examining health and risk behaviours and attitudes of young adult U.S. veterans.
Johnson et al.	2016	US	91%	N=700 veterans with probable PTSD	- Not specified	Analysis of archived clinical data.
Metrik et al.	2016	US	94.7%	N=301 veterans	- OEF/OIF/OND	VHA veterans based on self-reported

						lifetime CU.
Sterniczuk & Whelan	2016	Canada	85.0%	N=120 CAF veterans	- Not specified	CAF veterans who report undergoing treatment for PTSD.
Short et al.	2016	U.S.	94.7%	N=94 CUD+ veterans	- Not specified	Self-report and behavioral analyses in treatment seeking veterans.
Jobe-Shields et al.	2015	U.S.	92.0%	N=94 treatment-seeking veterans with comorbid PTSD/SUD	- 59.6% of sample OEF/OIF/OND	Analysis of baseline data of large RCT (2.1% were active military).
Earleywine & Bolles	2014	US	100%	N= 653 combat-exposed veterans	- Not specified	Online survey of veterans who use cannabis >1 time/wk.
Farris et al.	2014	U.S.	95.0%	N= 100 cannabis dependent veterans	- 70% served during 1980-1990 8% OEF/OIF	Baseline data of larger self-guided cannabis quit study.
Flanagan et al.	2014	US	87.3%	N=97 veterans	- 64.9% OEF/OIF	Baseline assessment of RCT evaluating psychosocial treatment for co-occurring PTSD/SUD.
Boden et al.	2013	US	94.7%	N = 94 cannabis dependent veterans	- Not specified	Participants of larger predictors of cannabis relapse study following a self-initiated quit attempt.
Connell et al	2013	South Africa	100%	N= 54 veterans	- South African Border War	Online survey.
Cucciare et al.	2011	U.S.	100%	N=880 veterans with EtOH misuse	- Not specified	Males receiving care in VA outpatient mental health clinics receiving brief EtOH intervention.
Okulate & Jones	2006	Nigeria	99.8%	n = 878 veterans	- Liberian and Sierra-Leonean operations	All hospitalized patients between 1990-1994.
Fu et al.	2002	U.S.	100%	N=3,360 twin pairs	- Vietnam Era	Co-twin control design
Lin et al.	1996	U.S.	100%	N=1,874 twin pairs	- Vietnam Era	Co-twin control design. Telephone interview, subsample of VET Registry.
Radnitz et al.	1996	U.S.	Not	N=125	- Not specified	Data regarding psychiatric comorbidity in

			reported			sample of trauma exposed veterans with spinal cord injury.
Scherrer et al.	1996	U.S.	100%	N= 99 twin pairs (CUD discordant) and 1,697 monozygotic index twins	- Vietnam Era	Co-twin control design. Telephone survey of VET Registry members

OCD = obsessive-compulsive disorder; VHA = Veterans Health Administration; OEF = Operation Enduring Freedom; OIF = Operation Iraqi Freedom; OND = Operation New Dawn; SU = substance use; PTSD = posttraumatic stress disorder; CU = cannabis use; CAPS = clinician-administered PTSD scale for DSM-5; SCID = Structured Clinical Interview for DSM; EtOH = alcohol; CAF = Canadian Armed Forces; VET = Vietnam Era Twin; CUD = cannabis use disorder; RCT = randomized controlled trial; FY = fiscal year; VA = Veterans Affairs; SU = substance use; SUD = substance use disorder

Table 3. Studies investigating cannabis use and physical health.

Author	Year	Location	Sex Ratio (% male)	Sample Size	Conflict	Study Desi
RANDOMIZED CONTROLLED TRIAL						
Rosen et al	2019	U.S.	81.0%	N=257 veterans with joint pain	-OEF/OIF/OND	Single-blin PM, Pain m
Rintala et al.	2010	U.S.	71.4%	N=7 veterans with spinal cord injury	- Not specified	Double-blin 25mg/d) vs (25-75mg/d days.
LONGTUDINAL STUDIES						
Adams et al.	2018	U.S.	100%	N=3099 HIV+ veterans	- Not specified	Analysis of
CROSS-SECTIONAL STUDIES						
Lovejoy et al.	2016	U.S.	94.0%	N=214 veterans with chronic non-cancer pain and SUD history	- Not specified	Data extrac records.
Hefner et al	2015	U.S.	91.1%	N = 506,657 filled at least 1 opioid prescription	- Not specified	National sa with non-ca receiving o FY2012.
Green et al.	2010	U.S.	94.3%	N=6351 HIV+ and HIV- veterans	- Not specified	Analysis of

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OEF/OIF/OND = Operation Enduring Freedom; Operation Iraqi Freedom/ Operation New Dawn; RCT = randomized controlled trial; SBIRT-PM = Screening Brief Intervention and referral to Treatment – Pain Module; TAU = Treatment as Usual; VACS = Veterans Aging Cohort Study; HIV = Human Immunodeficiency Virus; SUD = Substance Use Disorders; VHA = Veterans Health Administration; FY = fiscal year