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# Medical Marijuana for the Treatment of Post-Traumatic Stress Disorder

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## Table of Contents

	Page #
Introduction	2
Purpose of the Evidence Review	2
Background	2
Scope of the Evidence Review	2
List of key questions	2
Conflict of interest	2
Methods	3
Literature Search	3
Inclusion and Exclusion Criteria	3
Quality assessment	3
Studies submitted by the public	4
Results	4
Articles included (Table 1)	4
Articles excluded (Table 2)	5
Description of the Items Submitted with the Petition	9
Current Research	13
Conclusions	13
Appendix 1 Search Terms	15
Appendix 2 Description of Study Types	16
Appendix 3 GRADE Methodology to Assess Overall Quality of Evidence	17

## **Introduction**

### **Purpose of the Evidence Review**

This review updates a report submitted in 2012 that evaluates evidence on cannabis use in adults for the treatment of Post-Traumatic Stress Disorder (PTSD). The Arizona Department of Health Services (ADHS) funded this report to assist in assessing PTSD as a condition to add to those that qualify for the use of medical marijuana in Arizona.

### **Background**

Pursuant to A.R.S. § 36-2801.01, the public may petition the Arizona Department of Health Services (ADHS) to add debilitating medical conditions to those listed in A.R.S. 36-2801(3). The ADHS established the manner in which it shall consider petitions to add debilitating medical conditions in A.A.C. R9-17-106. A.A.C. R9-17-106(C) states, ADHS “shall accept requests for the addition of a medical condition to the list of debilitating medical conditions in R9-17-201 in January and July of each calendar year starting in January 2012”. After receiving requests for adding conditions the ADHS requests a report on the scientific evidence on the use of cannabis for this condition from the University of Arizona College of Public Health. In addition the Department holds a public hearing to hear public testimony on the condition and its treatment with cannabis. The Department Medical Advisory Committee then considers the totality of the evidence in deciding to add a condition to the list, or not. A petition to add PTSD was received in 2012 and again in 2013. This report updates the evidence report completed in response to the 2012 request.

### **Scope of the Evidence Review**

This evidence review update covers the time period from the completion of the first review to December 2013.

### **List of Key Questions**

1. What are the benefits (short and long-term benefits) of cannabis use for the treatment of PTSD?
2. What are the harms (short and long-term harms) of cannabis use for the treatment of PTSD?

### **Conflicts of Interest**

The authors have no conflicts of interest.

## Methods

### Literature Search and Strategy

The topics of cannabis use and migraine headaches were searched in the following databases: The Cochrane Library, Ovid MEDLINE®, Web of Science, Dynamed, Google Scholar, National Center for Complimentary and Alternative Medicine, and PsycINFO. The time period for the search was January 2012 until the present. In addition, the Embase database has recently been added to those available at the University of Arizona library. Since it was not included in the search conducted in 2012, this database was searched for any publications within the past 5 years. Bibliographies in the articles identified through these databases were hand searched for additional pertinent articles. A detailed description of the search terms can be found in Appendix 1.

### Inclusion and Exclusion Criteria

Studies that met all of the following criteria were included:

1. Evaluated adults ( $\geq 18$  years old) with PTSD (studies of adolescents are included if they contain material that appears to be pertinent for adults)
2. English language
3. Human study
4. Were relevant to one of the key questions

Studies that were excluded include those that were:

1. Animal studies
2. Editorials or opinions
3. Descriptions of biochemical and pathophysiological pathways
4. Not relevant to the key questions

The original intent was to restrict the search to clinical trials, cohort and case control studies. Due to the paucity of studies of this type found, we also included cross sectional studies and case reports.

### Quality Assessment

Types of studies available to assess are listed and described in Appendix 2. Observational studies were assessed using the main domains described in tools commonly used ( Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomized intervention studies. *Health Technology Assessment* 2003;7(27) ). The overall quality of the evidence is ranked using GRADE methodology demonstrated in Appendix 3. (Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. *Methods Guide for Comparative Effectiveness Reviews*. Rockville, MD. Available at: <http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60>.)

## Studies Submitted by the Public

Any scientific literature submitted by the public in support of including PTSD was also assessed using the same inclusion and exclusion criteria and assessment methodology.

## Results

There were 92 articles found in the search; 4 met the inclusion criteria, 88 did not (listed in Table 2). There were 2 articles from the material submitted by the public that were also assessed for quality. This resulted in 6 articles for assessment (see Table 1).

**Table 1**  
**Articles Included in the Review**

Article and Citation	Description and Design of Study	Findings	Quality
Reznik I. Post-traumatic stress disorder and medical cannabis use: a naturalistic observational study. <i>Addict Behav</i> 2010;35:64-67.	Prospective cohort. The exact number is unclear but appears to be about 80 PTSD patients who applied for and obtained a license for medical cannabis in Israel, followed for "about three years".	"More than 50%" also used conventional PTSD treatments. Daily cannabis dose was "in the range of 2-3 gr/day," "In most cases" there was an improvement in quality of life and pain scores and positive changes in CAPS scores. No serious adverse events were reported.	<b>Very Low Quality.</b> Incomplete reporting of data makes analysis impossible. There are no statistics provided. Self-selected group. This study has the potential to be of higher quality with a more complete presentation of methods and data.
Boden MT, et al. Posttraumatic stress disorder and cannabis use characteristics among military veterans with cannabis dependence. <i>Am J Addict</i> 2013;22:277-284.	Cross-sectional study of 94 cannabis dependent military veterans in California; 37 with PTSD and 57 without. All expressed interest in quitting use of marijuana.	Those with PTSD reported increased use of cannabis to cope, higher severity of cannabis withdrawal, and more craving of cannabis. The authors state that the findings point out "the pernicious feedback loop between PTSD symptoms and cannabis use."	<b>Low Quality.</b> Validated tools were used for diagnosis, symptom severity, motives for cannabis use, problems caused by cannabis use, and withdrawal symptoms. Multivariate statistical analyses were performed to control for confounders. However, the cross-sectional study design relied upon self-reported measures and has the potential for recall bias. The self-selected patients were those with a diagnosed cannabis dependency who wanted to stop cannabis use.
Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in PTSD. <i>CNS Neuroscience and Therapeutics</i> 2009;15:84-89.	Case series assessed retrospectively via chart review. 47 patients with PTSD and treatment-resistant nightmares given <b>nabilone</b> , 2004-2006. All patients were on other medications for PTSD.	28 had cessation of nightmares, 6 had a reduction. (total of 72% improvement). Only 4 of 32 were able to discontinue nabilone without nightmare recurrence.	<b>Low Quality.</b> Small numbers, convenience sample, self-reporting of symptoms, no placebo control, retrospective assessment by investigator who was the treating clinician, without validation.
Passie T, et al. Mitigation of post-traumatic stress symptoms by cannabis resin: a review of the clinical and neurobiological evidence. <i>Drug Test Analysis</i> 2012;4:649-659.	Case report of 19 year old male, a long-time victim of sadistic sexual abuse by his father.	His use of cannabis resulted in reported improvement in stress, anxiety and flashbacks. The cannabis resin used was from turkey and contained both THC and CBD.	<b>Very Low Quality.</b> Single case report.

Bujarski SJ, et al. Marijuana use among traumatic event-exposed adolescents: Posttraumatic stress symptom frequency predicts coping motivations for use. <i>Addictive Behaviors</i> 2012;37:53-59.	Cross sectional study of 61 adolescents (3/4 were male) ages 14-17, 95 % Caucasian, marijuana users. They were treatment seeking in a private group-based residential facility, who reported one or more traumatic events.	Past two-week ptsd stress symptoms predicted coping motives for marijuana use after controlling for other variables.	<b>Low Quality.</b> Small sample with limited power, self-selected subjects, adolescents not adults (indirectness), potential recall bias. Standard, validated tools were used for data collection and statistical analysis did control for potential confounders.
Canadian Agency for Drugs Technology and Health. Cannabinoids for the treatment of post-traumatic stress disorder: A review of the clinical effectiveness and guidelines (structured abstract). In: Health technology assessment database. ; 2012. <a href="http://onlinelibrary.wiley.com.ezproxy1.library.arizona.edu/o/cochrane/clhta/articles/HTA-32012000694/frame.html">http://onlinelibrary.wiley.com.ezproxy1.library.arizona.edu/o/cochrane/clhta/articles/HTA-32012000694/frame.html</a> .	A systematic review of the evidence for the effectiveness of cannabinoids for treatment of PTSD. Completed in June 2012.	The evidence on the use of cannabinoids for PTSD is very limited. This review essentially agrees with the one the COPH conducted for ADHS in 2012.	<b>High Quality Systematic Rapid Review</b>

**Table 2**

**Articles Not Included**

Study	Exclusion Reasoning
13th hungarian congress of neuropsychopharmacology. <i>Neuropsychopharmacologia Hungarica</i> . 2010;12.	The study did not meet inclusion criteria (findings were not published in English).
Abadi MH, Shamblen SR, Johnson K, et al. Examining human rights and mental health among women in drug abuse treatment centers in afghanistan. <i>Int J Womens Health</i> . 2012;4(1):155-165.	The study did not address key questions and did not involve cannabis use.
Ahuja AS, Crome I, Williams R. Engaging young people who misuse substances in treatment. <i>Curr Opin Psychiatry</i> . 2013;26(4):335-342.	The study involved youth not adults and does not address PTSD.
Akirav I. The role of cannabinoids in modulating emotional and nonemotional memory processes in the hippocampus. <i>Front Behav Neurosci</i> . 2011.	The study was a description of biochemical pathways.
Alao A. Cannabis-induced atrial fibrillation in a patient with traumatic brain injury. <i>J Neuropsychiatry Clin Neurosci</i> . 2012;24(2):21-22.	The case report did not involve PTSD.
Auxemery Y. Etiopathogenic perspectives on chronic psycho traumatic and chronic psychotic symptoms: The hypothesis of a hyperdopaminergic endophenotype of PTSD. <i>Med Hypotheses</i> . 2012; 79(5):667-672.	The study did not address the key questions and did not involve cannabis use.
Bailey C, Normandin M, Henry S, et al. The use of 11C]OMAR and positron emission tomography to investigate the pathophysiology of posttraumatic stress disorder. <i>J Cereb Blood Flow Metab</i> . 2012;32:S24.	The study did not address the key questions nor did it involve cannabis use.
Baminger H. The many faces of therapeutic competence. <i>J Neurol Neurochir Psychiatr</i> . 2009;10(2):88-90.	The study did not meet inclusion criteria (findings were not published in English).
Batki SL, Canfield KM, Ploutz-Snyder R. Psychiatric and substance use disorders among methadone maintenance patients with chronic hepatitis C infection: Effects on eligibility for hepatitis C treatment. <i>Am J Addict</i> . 2011;20(4):312-318.	The study did not address the key questions (did not involve cannabis use or subjects with PTSD).
Bessa MA, Mitsuhiro SS, Chalem E, Barros MC, Guinsburg R, Laranjeira R. Correlates of substance use during adolescent pregnancy in São Paulo, Brazil. <i>Rev Bras Psiquiatr</i> . 2010 Mar;32(1):66-9.	The study involved youth not adults.
Bhangoo RK, Carter CS. Very early interventions in psychotic disorders. <i>Psychiatr Clin North Am</i> . 2009;32(1):81-94. Bowles DW. Persons registered for medical marijuana in the united states. <i>J Palliative Med</i> . 2012;15(1):9-11.	The study involved youth not adults and did not address cannabis as a treatment. The study reviewed demographics information of adults registered for medical marijuana in various states. PTSD is the leading indication for use in New Mexico, but the review did not discuss cannabis as treatment for PTSD.
Bonn-Miller MO, Bucossi MM, Trafton JA. The underdiagnosis of cannabis use disorders and other Axis-I disorders among military veterans within VHA. <i>Mil Med</i> . 2012 Jul;177(7):786-8.	The study involved the under-diagnosis of cannabis use and posttraumatic stress disorders in within the Veteran's Health Administration, but did not address cannabis use as treatment for PTSD.
Bonn-Miller MO, Harris AH, Trafton JA. Prevalence of cannabis use disorder diagnoses among veterans in 2002, 2008, and 2009. <i>Psychol Serv</i> . 2012 Nov;9(4):404-16.	The study did not involve PTSD.

Bujarski SJ, Feldner MT, Lewis SF, Babson KA, Trainor CD, Leen-Feldner E, Badour CL, Bonn-Miller MO. Marijuana use among traumatic event-exposed adolescents: posttraumatic stress symptom frequency predicts coping motivations for use. <i>Addict Behav.</i> 2012 Jan;37(1):53-9. doi: 10.1016/j.addbeh.2011.08.009.	The study involved adolescents and was not a study of treatment for PTSD. The study confirmed the associated between substance abuse and PTSD.
Burgo-Black L, C Hunt ,S., Spelman J. Post combat care. <i>J Gen Intern Med.</i> 2011;26:S509-S510.	The study is a case report and does not involve the cannabis use as treatment for PTSD.
Casher MI, Gih D, Bess JD. Benzodiazepines and stimulants for patients with substance use disorders. <i>Curr Psychiatry.</i> 2011;10(5):58-67.	The study did not address the key questions.
Chan Y-, Huang H, Sieu N, Unutzer J. Substance screening and referral for substance abuse treatment in an integrated mental health care program. <i>Psychiatr Serv.</i> 2013;64(1):88-90.	The study did not address the key questions.
Chen T, Masson CL, Sorensen JL, Greenberg B. Residential treatment modifications: Adjunctive services to accommodate clients on methadone. <i>Am J Drug Alcohol Abuse.</i> 2009;35(2):91-94.	The study did not involve cannabis use.
Chen Y, Huang W, Constantini S. Concepts and strategies for clinical management of blast-induced traumatic brain injury and posttraumatic stress disorder. <i>J Neuropsychiatry Clin Neurosci.</i> 2013;25(2):103-110.	The study did not address the key questions.
Clark DB, Pollock N, Bukstein OG, Mezzich AC, Bromberger JT, Donovan JE. Gender and comorbid psychopathology in adolescents with alcohol dependence. <i>J Am Acad Child Adolesc Psychiatry.</i> 1997 Sep;36(9):1195-203.	The study involved youth not adults and studied alcohol use not cannabis use.
Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. <i>Prog Brain Res.</i> 2000;126:325-41. Review.	The study did not address the key questions.
Cucciare MA, Simpson T, Hoggatt KJ, Gifford E, Timko C. Substance use among women veterans: Epidemiology to evidence-based treatment. <i>J Addict Dis.</i> 2013;32(2):119-139.	The study did not address the key questions nor did it address cannabis use as treatment for PTSD.
Dunlop BW, Mansson E, Gerardi M. Pharmacological innovations for posttraumatic stress disorder and medication-enhanced psychotherapy. <i>Curr Pharm Des.</i> 2012;18(35):5645-5658.	The study was a systematic review article and did not address the key questions.
Dworkind MA. Medical marijuana revisited. <i>CMAJ.</i> 2013;185(12):1067.	The study did not address the key questions nor did it meet inclusion criteria.
Escamilla M, LaVoy M, Moore BA, Krakow B. Management of post-traumatic nightmares: A review of pharmacologic and nonpharmacologic treatments since 2010. <i>Curr Psychiatry Rep.</i> 2012;14(5):529-535.	The study did not address the key questions nor did it address cannabis use as a treatment for PTSD.
Finan PH, Zautra AJ. Fibromyalgia and fatigue: Central processing, widespread dysfunction. <i>PM R.</i> 2010;2(5):431-437.	The study did not address the key questions.
Fryers T, Brugha T. Childhood determinants of adult psychiatric disorder. <i>Clin Pract Epidemiol Ment Health.</i> 2013;9:1-50.	The study did not address cannabis use as treatment for PTSD.
Fulton HG, Barrett SP, MacIsaac C, Stewart SH. The relationship between self-reported substance use and psychiatric symptoms in low-threshold methadone maintenance treatment clients. <i>Harm Reduct J.</i> 2011;8.	The study did not address the key questions.
Ganon-Elazar E, Akirav I. Cannabinoids prevent the development of behavioral and endocrine alterations in a rat model of intense stress. <i>Neuropsychopharmacology.</i> 2012 Jan;37(2):456-66. doi: 10.1038/npp.2011.204.	The study involved animals not humans.
Gilhotra N, Dhingra D. Neurochemical modulation of anxiety disorders. <i>Int J Pharmacy Pharm Sci.</i> 2010;2:1-6.	The study did not address the key questions.
Greenfield SF, Back SE, Lawson K, Brady KT. Substance abuse in women. <i>Psychiatr Clin North Am.</i> 2010;33(2):339-355.	The study did not involve subjects with PTSD.
Griebel G, Holmes A. 50 years of hurdles and hope in anxiolytic drug discovery. <i>Nat Rev Drug Discov.</i> 2013;12(9):667-687.	The study did not address the key questions (did not involve cannabis use or subjects with PTSD).
Hainline B. Neuropathic pain: Mind-body considerations. <i>Neurol Clin.</i> 2011;29(1):19-33.	The study did not address the key questions (did not involve cannabis use or subjects with PTSD).
Harrington M, Robinson J, Bolton S-, Sareen J, Bolton JM. A longitudinal study of risk factors for incident drug use in adults: Findings from a representative sample of the US population. <i>Can J Psychiatry.</i> 2011;56(11):686-695.	The study did not address cannabis use as treatment for PTSD.
Hartwell S, Deng X, Fisher W, et al. Predictors of accessing substance abuse services among individuals with mental disorders released from correctional custody. <i>J Dual Diagn.</i> 2013;9(1):11-22.	The study did not address cannabis use nor did it address treatment for PTSD.
Hauer D, Kaufmann I, Strewé C, Briegel I, Campolongo P, Schelling G. The role of glucocorticoids, catecholamines and endocannabinoids in the development of traumatic memories and posttraumatic stress symptoms in survivors of critical illness. <i>Neurobiol Learn Mem.</i> 2013.	The study was a description of biochemical pathways.
Havemann-Reinecke U. How do addictive drugs act in the brain? implications for (pharmaco)therapeutic strategies. <i>Naunyn-Schmiedeberg's Arch Pharmacol.</i> 2013;386:S31.	The study was a description of biochemical pathways.

Havens JR, Oser CB, Knudsen HK, et al. Individual and network factors associated with non-fatal overdose among rural appalachian drug users. <i>Drug Alcohol Depend.</i> 2011;115(1-2):107-112.	The study did not address the key questions.
Houlihan DJ. Psychostimulant treatment of combat-related posttraumatic stress disorder. <i>J Psychopharmacol.</i> 2011;25(11):1568-1572.	Cannabis was not used or reported in the case reports assessed in the study.
Hyman SM, Sinha R. Stress-related factors in cannabis use and misuse: Implications for prevention and treatment. <i>J Subst Abuse Treat.</i> 2009;36(4):400-413.	Excluded because review referenced studies used in the 2012 PTSD Report.
Jacobsen LK, Southwick SM, Kosten TR. Substance Use Disorders in Patients With Posttraumatic Stress Disorder: A Review of the Literature. <i>Am J Psychiatry.</i> 2001;158(8):1184-1190.	The study confirmed the association between PTSD and substance abuse disorders, but did not address treatment for PTSD.
Kroll JL. New directions in the conceptualization of psychotic disorders. <i>Curr Opin Psychiatry.</i> 2007 Nov;20(6):573-7. Review.	The study involved youth not adults.
Kupprat SA, Dayton A, Guschlbauer A, Halkitis PN. Case manager-reported utilization of support group, substance use and mental health services among HIV-positive women in new york city. <i>AIDS Care Psychol Socio-Med Asp AIDS HIV.</i> 2009;21(7):874-880.	The study did not address the key questions.
Larauche M, Mulak A, Tache Y. Stress and visceral pain: From animal models to clinical therapies. <i>Exp Neurol.</i> 2012;233(1):49-67.	The study did not address the key questions.
Latypov A. Healers and psychiatrists: The transformation of mental health care in tajikistan. <i>Transcult Psychiatry.</i> 2010;47(3):419-451.	The study did not address the key questions.
Lehner M, Wislowska-Stanek A, Plaznik A. Extinction of emotional response as a novel approach of pharmacotherapy of anxiety disorders. <i>Psychiatr Pol.</i> 2009;43(6):639-654.	The study did not involve cannabis use.
Lipschitz DS, Rasmusson AM, Anyan W, Gueorguieva R, Billingslea EM, Cromwell PF, Southwick SM. Posttraumatic stress disorder and substance use in inner-city adolescent girls. <i>J Nerv Ment Dis.</i> 2003 Nov;191(11):714-21.	The study involved adolescents and was not a study of treatment for PTSD. The study confirmed the associated between substance abuse and PTSD.
Lorenz R. On the application of cannabis in paediatrics and epileptology. <i>Neuro Endocrinol Lett.</i> 2004 Feb-Apr;25(1-2):40-4.	The study involved adolescents and strongly emphasized treatment for epilepsy.
Lutz B. Endocannabinoid signals in the control of emotion. <i>Curr Opin Pharmacol.</i> 2009;9(1):46-52.	The study was a description of biochemical pathways and did not involve cannabis use.
Mackesy-Amiti M, Donenberg GR, Ouellet LJ. Prevalence of psychiatric disorders among young injection drug users. <i>Drug Alcohol Depend.</i> 2012;124(1-2):70-78.	The study did not mention PTSD nor did it address cannabis use as treatment for PTSD.
Marco EM, Garcia-Gutierrez M, Bermudez-Silva F, et al. Endocannabinoid system and psychiatry: In search of a neurobiological basis for detrimental and potential therapeutic effects. <i>Front Behav Neurosci.</i> 2011.	The study did not address the key questions.
Nadew GT. Exposure to traumatic events, prevalence of posttraumatic stress disorder and alcohol abuse in Aboriginal communities. <i>Rural Remote Health.</i> 2012 Oct;12(4):1667.	The study did not involve cannabis use.
Neumeister A. The endocannabinoid system provides an avenue for evidence-based treatment development for PTSD. <i>Depress Anxiety.</i> 2013;30(2):93-96.	The study was an editorial and description of biochemical pathways.
Olson-Madden J, Brenner L, Harwood JEF, Emrick CD, Corrigan JD, Thompson C. Traumatic brain injury and psychiatric diagnoses in veterans seeking outpatient substance abuse treatment. <i>J Head Trauma Rehabil.</i> 2010;25(6):470-479.	The study emphasized the need for additional traumatic brain injury screenings and did not address cannabis use as treatment for PTSD.
Onaivi ES. Cannabinoid receptors in brain. pharmacogenetics, neuropharmacology, neurotoxicology, and potential therapeutic applications. <i>Int Rev Neurobiol.</i> 2009;88:335-369.	Excluded because review referenced biochemical pathway studies.
Onaivi ES. Endocannabinoid system, pharmacogenomics and response to therapy. <i>Pharmacogenomics.</i> 2010;11(7):907-910.	The study did not meet the inclusion criteria (editorial).
Ouimette P, Read JP, Wade M, Tirone V. Modeling associations between posttraumatic stress symptoms and substance use. <i>Addict Behav.</i> 2010;35(1):64-67.	The study did not involve cannabis use.
Petrosino S, Di Marzo V. FAAH and MAGL inhibitors: Therapeutic opportunities from regulating endocannabinoid levels. <i>Curr Opin Invest Drugs.</i> 2010;11(1):51-62.	Excluded because review referenced biochemical pathway studies.
Phelps N. Dronabinol for emotion-induced reflex epilepsy. <i>J Pharm Pract.</i> 2013;26(3):343-344.	The case report did not involve PTSD.
Rabinak CA, Angstadt M, Lyons M, et al. Cannabinoid modulation of prefrontal-limbic activation during fear extinction learning and recall in humans. <i>Neurobiol Learn Mem.</i> 2013.	The study was a description of biochemical pathways.
Rather YH, Bashir W, Ahmad Sheikh A, Aamin M, Arafat Zahgeer Y. Socio-demographic and clinical profile of substance abusers attending a regional drug de-addiction centre in chronic conflict area: Kashmir, india. <i>Malays J Med Sci.</i> 2013;20(3):31-38.	The study confirmed the association between mental disorders and substance abuse, but did not address treatment for PTSD.
Reijneveld SA, Crone MR, Verhulst FC, Verloove-Vanhorick SP. The effect of a severe disaster on the mental health of adolescents: a controlled study. <i>Lancet.</i> 2003 Aug 30;362(9385):691-6.	The study involved youth not adults.
Rohrbach LA, Grana R, Vernberg E, Sussman S, Sun P. Impact of hurricane Rita on adolescent substance use. <i>Psychiatry.</i> 2009 Fall;72(3):222-37.	The study involved youth not adults.
Rom S, Persidsky Y. Cannabinoid receptor 2: Potential role in immunomodulation and neuroinflammation. <i>J Neuroimmune Pharmacol.</i> 2013;8(3):608-620.	Excluded because review referenced biochemical pathway studies.

Santucci K. Psychiatric disease and drug abuse. <i>Curr Opin Pediatr.</i> 2012;24(2):233-237+283.	The study involved youth not adults and was a review of dual diagnosis of substance abuse and psychiatric disorders. The study did not involve PTSD.
Saunders KEA, Goodwin GM. The course of bipolar disorder. <i>Adv Psychiatr Treat.</i> 2010;16(5):318-328.	The study did not involve cannabis use.
Schelling G, Roozendaal B, Campolongo P, De Quervain D. Glucocorticoids and noradrenaline in severe stress exposure in humans. <i>Eur Neuropsychopharmacol.</i> 2010;20:S169-S170.	The study did not involve cannabis use.
Schiff M, Pat-Horenczyk R, Benbenishty R, Brom D, Baum N, Astor RA. High school students' posttraumatic symptoms, substance abuse and involvement in violence in the aftermath of war. <i>Soc Sci Med.</i> 2012 Oct;75(7):1321-8.	The study involved adolescents and was not a study of treatment for PTSD. The study confirmed the associated between substance abuse and PTSD.
Serrano A, Parsons LH. Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. <i>Pharmacol Ther.</i> 2011;132(3):215-241.	The study was a description of biochemical pathways.
Sinha R. How does stress increase risk of drug abuse and relapse? <i>Psychopharmacology.</i> 2001; 158: 343-359.	The study did not address the key questions.
Soler Gonzalez C, Lopez Pelayo H, Balcells Oliveira MM, Vazquez Vazquez JM. Posttraumatic psychosis and drug abuse. case study. <i>Eur Psychiatry.</i> 2012;27.	The study was a case report of posttraumatic brain injury, and did not involve cannabis use as treatment for PTSD.
Sriram A, Ward HE, Hassan A, et al. Valproate as a treatment for dopamine dysregulation syndrome (DDS) in parkinson's disease. <i>J Neurol.</i> 2013;260(2):521-527.	The study did not involve cannabis use.
Steckler T, Risbrough V. Pharmacological treatment of PTSD - established and new approaches. <i>Neuropharmacology.</i> 2012;62(2):617-627.	Review as of 2011 of pharmacological treatments for PTSD. Mentions cannabinoids only briefly and calls their use problematic.
Stevens JR, Prince JB. Schooling students with psychotic disorders. <i>Child Adolesc Psychiatr Clin North Am.</i> 2012;21(1):187-200.	The study involved youth not adults and not did involve cannabis use.
Subramaniam GA, Stitzer ML, Woody G, Fishman MJ, Kolodner K. Clinical characteristics of treatment-seeking adolescents with opioid versus cannabis/alcohol use disorders. <i>Drug Alcohol Depend.</i> 2009;99(1-3):141-149.	The study involved youth not adults.
The cutting edge of chemistry: A pharma matters report - april 2011. <i>Drugs Future.</i> 2011;36(7):551-561.	The study did not address the key questions.
Thomasius R, Sack P-, Petersen KU. DSM-IV axis-I comorbidity among illicit drug users seeking treatment for substance use disorders: Results from the multi-centre study of psychiatric comorbidity in drug addicts (MUPCDA). <i>Ment Health Subst Use: Dual Diagn.</i> 2010;3(3):182-192.	The study did not address the key questions.
Tidey JW. Using incentives to reduce substance use and other health risk behaviors among people with serious mental illness. <i>Prev Med.</i> 2012;55:S54-S60.	The study did not address the key questions.
Trezza V, Campolongo P. The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder. <i>Front Behav Neurosci.</i> 2013.	The study was a summary of studies involving biochemical pathways.
Tyrer P. From the editor's desk. <i>Br J Psychiatry.</i> 2009;195(4):378.	The study did not meet inclusion criteria (editorial).
Vasileiou I, Fotopoulou G, Matzourani M, Patsouris E, Theocharis S. Evidence for the involvement of cannabinoid receptors' polymorphisms in the pathophysiology of human diseases. <i>Expert Opin Ther Targets.</i> 2013;17(4):363-377.	The study did not involve cannabis use or subjects with PTSD.
Weich L, Pienaar W. Occurrence of comorbid substance use disorders among acute psychiatric inpatients at stikland hospital in the western cape, south africa. <i>Afr J Psychiatry (South Africa).</i> 2009;12(3):213-217.	The study did not address the key questions.
Whelan-Goodinson R, Ponsford J, Johnston L, Grant F. Psychiatric disorders following traumatic brain injury: Their nature and frequency. <i>J Head Trauma Rehabil.</i> 2009;24(5):324-332.	The study did not involve cannabis use.
White J, Mortensen LH, Batty GD. Cognitive ability in early adulthood as a predictor of habitual drug use during later military service and civilian life: the Vietnam Experience Study. <i>Drug Alcohol Depend.</i> 2012 Sep 1;125(1-2):164-8.	The study did not involve cannabis use.
Whitt A, Garland EL, Howard MO. Helium inhalation in adolescents: characteristics of users and prevalence of use. <i>J Psychoactive Drugs.</i> 2012 Nov-Dec;44(5):365-71.	The study did not address the key questions nor did it meet inclusion criteria.
Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in europe 2010. <i>Eur Neuropsychopharmacol.</i> 2011;21(9):655-679.	The study did not address the key questions.
Yager T, Laufer R, Gallops M. Some problems associated with war experience in men of the Vietnam generation. <i>Arch Gen Psychiatry.</i> 1984 Apr;41(4):327-33.	This study does not address the key questions.
Zatzick D, Donovan D, Dunn C, et al. Substance use and posttraumatic stress disorder symptoms in trauma center patients receiving mandated alcohol screening and brief intervention. <i>J Subst Abuse Treat.</i> 2012;43(4):410-417.	The study did not involve cannabis use.

Zlotnick C, Johnson J, Najavits LM. Randomized controlled pilot study of cognitive-behavioral therapy in a sample of incarcerated women with substance use disorder and PTSD. Behav Ther. 2009;40(4):325-336.	The study did not address the key questions nor did it involve cannabis use as treatment for PTSD.
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## Description of the Items Submitted with the Petition

Two notebooks containing paper copies of material submitted to ADHS in support of the petition were assessed, in the order that they appear in the notebooks.

1. Typed statement by William Johnson, M.D. a psychiatrist in Santa Fe, New Mexico, and a copy of his CV. He briefly describes his experience with PTSD patients whom he has certified for Medical Marijuana use since 2009. He reports favorable results although the numbers of patients is not listed and there is no systematic description of verified outcomes, adverse reactions, or any details on the patients and their diagnoses. This would be considered an incomplete description of a case series.
2. A manuscript by Greer GR and a team from Harbor-UCLA Medical Center and the University of California, San Diego that describes a study conducted in New Mexico. The manuscript appears to be in a format to be submitted to a medical journal. There is no evidence that it has been accepted or published. It is a cross sectional study of 80 patients who sought certification for MM use for PTSD and who screened positive for PTSD and a favorable response to MM before evaluation. They were administered a standard tool for assessing PTSD symptoms and were asked to answer the questions for a time period when they were using cannabis and for a time period when they were not. No verification of current or past marijuana use was conducted. Questions were not answered during a actual time period of use or non use of marijuana, the patients were asked to answer them as they would have during those periods. All scores for reported symptoms were significantly different for the use and non use periods. If this study were published it would be considered an extremely low quality study that suffers from self-selection, high probability of reporting bias, and no validation. The authors state in the conclusion that it is not proof of marijuana efficacy for PTSD treatment. The bibliography included 16 citations, 3 of which looked potentially relevant and that were not in the 2012 review. These were obtained and assessed.
  - a. One is described in #20 below
  - b. One was a study on rats.
  - c. One was a description of proposed biochemical pathways for extinction of aversive memories.

3. A manuscript by Krumm BA, Sage Neuroscience Center in Albuquerque. It was submitted somewhere April 20, 2012. It appears it might be intended for either a medical journal or as a request to the DEA to reconsider re-classifying marijuana. It is a description of proposed neurological and biochemical pathways via which marijuana works to treat PTSD.
4. A re- print of a study by Rabinak CA, et al. Cannabinoid facilitation of fear extinction memory recall in humans. *Neuropharmacology* 2012; <http://dx.doi.org/10.1016/j.neuropharm.2012.06.063> This is a study using 29 healthy volunteers who were subjected and sensitized to loud noise and then randomized to synthetic THC (Marinol) or placebo. The THC helped with extinction of conditioned fear as measured by skin conductance. This would be considered an interesting, fairly high quality controlled trial, but not directly pertinent, research project. It should be noted that the agent used was dronabinol, not cannabis.
5. Re print of a study by Rabinak CA, et al. This appears to be the same study cohort as in #4 only the fear extinction was studied by MRI imaging, with the same results as using skin conductance.
6. A CV for CA Rabinak, Ph.D., the lead author of studies described in 4 and 5 above.
7. A document titled “The Use of Medical Cannabis to Treat PTSD” by Dr. Sue Sisley. This appears, possibly, to be written as a critique of the decision by the state of Colorado to not include PTSD as a certifiable condition in the MM program. This document is an advocacy piece--the exact purpose of it is not described--that makes contradictory assertions. In several places it states that recent studies demonstrate “the potential benefits of the use of cannabis for PTSD” yet in other places asserts that the benefits are “scientifically proven” and “Hundreds of recent studies indicate that cannabis is an effective treatment for PTSD.” The statements on effectiveness appear to be based on animal studies, studies of biochemical and anatomical pathways, preliminary studies on neurological functions, and case reports. There are no controlled or uncontrolled clinical trials described that use MM for treatment of PTSD.
8. Article: Neumeister A, et al. Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study. *Molecular Psychiatry* 2013;18: 1034-1040. A study of those with PTSD (N=25) and controls (35) using MRI and PET scans with CB1 receptor antagonist radiotracer. Results suggest that CB1 signaling might be involved with PTSD. It is an interesting study of physiology and biochemical pathways and suggests that CB1 receptor signaling may be involved in the etiology of PTSD. It provides no evidence of effectiveness of MM in treatment of PTSD.
9. Article: Trezza V, Campolongo P. The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder.

- Frontiers in Behavioral Neuroscience 2013;7:1-5. A description of possible neurobiological basis of PTSD and how endocannabinoids might be involved.
10. Article: Passie T, et al. Mitigation of PTSD by Cannabis resin: A review of the clinical and neurobiological evidence. Drug Test Analysis 2012;4:649-659. This is a case report of one patient who reports relief of PTSD symptoms by smoking cannabis resin. It then describes possible mechanisms by which cannabis might work. The authors conclude that “further studies are warranted in order to evaluate the therapeutic potential of cannabinoids in PTSD.” This article has been included in the table of assessed studies.
  11. Article: Ganon-Elazar Eti, Akirav I. Cannabinoids prevent the development of behavioral and endocrine alterations in a rat model of intense stress. Neuropsychopharmacology 2012;37:456-466. This is a study of biochemical pathways in rats.
  12. Article: Akirov I. The role of cannabinoids in modulating emotional and non-emotional memory processes in the hippocampus. Front Behav Neurosci 2011;5:34 This is a review of possible biochemical and anatomical effects of cannabinoids; what is known and what is not.
  13. Article: Ganon-Elazar Eti, Akirav I. Cannabinoid receptor activation in the basolateral amygdala blocks the effects of stress on the conditioning and extinction of inhibitory avoidance. Journal of Neuroscience 2009;29:11078-11088. This is a study of biochemical pathways in rats.
  14. Article: Fusar-Poli P, et al. Distinct effects of 9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. This was a study of 15 healthy males given 9-tetrahydrocannabinol (THC), cannabidiol (CBD), or placebo. Outcomes included MRI scanning, skin conductance and ratings of anxiety. THC and CBD had opposite effects on measures of anxiety. This was a small and interesting study of anatomical and biochemical pathways.
  15. Article: Resstel L, et al. 5-HT<sub>1A</sub> receptors are involved in the cannabidiol-induced attenuation of behavioral and cardiovascular responses to acute restraint stress in rats. British J of Pharmacology 2009;156:181-188. Study of biochemical pathways in rats.
  16. Article: Chhatwal JP, et al. Functional interactions between endocannabinoid and CCK neurotransmitter systems may be critical for extinction learning. Neuropsychopharmacology 2008; 1-13. This is a review of proposed biochemical and anatomical pathways of conditioned fear and proposed mechanisms of cannabinoids.
  17. Article: Chhatwal JP, et al. Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. Neuropsychopharmacology 2005;30:516-524. A review of the proposed biochemical basis of cannabinoids as anti-anxiety treatments.

18. Article: Lin HC, et al. Effects of intra-amygdala infusion of CBI receptor agonists on the reconsolidation of fear-potentiated startle. *Learning and Memory* 2006;13:316-321. This is a rat study of biochemical pathways.
19. Article: Pamplona FA, et al. The cannabinoid receptor agonist WIN 55,212-2 facilitates the extinction of contextual fear memory and spatial memory in rats. *Psychopharmacology* 2006; volume and pages not listed. This is a rat study of biochemical pathways.
20. Article: Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in PTSD. *CNS Neuroscience and Therapeutics* 2009;15:84-89. This is a report of a cohort of 47 patients with PTSD referred to a Canadian referral center who had treatment-resistant nightmares. They were given nabilone. Later their charts were reviewed. 72% reported cessation of nightmares or reduction in intensity. The authors recognize the limitations of the study such as self-reporting of symptoms, no placebo, retrospective assessment, and small numbers. However, it is one of the few human studies available. It should be noted that the intervention used was nabilone, not marijuana, and that nabilone is an FDA approved drug, although for other conditions, not PTSD. It was approved in 1985 for treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemetics and for use in treatment of anorexia and weight loss in patients with AIDS. This article has been included in the table of assessed studies.
21. Article: Marsicano G, et al. The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 2002;418: 530-534. Study of biochemical pathways in mice.
22. Commentary by Tod Mikuriya titled Cannabis Eases Post Traumatic Stress. It is not clear where and when it was published. It describes briefly the results of over 9000 Californians whose cannabis the author has monitored. General statements are made about the effects on those with PTSD but no data are provided.
23. A report from the New Mexico Medical Advisory Board to the Medical Cannabis Program. This is a report from a public hearing on November 7, 2012. There were several actions taken, the one pertinent to this report involved consideration of removing PTSD from the list of approved conditions in New Mexico. The report states that (at the time of the report) 3350 patients were enrolled in the New Mexico medical cannabis program for treatment of PTSD (42 % of those in the program). A petition was submitted by an individual psychiatrist to have PTSD removed from the list. His position was supported by the Psychiatric Association of New Mexico and the American Psychiatric Association, but the Medical Advisory Board objected to the position of these two professional organizations over procedural issues and lack of transparency. The paper states that there had been no reports of serious adverse events from the use of marijuana for PTSD. It is not clear

if the system to monitor for adverse reactions is an active or passive reporting system. The Medical Advisory Board recommended rejection of the petition.

24. A document titled, Post-Traumatic Stress Disorder and the Oregon Medical Marijuana Program. It appears to be some kind of background paper prepared for policy makers in Oregon that describes some difficulties getting conditions added to the approved list in Oregon. It includes the Oregon statute that established the program, a description of administrative difficulties with the program, a table that lists details about medical marijuana programs in other states, and the document listed in #23 above.
25. A packet of information submitted by a group called Four Freedoms to the Michigan Medical Marijuana Review Panel in response to their decision to deny PTSD as a qualifying condition. The material contains: a cover letter, not dated ; a reprint from an online source called Reason, dated march 22, 2013, that describes personal stories of veterans with PTSD; s story from MAPS Bulletin Annual Report (MAPS, we think is the Multidisciplinary Association for Psychedelic Studies) that describes the proposed study by Dr. Sue Sisely; a power point presentation by Mordechai Mashiah at a conference in Tucson on April 28, 2012 that describes a study in Israel of 29 subjects, 10 of whom completed the whole study; an article by Ware MA, et al on treatment of neuropathic pain with cannabis; an article by Abrams DI, et al on the interaction of cannabinoids and opioids in chronic pain; articles described in #10,13,14, 15,16,17,18,19,20 above; and an article by Pacher P, et al of 38 pages that reviews the endocannabinoid system and possible targets for pharmacotherapy, published in Pharmacology Review in 2006, which did not list PTSD.

## **Current Research**

A search of the clinical trials data base found only one study titled “Add on Study on  $\Delta$ 9-THC Treatment for Posttraumatic Stress Disorders (PTSD)  
<http://ClinicalTrials.gov/show/NCT00965809>”.

## **Conclusions**

There is a growing body of evidence concerning the basic science of cannabinoid receptors and the potential effects of cannabinoids in animals and humans.

Observational studies of varying quality demonstrate an association between PTSD and the use of various substances such as alcohol, cocaine and marijuana and that those with PTSD report the use of these substances to cope with the symptoms of PTSD. There is a high degree of certainty of this association but it is not possible to determine if PTSD causes alcohol and other substance use, the reverse, or if both are associated with another condition.

The evidence regarding the effects of using marijuana or other cannabinoids to treat the symptoms of PTSD in humans consists of the following:

- Case reports
- A case series of low quality using nabilone, not marijuana (with beneficial effects on nightmare frequency)
- A prospective cohort of very low quality (with beneficial effects on PTSD symptoms and quality of life)
- A cross sectional study of low quality (with harmful effects of increased use of cannabis to cope, severity of cannabis withdrawal, and craving of cannabis.)
- A cross sectional study of low quality validating the correlation between increase PTSD symptoms and increased marijuana use for coping.

The totality of this evidence should be considered very low quality with a high degree of uncertainty.

# Appendix 1

## Search Terms

“Stress Disorders, Post-Traumatic”[Mesh]

Covers these Entry Terms:

- Post-Traumatic Stress Disorder
- Stress Disorder, Post-Traumatic
- Stress Disorders, Post Traumatic
- PTSD
- Stress Disorder, Post Traumatic
- Neuroses, Posttraumatic
- Posttraumatic Neuroses
- Posttraumatic Stress Disorders
- Posttraumatic Stress Disorder
- Stress Disorder, Posttraumatic
- Stress Disorders, Posttraumatic
- Neuroses, Post-Traumatic
- Neuroses, Post Traumatic
- Post-Traumatic Neuroses
- Post-Traumatic Stress Disorders
- Post Traumatic Stress Disorders
- Chronic Post-Traumatic Stress Disorder
- Chronic Post Traumatic Stress Disorder
- Delayed Onset Post-Traumatic Stress Disorder
- Delayed Onset Post Traumatic Stress Disorder
- Acute Post-Traumatic Stress Disorder
- Acute Post Traumatic Stress Disorder

ANDED with:

((“cannabis”[Mesh] OR “marijuana”[All Fields]) OR (“cannabis”[Mesh Terms] OR “cannabis”[All Fields] OR “marihuana”[All Fields]) OR “medical marijuana”[All Fields] OR “Marijuana Smoking”[Mesh] OR “cannabinoids”[Mesh] OR “cannabis”[Mesh] OR “Tetrahydrocannabinol”[Mesh])

## Appendix 2

### BOX 1 Taxonomy of study designs to assess the effectiveness of an intervention

#### Experimental designs

A study in which the investigator has control over at least some study conditions, particularly decisions concerning the allocation of participants to different intervention groups.

1. **Randomised controlled trial**

Participants are randomly allocated to intervention or control groups and followed up over time to assess any differences in outcome rates. Randomisation with allocation concealment ensures that on average known and unknown determinants of outcome are evenly distributed between groups.

2. **Quasi-randomised trial**

Participants are allocated to intervention or control groups by the investigator, but the method of allocation falls short of genuine randomisation and allocation concealment (e.g. allocated by date of birth, hospital record number, etc.)

3. **Non-randomised trial/quasi-experimental study**

The investigator has control over the allocation of participants to groups, but does not attempt randomisation (e.g. patient or physician preference). Differs from a 'cohort study' in that the intention is experimental rather than observational.

#### Observational designs

A study in which natural variation in interventions (or exposure) among study participants is investigated to explore the effect of the interventions (or exposure) on health outcomes.

4. **Controlled before-and-after study**

A follow-up study of participants who have received an intervention and those who have not, measuring the outcome variable both at baseline and after the intervention period, comparing either final values if the groups are comparable at baseline, or change scores. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.

5. **Concurrent cohort study**

A follow-up study that compares outcomes between participants who have received an intervention and those who have not. Participants are studied during the same (concurrent) period either prospectively or, more commonly, retrospectively.

6. **Historical cohort study**

A variation on the traditional cohort study where the outcome from a new intervention is established for participants studied in one period and compared with those who did not receive the intervention in a previous period, i.e. participants are not studied concurrently.

7. **Case-control study**

Participants with and without a given outcome are identified (cases and controls respectively) and exposure to a given intervention(s) between the two groups compared.

8. **Before-and-after study**

Comparison of outcomes from study participants before and after an intervention is introduced. The before and after measurements may be made in the same participants, or in different samples. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.

9. **Cross-sectional study**

Examination of the relationship between disease and other variables of interest as they exist in a defined population at one particular time point.

10. **Case series**

Description of a number of cases of an intervention and outcome (no comparison with a control group).

### Appendix 3

#### GRADE Method to Assess Overall Quality of the Evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or
	Very low	Imprecision -1 Serious -2 Very serious  Publication bias -1 Likely -2 Very likely	+1 Would suggest a spurious effect when results show no effect