MDH Minnesota Department *of* Health
OFFICE OF MEDICAL CANNABIS

Post-traumatic Stress Disorder (PTSD)

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Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies of cannabis therapy are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Though the MN medical cannabis program does not allow smoked or vaporized dried cannabis, studies using these forms of cannabis administration were allowed for insight they could provide. Finally, the federal government-maintained web site of clinical trials, clinicatrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Post-traumatic stress disorder (PTSD; both "post-traumatic" and "posttraumatic" are used in different sources) is a mental disorder that evokes severe distress, chronic suffering and impairment. Its core symptoms comprise re-experiencing traumatic content, persistent avoidance of traumatic content, negative alterations in cognitions, and arousal and reactivity (American Psychiatric Association 2013). This condition causes significant occupational, medical, and psychosocial disability, and its consequences are enormously costly, not only to

the survivors and their family, but also to the health care system and society. Work impairment associated with PTSD is similar to the amount of work impairment associated with major depression (Brunello 2001).

The Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is the 2013 update to the American Psychiatric Association's classification and diagnostic tool. In the U.S. the DSM serves as the primary authority for psychiatric diagnosis. In prior editions of the DSM PTSD was grouped under anxiety disorders. In DSM-5 PTSD is no longer classified as an anxiety disorder, but instead falls under a new chapter, "Trauma- and Stressor-Related Disorders." In addition to this change of conceptualization and categorization, several changes were made in the diagnostic criteria. In order to be diagnosed with PTSD according to the DSM-5, a person needs to fill Criteria A through H, what is presented here summarizes the DSM-5 criteria (American Psychiatric Association 2013:

Criterion A – a person was exposed to one or more event(s) that involved death or threatened death, actual or threatened serious injury, or threatened sexual violation. In addition, these events were experienced in one or more of the following ways:

1. The event was experienced by the person
2. The event was witnessed by the person as it occurred to someone else
3. The person learned about an event where a close relative or friend experienced an actual or threatened violent or accidental death
4. The experienced repeated exposure to distressing details of an event, such as a police officer repeatedly hearing details about child sexual abuse

Criterion B – A person experiences at least one of the following intrusive symptoms associated with the traumatic event:

1. Reoccurring, involuntary, and intrusive upsetting memories of the traumatic event
2. Repeated upsetting dreams where the content of the dreams is related to the traumatic event
3. The experience of some types of dissociation (for example, flashbacks) where the person feels as though the traumatic event is happening again
4. Strong and persistent distress upon exposure to cues that are either inside or outside of a person's body that are connected to the person's traumatic evet
5. Strong bodily reactions (for example, increased heart rate) upon exposure to a reminder of the traumatic event

Criterion C – Frequent avoidance of reminders associated with the traumatic event, as demonstrated by one of the following:

1. Avoidance of thoughts, feelings, or physical sensations that bring up memories of the traumatic event
2. Avoidance of people, places, conversations, activities, objects, or situations that bring up memories of the traumatic event

Criterion D – At least two of the following negative changes in thoughts and mood that occurred or worsened following the experience of the traumatic event:

1. The inability to remember an important aspect of the traumatic event
2. Persistent and elevated negative evaluations about one's self, others, or the world (for example, "I am unlovable," or "The world is an evil place")
3. Elevated self-blame or blame of others about the cause or consequence of a traumatic event
4. A negative emotional state (for example, shame, anger, fear) that is pervasive
5. Loss of interest in activities that one used to enjoy
6. Feeling detached from others
7. The inability to experience positive emotions (for example, happiness, love, joy)

Criterion E – At least two of the following changes in arousal that started or worsened following the experience of a traumatic event:

1. Irritability or aggressive behavior
2. Impulsive or self-destructive behavior
3. Feeling constantly "on guard" or like danger is lurking around every corner (or hypervigilance)
4. Heightened startle response
5. Difficulty concentrating
6. Problems sleeping

Criterion F – the above symptoms last for more than one month

Criterion G – The symptoms bring about considerable distress and/or interfere greatly with a number of different areas of a person's life.

Criterion H – The symptoms are not due to a separate medical condition or some form of substance use.

Prevalence

A nationally representative face-to-face household survey of adult conducted in 2001-2003 using a fully structured diagnostic interview found 3.5% of the US adult population met DSM-IV criteria for PTSD (Kessler 2005). As part of an assessment of psychiatric morbidity among adults in England participants completed a screening tool for PTSD. The screening tool is aligned with some DSM-IV criteria categories, but authors indicate positive screening is likely to over-estimate PTSD prevalence based on a full clinical assessment. A total of 3.0% screened positive for PTSD, with a positive screening test decreasing from 4.7% among 16-24 year olds to 0.6% of adults aged 75 and over. No significant gender difference was found (McManus 2008).

Lifetime prevalence of PTSD has been estimated at 7.8%. Among groups at higher risk prevalence is higher. It has been estimated at over 50% among survivors of rape (Kessler 1995).

Current Therapies

Clinical practice guidelines are generally consistent in recommending certain forms of trauma-focused psychotherapy as first-line therapy for PTSD. The methods with most evidence of effectiveness are cognitive behavioral therapies (CBT), exposure therapy, and eye movement desensitization and reprocessing (EMDR) (Forbes 2010, VA/DoD PTSD guideline 2010). Though there is evidence that these psychotherapies have beneficial effects for some PTSD patients (Bradley 2005, Cloitre 2009, Steenkamp 2015, VA/DoD PTSD guideline 2010, Watts 2013), meta-analyses of clinical trials of these methods indicate the proportion of PTSD patients that achieve clinically significant symptom improvement is approximately 50% (Bradley 2005, Steenkamp 2015) and those with clinically significant symptom improvement often still have a substantial symptom burden (Bradley 2005). There is concern that the expansive exclusion criteria in most clinical trials of therapy for PTSD limit the degree to which their results can be generalized to the full range of persons with PTSD (Bradley 2005, Schottenbauer 2008). For example, in a review and meta-analysis of 26 studies of psychotherapy for PTSD the authors found that 46% of the studies excluded patients for suicide risk, 62% excluded patients for drug or alcohol use, and 62% used some version of "serious comorbidity" as an exclusion criterion (Bradley 2005). Interpretation of clinical trial results is complicated by a relatively high dropout rate (typically in range of 25 to 30%) that often isn't fully accounted for in analyses (Bradley 2005, Cloitre 2009, Schottenbauer 2008, Steenkamp 2015). Little is known about persistence of symptom improvement over time (Bradley 2005, Steenkamp 2015).

There is evidence of effectiveness of some pharmaceutical agents in treating PTSD, but their role appears to be secondary to psychotherapy. A recent meta-analysis of pharmacotherapy for PTSD commissioned by the World Health Organization assessed 51 randomized controlled trials. The authors found evidence of effectiveness for some selective serotonin reuptake inhibitors (SSRIs), but with relatively small effect sizes whose clinical relevance is unclear (Hoskins 2015). Authors of another meta-analysis reached a tentative conclusion that psychotherapy may be more effective than medication for the treatment of PTSD (Watts 2013). Most current clinical guidelines for treatment of PTSD consider medication a second-line therapy (Forbes 2010, VA/DoD PTSD guideline 2010). A Cochrane Collaboration review published in 2010 concluded there is not enough evidence available to support refute the effectiveness of combined psychological therapy and pharmacotherapy compared to either of these interventions alone (Hetrick 2010).

Among authors of review articles and meta-analyses of therapies for PTSD patients there is widespread agreement that on the need for improvement in existing PTSD treatments as well as the development and testing of novel evidence-based treatment strategies (Bradley 2005, Brunello 2001, Hetrick 2010, Hoskins 2015, Steenkamp 2015).

Pre-Clinical Research

There are numerous published articles on laboratory and animal research studies with findings likely relevant to PTSD. Presented here are just a few. de Bitencourt (2013) was chosen because it is a review article that covers many of these studies. Rabinak (2013) and Das (2013) were chosen because they present human models likely relevant to PTSD.

de Bitencourt RM, Pamplona FA, Takahashi RN. A current overview of cannabinoids and glucocorticoids in facilitating extinction of aversive memories: Potential extinction enhancers. *Neuropharm* 2013;64:389-395.

This paper outlines animal models of fear extinction and describes how these models have been used to examine the potential of extinction enhancing agents which specifically alter the endocannabinoid and glucocorticoid systems. Fear extinction is the gradual reduction in fear responses when an animal or person is exposed to a stimulus that once evoked a fear reaction.

There are a variety of methods of studying fear conditioning in animals, but they typically use a classic fear conditioning protocol. In this protocol, a previously neutral conditioned stimulus (CS) is paired with an unconditioned stimulus (US) such as a foot shock. In this method a scientist will play a tone (CS) before mildly electrocuting a rat's foot. Eventually, exposing the rat to only the US (e.g. the tone) without the CS (foot shock) will cause the rat to express fear behavior, hormonal changes, and other physiological responses. During extinction, conditioned fear response gradually decreases through re-learning with repeated omission of the aversive stimulus. Conditioned fear is also studied with operant conditioning paradigms, in which the US presentation occurs when the animal expresses (or refuses to express) a given behavior.

The review cites 16 studies that affirm the important role of the endocannabinoid system in the extinction of aversive memories, including several that showed stimulation of the CB1 receptors facilitated fear extinction. The final section of the paper concludes with a summary of the studies showing interaction between the glucocorticoid system and the endocannabinoid system.

Rabinak CA, Angstadt M, Sripada CS, Abelson JL, Liberzon I, Milad MR, Phan KL. Cannabinoid facilitation of fear extinction memory recall in humans. *Neuropharmacology* 2013;64:396-402.

A first-line approach to treat anxiety disorders is exposure-based therapy, which relies on extinction processes such as repeatedly exposing the patient to stimuli associated with the traumatic, fear-related memory. However, a significant number of patients fail to maintain their gains, partly attributed to the fact that this inhibitory learning and its maintenance is temporary and conditioned fear responses can return. This randomized, double-blind, placebo-controlled, between-subjects study was designed to test the impact of THC on fear extinction in humans. Animal studies had previously shown that activation of the cannabinoid system during

extinction learning enhances fear extinction and its retention. Specifically, CB1 receptor agonists such as THC had been shown in animal studies to facilitate extinction recall by preventing recovery of extinguished fear in rats. However, this phenomenon had not been investigated in humans. Twenty-nine healthy volunteers age 21-45 were recruited and randomized to receive either THC (7.5 mg MARINOL) or placebo on day 2 of a 3-day Pavlovian fear extinction paradigm with skin conductance response used to measure conditioned-fear responses and extinction learning:

- Day 1: Fear Acquisition
    - Participants sat at a computer with headphones. The subject would be shown colored boxes of three different colors, one box at a time for 4 seconds each. A loud noise was played when blue and yellow boxes were displayed, but not when red boxes were shown.
- Day 2: Extinction Learning
    - The computer displayed only blue boxes and red boxes; no loud noise was played.
- Day 3: Extinction Memory Recall Test
    - To assess extinction memory learning, boxes of all three colors were displayed. No loud noise was played.

Results showed evidence that pre-extinction administration of THC facilitates extinction of conditioned fear in humans. Participants that had received placebo during extinction learning exhibited spontaneous recovery of fear at appearance of the blue box on day 3 – fear that had been extinguished on day 2. Patients who received THC on day 2 experienced less of the spontaneous recovery of fear. Notably, THC did not affect extinction learning during day 2, but only decreased spontaneous recovery of fear.

Das RK, Kamboj SK, Ramadas M, Yogan K, Gupta V, Redman E, Morgan CJ. Cannabidiol enhances consolidation of explicit fear extinction in humans. *Psychopharmacology* 2013;226:781-792.

This is the first study of whether cannabidiol (CBD) facilitates extinction learning in humans. Forty-eight healthy volunteers, age 18-35, were recruited for this double-blind, placebo-controlled between-subjects study in which a Pavlovian fear-conditioning paradigm was used. Participants were divided into one of three groups: CBD pre-extinction and placebo post-extinction, placebo pre-extinction and CBD post-extinction, and placebo pre-extinction and post-extinction.

Day 1: Conditioning and Extinction

1. Conditioning
    a. In a computer simulation, participants were repeatedly shown two different-colored boxes, one at a time. Boxes of only one of the two colors would be accompanied by a shock a set percentage of the time.
    b. Throughout the presentations, shock expectancy ratings (0 to 5 scale of certainty) and skin conductance response were measured, as well as Mood Rating Scale (MRS) and Bodily Symptom Scale (BSS).

2. Extinction
    a. CBD pre-extinction group inhales CBD; other two groups inhale placebo
    b. Repeated presentation of the two colors of boxes, one at a time – this time with no shocks
    c. Throughout the presentations, shock expectancy ratings (0 to 5 scale of certainty) and skin conductance response were measured, as well as MRS and BSS.
    d. CBD-post-extinction group inhales CBD; other two groups inhale placebo

Day 2: Recall and Reinstatement
1. Repeated presentations of the boxes, in different contexts – both before (recall) and after (reinstatement) shocks were once again used with boxes of the one color.
2. Throughout the presentations, shock expectancy ratings (0 to 5 scale of certainty) and skin conductance response were measured, as well as MRS and BSS.

CBD given post-extinction enhanced consolidation of extinction learning as assessed by shock expectancy. CBD administered at either time produced trend level reduction in reinstatement of autonomic contextual responding. No acute effects of CBD were found on extinction. The authors conclude the findings provide evidence that CBD can enhance consolidation of extinction learning in humans and suggest that CBD may have potential as an adjunct to extinction-based therapies for anxiety disorders such as PTSD.

Clinical Trials

No randomized, controlled clinical trials have been completed for cannabis product therapy in PTSD patients. Two such trials are now being organized. The primary investigator for the larger of the two is Marcel Bonn-Miller from the Department of Psychiatry at the University of Pennsylvania and the VA National Center for PTSD. Three types of smoked cannabis (high THC; high CBD, high THC/high CBD) will be compared with each other and to placebo in alleviating symptoms and occurrence of adverse events among 76 U.S. veterans with treatment-resistant PTSD. Investigators plan to begin this study in the summer of 2016 with an estimated completion date of September, 2018. This study has funding from the state of Colorado's pool of money to support research, derived from taxes on retail marijuana. Study of Four Different Potencies of Smoked Marijuana in 76 Veterans With Chronic, Treatment-Resistant PTSD
(https://clinicaltrials.gov/ct2/show/NCT02759185?term=PTSD+cannabis&rank=1.)

The second trial, a triple-blinded cross-over study will compare three types of vaporized marijuana (high THC/low CBD; high THC/high CBD; low THC/low CBD) with each other and with to placebo in alleviating symptoms and occurrence of adverse events among 42 patients with treatment-resistant PTSD. Investigators plan to begin this study in the summer of 2016 with a December, 2016 estimated completion date. The sponsor for this study is Tilray, a Canadian marijuana producer. Evaluating Safety and Efficacy of Cannabis in Participants With Chronic Posttraumatic Stress Disorder
(https://clinicaltrials.gov/ct2/show/NCT02517424?term=PTSD+cannabis&rank=2).

Roitman P, Mechoulam R, Cooper-Kazaz R, Shalev A. Preliminary, open-label, pilot study of add-on oral Δ9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clinical Drug Investigation* 2014, 34:587-591.

This small, short-term, open-label (no control group) study assessed the safety and benefit of THC administered under the tongue. Ten adults with PTSD diagnosed > 1 year and < 3 years since the traumatic event were recruited at one outpatient clinic in Israel. Seven were men, average age was 52, and the traumatic event was war-related in 5, road accident in 3 and assult/rape in 2. All were receiving stable psychotropic medication for at least 4 weeks, with an average of more than four different medications. They remained on their stable regimen throughout the three week study. Outcome measures included Clinician-Administered PTSD Scale total score and three component scores, the Clinical Global Impression-Severity Scale (7 point scale from 1 "normal" to 7 "amongst the most severely ill patients"), Clinical Global Impression-Improvement Scale (7 point scale from 1 "very much improved") through 7 ("very much worse"), Pittsburgh Sleep Quality Index, Nightmare Frequency Questionnaire, and Nightmare Effects Survey. The THC was mixed with olive oil to achieve 2.5 mg/1 cc. Patients were instructed to take 1 cc under the tongue twice per day. After two days each was contacted by a study clinician to assess side effects. If well tolerated, the dose was increased to 2 cc twice per day (5 mg THC twice per day) and remained at that level. All patients went to the higher dose. Mild side effects were reported by four participants (dry mouth, headache, and dizziness); no participants stopped treatment because of side effects. Statistically significant improvement between baseline and end of study was seen for PTSD hyperarousal component score, both CGI-S and CGI-I, sleep quality, nightmare frequency, and nightmare effects. As the authors acknowledge, lack of a control group makes it difficult to determine whether the changes observed were due to oral THC or to variability in the course of PTSD or expectancy (placebo) effect. The study's small size and short duration are additional important limitations.

Observational Studies

Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. *J Psychoactive Drugs* 2014;46:73-77.

Retrospective study of the first 80 patients evaluated by one of the authors (Greer) for participation in the New Mexico Department of Health's Medical Cannabis Program for PTSD. In the article Greer explains that he was deluged with requests to be evaluated, so he set up a telephone screening process to prioritize who he would see. The screening process was developed around DSM-4 criteria for PTSD: "(1) the experience of and emotional response to a trauma that met the DSM-IV Criterion A for PTSD, (2) the presence of several of the major symptoms in Criteria B, C, and D (re-experiencing, avoidance, and hyperarousal) of PTSD when not using cannabis; (3) significant relief of several major PTSD symptoms when using cannabis; and (4) lack of any harm or problems in functioning resulting from cannabis use. All patients who met these screening criteria were evaluated. These were people who had found benefit in using marijuana for PTSD and were now looking for legal protection for their use. As part of the evaluation, patients were asked to think about their PTSD symptoms in the past and to fill out

the Clinician Administered Posttraumatic Scale for DSM-IV (CAPS) form twice: once for when they were using marijuana and once for when they were not using marijuana.

It is unclear what other information, if any, was collected from medical records, though the article notes duration of time periods off cannabis were not collected. When scores were compared, there was a 75% reduction in scores, for each of the three categories of PTSD symptoms and overall, when comparing periods of use vs. non-use of cannabis. As the authors note, a big caveat of these results, is that it was a carefully selected group of patients who expressed their belief that prior cannabis use helped their PTSD symptoms. There is potential for biased responses in order to get approved for the state marijuana program. The authors present some evidence in support of the proposition that there was a not a lot of bias of this sort. Another concern is that when patients responded to the CAPS for when they were not using marijuana, they could have been thinking of days immediately after they stopped using, when they could have been experiencing withdrawal side effects, some of which overlap with PTSD symptoms. The impact of this would be to exaggerate the difference in CAPS scores between periods of marijuana use and non-use. The authors' conclusion: "Because only patients who reported benefits from cannabis in reducing their PTSD were studied, no conclusions can be drawn as to what proportion or type of PTSD patients would benefit from treatment with cannabis or its constituents."

Bremner, D. J., Southwick, S. M., Darnell, A., & Charney, D. S. (1996). Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse. *American Journal of Psychiatry* 1996;153:369-375.

In this retrospective, longitudinal study, Vietnam War veterans were studied to observe the natural course of their PTSD symptoms in the twenty plus years after the war. All 61 veterans involved in the study had combat experience and were interviewed during an inpatient stay for PTSD treatment during the early 1990s. Assessment tools gathered, for two-year intervals, presence of a list of PTSD symptoms; abuse of alcohol, marijuana (abuse not clearly defined), heroin, benzodiazepines, and cocaine; and perceptions of relief and exacerbation of PTSD symptoms by these drugs. Interviews collected retrospective data on the veterans' experiences in the two years preceding their war experience, during the war, and after their combat experience through 1992.

Compared to the two-year, pre-combat period, there was a significant increase in alcohol, marijuana, and cocaine abuse during the war and in all five of the drug categories studied in the years immediately after their combat experience, consistent with the belief that at least some use of these drugs in PTSD patients is self-medication of symptoms. Participants in general found alcohol and heroin helpful for PTSD symptoms in the hyperarousal and intrusive categories and benzodiazepines and marijuana helpful for hyperarousal symptoms, while cocaine had a tendency to worsen symptoms in the hyperarousal category.

Caution must be taken when interpreting these results, since the authors acknowledge multiple factors that confound the data and that limit the findings' generalizability. For instance, PTSD patients with noncombat traumas, such as childhood abuse, may have a

different symptom progression from combat veterans. And, despite methodology to help participants recall the nature of timing and symptoms years ago, some of those recollections might have been inaccurate. While the findings are consistent with the hypothesis that PTSD patients self-medicate with alcohol and other substances, it is possible that alcohol and substance abuse occurred independently from PTSD symptom progression. Only association and not causation can be assessed with this study.

Wilkinson ST, Stefanovics E, Rosenheck RA. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. *The Journal of Clinical Psychiatry* 2015;76:1174-1180.

American veterans diagnosed with PTSD and admitted to specialized Veterans Affairs PTSD treatment programs from 1992 to 2011 were included in this study (n=12,770; mean age=51.7 years; 96.7% male). Documentation at admission of consuming 2 or more drinks per occasion and use of any illicit drugs other than marijuana during the 30 days prior to admission excluded 34,540 of 47,310 potential participants (73%). Use of marijuana, alcohol, and other drugs, PTSD symptom severity, co-morbid psychiatric diagnoses, PTSD treatment program characteristics, community adjustment variables, and demographics were collected at program admission. Use of marijuana, alcohol abuse, abuse of other drugs, PTSD symptom severity, employment status and violent behavior were assessed at 4 months after discharge.

The 12,770 study subjects were divided into four groups based on marijuana use at admission and at four months after discharge: Never Users (89%), Stoppers (2% - use at admission, but not at four months post-discharge), Continuing users (2%) and Starters (7% - no use at admission, but use at 4 months post-discharge).

The authors describe several statistically significant findings. Higher measures of symptom severity at four months post-discharge were observed among Starters and Continuing Users compared to Never Users and Stoppers. Continuing Users had shorter lengths of stay in treatment programs compared to Never-Users and Stoppers. Starters showed higher measures of violent behavior at follow up compared to all other groups.

Though the authors say the findings suggest marijuana use may worsen PTSD symptoms or nullify the benefits of specialized intensive treatment, they acknowledge the results could also mean PTSD patients refractory to treatment are more likely to use marijuana in an attempt to self-medicate. Though this study is longitudinal, it shows only associations and cannot determine causation (again, as admitted by the authors). Violence was measured on a narrow scale, ranging from 0 (least violent) to 4 (most violent). And at 4 months post-discharge the four groups had a narrow range of mean scores: Starters = 1.25; Continuing Users = 0.93; Never-Users = 0.87; Stoppers = 0.76. The score for Starters was statistically significantly higher than for the other groups, but it is not clear how meaningful the difference between 1.25 and the other scores is. In addition, Starters had more frequent alcohol abuse than the other groups 4 months post-discharge (which is related to violence).

There are a few additional limitations to interpreting the results. Analyses adjusted for measured differences among groups at baseline but it is quite possible unmeasured differences

could have resulted in biased results. Perceptions of short-term symptom relief from cannabis were not assessed. The ability to generalize the results to all veteran PTSD patients is limited by subjects being admitted to specialized treatment programs and by excluding 73% of such patients because of alcohol use and use of illicit drugs other than marijuana.

Bonn-Miller MO, Babson KA, Vandrey R. Using cannabis to help you sleep: Heightened frequency of medical cannabis use among those with PTSD. *Drug and Alcohol Dependence* 2014;136:162-165.

Why do patients with PTSD use medicinal cannabis compared to patients who do not have PTSD? Is the interaction between PTSD and PTSD-specific, cannabis-use motivations associated with more frequent use of medicinal cannabis? These questions were the authors' focus in this study.

To answer these questions, 170 adults who obtained their medicinal cannabis from a single dispensary in San Francisco were studied. Each participant completed the PTSD checklist – Civilian Version, a 17-item questionnaire where respondents indicate the presence and severity of PTSD symptoms. Following recommendations of community samples, a score of 30 was used as a cut-off to form two groups, those without PTSD and those with probable PTSD. Participants also filled out questionnaires about frequency of cannabis use in the past 30 days and motivation for cannabis use. For the cannabis use questionnaire respondents rated how often they used cannabis (5-point scale: 1=almost never/never to 5=almost always/always) for each of 36 reasons, comprising 12 domains (enjoyment, conformity, coping, experimentation, boredom, alcohol, celebration, altered perception, social anxiety, low risk, sleep, and availability).

Analysis showed that individuals with probable PTSD reported greater motivation to use cannabis for sleep and coping reasons compared to those without PTSD. No association was found between PTSD and any of the other use motivations. Hierarchical regression also demonstrated that sleep motivation predicted past 30-day cannabis use frequency. But, being in the probable PTSD group did not predict past 30-day cannabis use frequency.

The authors noted several important limitations to their study. First, cause-effect conclusions cannot be drawn from a cross-sectional design. The study sample was narrow: mostly male patients from a single dispensary in San Francisco limits the findings' generalizability. Data were self-reported, so they are potentially biased. Last, volunteers were not diagnosed with PTSD, and behavioral/interview-based verification of symptom severity was not conducted.

Bonn-Miller MO, Babson KA, Vujanovic AA, Feldner MT, Sleep problems and PTSD symptoms interact to predict marijuana use coping motives: A preliminary investigation. *J Dual Diagnosis* 2010;6:111-122.

In this study, Bonn-Miller, Babson et al. aimed to uncover what factors affect the association between PTSD and coping-motivated cannabis use. They hypothesized that greater sleep difficulties and more severe PTSD symptoms (excluding sleep problems) are associated

with higher levels of coping-motivated cannabis use and that the interaction between sleep problems and PTSD symptom severity would be greater than either factor alone. Participants were recruited through newspaper advertisements, flyers, and announcements that described a laboratory study on "stressful life events." Twenty (mean age = 34 years; 75% female) met DSM-IV criteria for PTSD and were currently using marijuana (past 30 days); this group formed the study cohort. Validated tools were used to collect information on sleep quality and motivations for marijuana use.

Using multiple hierarchical regression, a statistically significant, positive association between sleep difficulties and the degree of coping motivations was observed. However, the regression analysis did not reveal a statistically significant, direct relationship between symptom severity and coping-motivated cannabis use. Results showed a statistically significant interaction between sleep difficulties and symptom severity beyond the main effects of each. This interaction occurred independently of symptom severity. Neither symptom severity nor sleep problems were related to other motivations of cannabis use, such as social or conformity motivations. The authors conclude, "These findings highlight sleep problems as the primary driving force of the interaction, suggesting that individuals at highest risk for using marijuana for coping reasons are those with high levels of sleep problems."

The authors acknowledge the limitations of this study: small, mostly female study sample; cross-sectional design that precludes assessing temporal relationship among PTSD symptom severity, sleep problems, and coping-oriented marijuana use; and self-report measurements (especially sleep quality). They describe need for a larger study of prospective design with direct observation of sleep to replicate and extend the findings of this study.

Bonn-Miller MO, Vujanovic AA, Drescher KD. Cannabis use among military veterans after residential treatment for posttraumatic stress disorder. *Psychology of Addictive Behaviors* 2011;25:485-491.

This paper studied substance use patterns after treatment discharge among 432 male Veterans admitted to a VA residential rehabilitation program for PTSD. The program admits veterans with severe PTSD symptoms that have not been successfully ameliorated with inpatient treatment. The veterans are required to be free of substance use at least 15 days prior to admission. The authors hypothesized that lower levels of change in PTSD symptom severity between treatment intake and discharge would significantly predict higher frequency of cannabis use 4 months after discharge.

To test this hypothesis, data on PTSD symptom severity and substance use (alcohol, cannabis, cocaine, opiates, amphetamines) were collected at admission and discharge from the residential treatment program and four months after discharge. 8.1% reported cannabis use during the 2 months prior to admission and 54.3% of these were again using cannabis 4 months after discharge. Among the 92% not using cannabis during the 2 months prior to admission 10.1% were using it 4 months after discharge. Using linear regression, several findings were reported. Lower levels of symptom improvement between intake and discharge predicted greater cannabis use four-month after discharge in a statistically significant manner. Frequency

of cannabis use during the two months preceding intake in the program predicted cannabis use at the four-month follow-up. Smaller levels of improvement in PTSD avoidance/numbing and hyperarousal symptom severity were observed to incrementally predict cannabis use at follow-up in a statistically significant way.

Based on these findings, the authors hypothesized that veterans with lower symptom improvement may use cannabis as an alternative method of coping. The study's results suggest that veterans with high levels of hyperarousal symptoms, such as irritability or sleep disturbance, may be especially likely to consume cannabis.

However, several factors confound these findings and interpretations. Structured diagnostic interviews were not conducted, so study participants may have had other mental-health or personality disorders. Data collection and veterans' benefits eligibility determination were conducted at the same facility, leading to possible bias in veterans' self-reported symptom severity and substance consumption. Only combat-exposure trauma was studied, so findings may not apply to other kinds of trauma. Only male veterans were studied.
Finally, substance use severity (e.g., substance use or dependence, drug potency, etc.) was not examined

Bonn-Miller MO, Vujanovic AA, Feldner MT, Bernstein A Zvolensky MJ. Posttraumatic stress symptom severity predicts marijuana use coping motives among traumatic event-exposed marijuana users. *J Traumatic Stress* 2007;20:577-586.

What motivates people with posttraumatic stress symptoms to use cannabis was investigated in this cross-sectional study. This study included community-recruited volunteers from a Vermont college town who were current cannabis smokers and had experienced a traumatic event, as defined by the DSM-IV. The authors hypothesized that more severe symptoms would be associated with higher levels of coping-motivated use, even when accounting for the level of participants' levels of cannabis, cigarette, and alcohol consumption. They further hypothesized that no other motivations would be associated with symptom severity.

Using hierarchical linear regression analysis, the authors confirmed their three hypotheses. Interestingly, they also found no evidence linking posttraumatic stress symptoms to the frequency of cannabis use in the past thirty days.

A number of confounding factors limit these findings, however, the authors note. First, the method of recruitment and screening participants may limit the variability of posttraumatic stress symptoms. Study participants were demographically homogenous (young; mean age = 19.4 years) and experienced a narrow range of life traumas, limiting the generalizability of the findings. Results were vulnerable to reporting errors, since data were collected from participant self-reports. Importantly, volunteers with traumatic events were studied; participants were not required to be diagnosed with PTSD.

National Medical Organization Recommendations

American Psychiatric Association

"Because of the lack of any credible studies demonstrating clinical effectiveness, the APA cannot endorse the use of medical marijuana for the treatment of post-traumatic stress disorder (PTSE). The Council on Research and Quality Care reviewed available evidence regarding the use of marijuana in the treatment of PTSD (1-6) and concluded that no published evidence of sufficient quality exists in the medical literature to support the practice." (Approved by APA Board of Trustees July 20, 2013).

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