

The Benefits and Harms of Cannabis Use in Chronic Pain or PTSD: A Systematic Review

VA Portland Health Care System
Evidence-based Synthesis Program

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Presentation Overview

- Background
 - Changing culture of cannabis in the U.S.
- Methods
- Results
 - Chronic pain, PTSD, Harms
- Panel Discussion
 - Clinical considerations and implications
- Participant Questions



VA Evidence-based Synthesis Program Overview

- Sponsored by VA Office of Research and Development and the Quality Enhancement Research Initiative (QUERI)
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers, and policy-makers, as they work to improve the health and healthcare of Veterans



VA Evidence-based Synthesis Program:

Evidence syntheses on important clinical practice topics relevant to Veterans help:

- develop clinical policies informed by evidence the implementation of effective services
- support VA clinical practice guidelines and performance measures
- guide future research to address clinical knowledge gaps

Topic Nomination:

<http://www.hsrd.research.va.gov/publications/esp/TopicNomination.cfm>



Portland VA Evidence-based Synthesis Program: Current Report

Background: Cannabis is increasingly available for the treatment of chronic pain and PTSD, yet its efficacy remains uncertain

Purpose: To systematically review the benefits and harms of cannabis for treating chronic pain or PTSD in adults

Full Report (Kansagara, et al.) available at the VA ESP website:

<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>



Poll Question #1

- What is your primary role (pick one)?
 - VA Clinician
 - VA Researcher
 - VA Administrator, manager or policy maker
 - Non-VA Employee
 - Other



Poll Question #2

- Have you encountered a patient who uses cannabis for chronic pain or PTSD?
 - I have encountered one or more patients who use cannabis for chronic pain only.
 - I have encountered one or more patients who use cannabis for PTSD only.
 - I have encountered patients who report using cannabis for both chronic pain and PTSD.
 - I have never encountered a patient who reported using cannabis for pain or PTSD.
 - I am not a clinician.



Poll Question #3

Do you recommend the medicinal use of cannabis for chronic pain or PTSD?

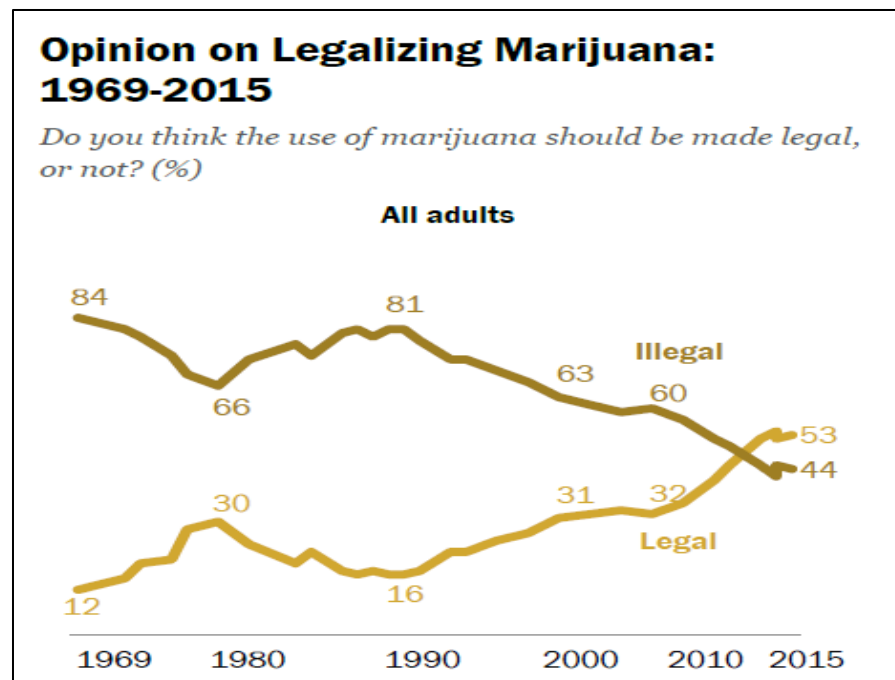
- Yes, for both.
- Yes, for chronic pain, but not PTSD
- Yes for PTSD, but not chronic pain
- Uncertain

See Alder & Colbert (2013) for a similar NEJM poll related to medicinal cannabis



Cannabis in the U.S.

- Greater proportions of the U.S. population view cannabis as acceptable (Pew Research Center, 2015)



Background on Cannabis

- Cannabis has 3 major species:
 - Sativa – most common
 - Indica
 - Ruderalis



Background on Cannabis

- Delta-9-tetrahydrocannabinol (THC)
 - Most studied
 - Considered the major active molecule of cannabis
- Cannabidiol (CBD)
 - Believed to have some medical benefits, but without the euphoria produced by THC
- Potency
 - Recent increase in the potency of cannabis (Pierre, 2017)
 - Labeling inaccuracies (Vandrey et al., 2015)



Background on Cannabis

- Numerous routes of administration
 - Smoking, edibles, tinctures, transdermal patch, suppository, topical cream, eat the raw plant, beverage, dabbing
- Different routes of administration have different effects
- ~40% of medical cannabis users use “vaping” as a route of administration (Cranford et al., 2016)



Cannabis Use for Chronic Pain

- Of patients seeking state-sanctioned medical marijuana, the most common reason is for chronic pain (~80%) (Ilgen et al., 2013)
- 20-40% of patients prescribed opioids report concurrent use of cannabis (Degenhardt et al., 2015; Reinfeld et al., 2009)



Cannabis Use for PTSD

- Over one-third of patients seeking state-sanctioned medical cannabis list PTSD as the primary reason (Bowles, 2012)
- 15% of Veterans who are treated in VA outpatient PTSD clinics report recent cannabis use (Boden et al., 2013)



VA Cannabis Policy



- **H.R. 2577**
 - Would allow federally-employed physicians working for the Veterans Health Administration to recommend cannabis for medical purposes to Veterans if appropriate in states that have legalized its use.



ESP Methods

Topic Development

- Key Questions.
- PICOTS (Population, Intervention, Comparator, Outcomes, Timing, Study Design).

Data Sources and Search

- MEDLINE, EMBASE, PubMed, PsycINFO, Cochrane databases to February 2016.
- Clinical trial registries; technical advisors; reference lists.

Study Selection

- English-language intervention trials.
- Rigorously designed observational studies with control group.
- Plant-based cannabis preparations.



PICOTS

- Population
 - Non-pregnant adults with chronic pain or PTSD (effectiveness)
 - Chronic pain, PTSD, and general population (harms)
- Intervention
 - Plant-based cannabis preparations
 - Included pharmaceutically prepared products
- Comparator
 - Placebo, non-users

PICOTS

- Outcomes
 - Chronic Pain: Pain intensity and function, spasticity
 - PTSD: Symptom severity
 - Mood, sleep, quality of life, health care utilization
 - Harms: medical and mental health harms
- Time
 - Any length of follow-up time
- Study Design
 - Systematic reviews, RCTs, rigorously designed observational studies with control group, case series

ESP Methods

Data Abstraction

- Study design, setting, patient population, intervention, follow-up, important co-interventions, health outcomes, healthcare utilization, and harms.
- Dual investigator abstraction process.

Quality Assessment

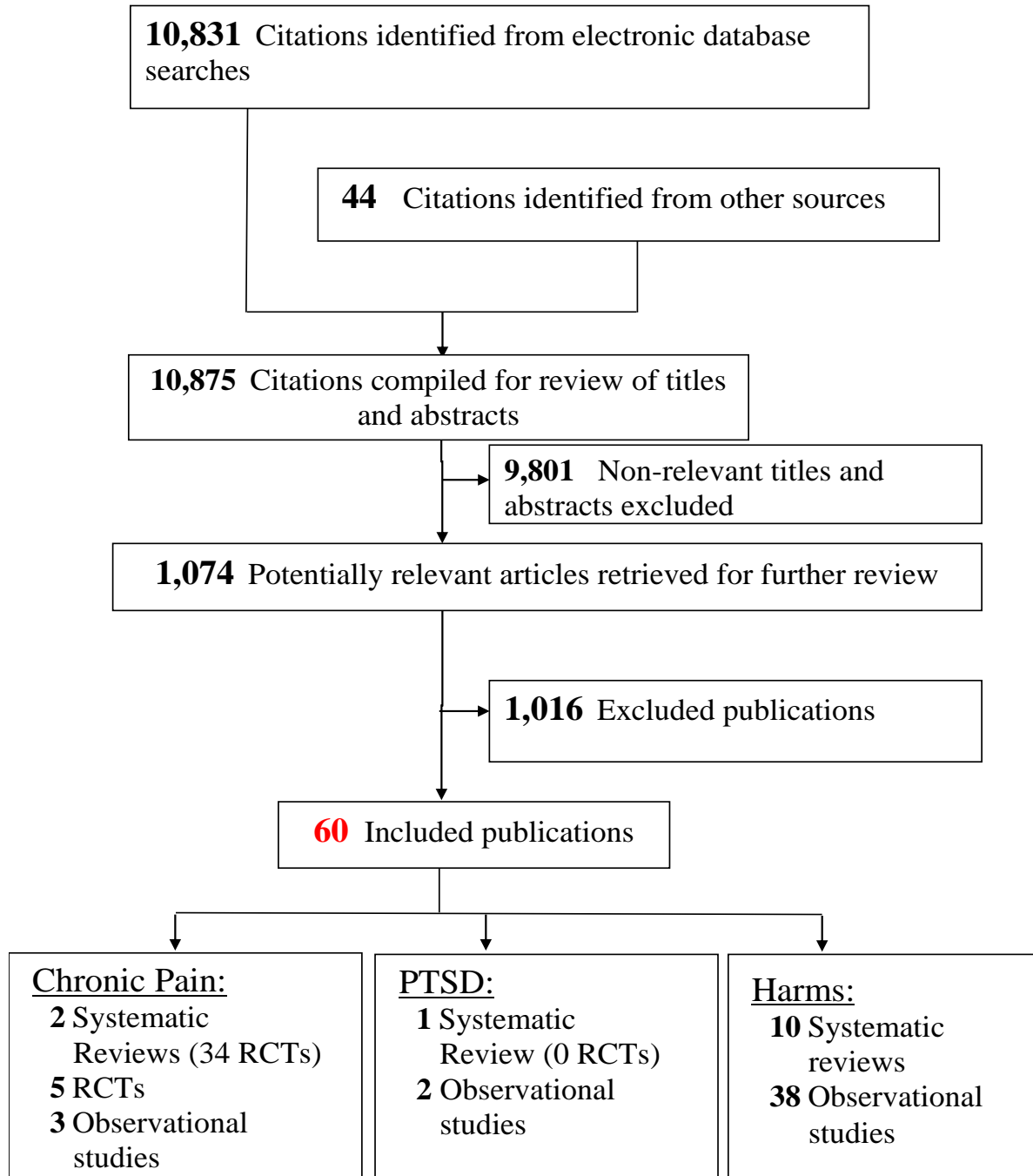
- Risk of Bias (ROB) assessed utilized published assessment tools:
 - Trials (Cochrane), Observational (Newcastle-Ottawa).
- ROB rated as High, Low, or Unclear.

Data Synthesis

- Could not combine findings in meta-analysis.
- Strength of Evidence (SOE) for each outcome classified as high, moderate, low, or insufficient.
 - Consistency, coherence, and applicability of the body of evidence; internal validity of individual studies.



Literature Flow



Strength of Evidence for Chronic Pain

Pain Condition	Number of studies/ROB	SOE	Primary Intervention of Low ROB studies	Limitations
Multiple Sclerosis	<ul style="list-style-type: none"> - 4 Low ROB (N=1017) - 3 Unclear ROB - 7 High ROB 	Low – Pain, spasticity, and sleep	<ul style="list-style-type: none"> - Nabiximols (2.7 mg THC/2.5 mg CBD) - THC (2.5mg) capsules 	Inconsistent results; restrictive entry criteria
Neuropathy	<ul style="list-style-type: none"> - 2 Low ROB (N=62) - 4 Unclear ROB - 12 High ROB 	Insufficient	<ul style="list-style-type: none"> - Smoked: % THC = 0, 2.5, 6, 9 - Vaporized: % THC = 1.29, 3.55 	Small N; inconsistent results below clinical threshold
Other/mixed	<ul style="list-style-type: none"> - 2 Low ROB (N=465) - 3 Unclear ROB - 3 High ROB 	Insufficient	<ul style="list-style-type: none"> - 12.5% ± 1.5% THC - 1:1 THC/CBD, CBD only, THC only 	One small (n=34) trial; observational study, high attrition
Cancer	<ul style="list-style-type: none"> - 2 Unclear ROB 	Insufficient	N/A	Use of non-validated measures, high attrition

Ongoing Studies: Chronic Pain

- 7 RCTs
 - Musculoskeletal pain (2), cancer (2), spinal cord injury (1), ulcerative colitis (1), mixed conditions (1)
 - Various routes of administration: oral capsule or vaporized
 - Examine various potencies and ratios of CBD:THC



PTSD Results

- Included studies were limited to those that included a non-cannabis using comparison group
- 1 Systematic review and 2 observational studies provided **insufficient evidence** related to the effectiveness of cannabis for treating PTSD



PTSD Results: Wilkenson et al. 2016

Systematic Review

- None of the studies included in the Wilkinson et al., 2016 systematic review met our inclusion criteria even though it included a broader range of preparations including synthetics. Their findings:
 - “The strength of evidence for the use of medical marijuana for psychiatric indications of PTSD... is very low at the present time.”
 - “The consequences of chronic cannabinoid exposure includes tolerance, dependence, and withdrawal. Early and persistent marijuana use has been associated with the emergence of psychosis. Marijuana impairs attention, memory, IQ, and driving ability.”



Summary of Included PTSD Studies and Results

Study, setting, design , N, Risk of bias	Sample description Mean age % male	Description and duration of cannabis use and comparators	Primary findings
<p>Wilkinson 2015 Retrospective cohort study N=2276 Medium ROB</p>	<p>All Veterans referred for intensive PTSD treatment. Excluded those with prior drug or alcohol use. Mean age 51.7 96.7% male</p>	<p>Self-reported cannabis use, 4-month follow-up:</p> <ul style="list-style-type: none"> • 850 never users • 299 stoppers (use at admission, not follow-up) • 296 continuing users (admission and follow-up) • 831 starters (no use at admission, use at follow-up) <p>Usual medical care including psychotropic medications and psychotherapy provided to all participants</p>	<p>Continuing users and starters had significantly worse PTSD symptoms than never users and stoppers: F=21.47, P<.0001</p>
<p>Johnson 2016 Matched case control cross sectional study N=700 High ROB</p>	<p>All Veterans with a probable PTSD diagnosis referred for a primary care/mental health integration program based on clinical need following mental health screening or clinical judgment. Mean age 47.1 91.0% male</p>	<p>Self-reported cannabis use within 3 months of the assessment (n=350)</p> <p>Compared to no lifetime cannabis use reported at the time of assessment (n=350)</p> <p>Users were matched to non-users on age and gender</p>	<p>Users had significantly worse PTSD symptoms than non-users: t (349) = 0.11, P=.91</p>

PTSD Ongoing Studies

- 3 RCTs: Effectiveness of cannabis for treating PTSD, effects of CBD vs. THC content, and effects of CBT-Insomnia on cannabis use
- 4 observational studies: Cannabis use and exposure therapy, PTSD, other clinical outcomes, functional outcomes, and sleep
- Will provide stronger evidence related to effectiveness and harms in the next few years



Harms Associated with Cannabis Use

- Cannabis use is associated with a higher likelihood of adverse events, but not serious adverse events (Ware et al., 2015)
- General adverse events among patients with chronic pain
 - AEs: dizziness, lightheadedness, fatigue, muscle spasms, dry-mouth, short-term memory impairment
 - SAEs: suicide attempts, paranoia, and agitation



Mental Health Harms in General Population

Mental Health Harm	Findings/ Strength of Evidence (SOE)	Data Source	Limitations
Psychosis	Low strength evidence that a history of cannabis use was associated with an increase in risk of developing psychotic symptoms.	Systematic Review (Moore et al., 2007) -7 additional studies	Magnitude of risk uncertain.
Mania	Increased incidence of new-onset mania symptoms among populations without a diagnosis of bipolar disorder, (OR 2.97; 95% CI, 1.80 to 4.90)	Meta-analysis/ Systematic Review (Gibbs et al.,2015)	Small # of studies.
Suicide related behaviors	Suicide ideation (pooled OR 1.43; 95% CI, 1.13 to 1.83) Suicide attempt (pooled OR 2.23; 95% CI, 1.24 to 4.00) Death by suicide (OR 2.56; 95% CI, 1.25 to 5.27)	Meta analysis (Borges et al., 2016)	No data on acute cannabis use. Heterogeneity of exposure measurement.



Mental Health Harms Associated with Cannabis Use

Mental Health Harm	Findings/ Strength of Evidence (SOE)	Data Source	Limitations
Cognitive effects	<p>Moderate SOE that active, long-term cannabis use is associated with small negative effects on all domains of cognitive function;</p> <p>Insufficient evidence of long-term cognitive effects in past users.</p>	<p>Systematic Review (Schreiner et al., 2012)</p>	<p>Inconsistent data about past use.</p>
Cannabis Use Disorder (Pain pts)	<p>No evidence.</p> <p>Prevalence of cannabis misuse = 2.4% and dependence = 0.9%</p>	<p>Observational (Fleming et al., 2007)</p>	<p>Data are cross-sectional.</p>



Medical Harms Associated with Cannabis Use

Medical Harm	Findings/ Strength of Evidence (SOE)	Data Source	Limitations
Pulmonary Function	Moderate strength of evidence that there is <u>no adverse effect</u> for low levels of smoking among young adults.	<ul style="list-style-type: none"> - 2 Low ROB prospective, cohort (N = 6053) - 1 systematic review (N = 851) 	No data on heavy use or on older, chronically ill patients.
Cardiovascular	<u>Insufficient evidence</u> of cardiovascular harms in short or long term light cannabis use.	- 2 High ROB observational	Recall bias, no data about longitudinal exposure.



Medical Harms Associated with Cannabis Use

Medical Harm	Findings/ Strength of Evidence (SOE)	Data Source	Limitations
Lung Cancer	Low SOE that there is <u>no association</u> between light cannabis use and lung cancer.	<ul style="list-style-type: none"> - 1 patient-level meta-analysis of 6 case-control studies (2150 cases) - 1 High ROB cohort study (N = 49,231) 	Recall bias, light users.
Head and Neck Cancer	Low SOE that there is <u>no association</u> between head and neck cancer and cannabis use.	<ul style="list-style-type: none"> - Meta-analysis of 9 case-control studies (5732 cases) 	Imprecise exposure measurement, recall bias.



Medical Harms Associated with Cannabis Use

Medical Harm	Findings/ Strength of Evidence (SOE)	Data Source	Limitations
Testicular Cancer	<u>Insufficient evidence</u> of association.	- Meta-analysis of 3 High ROB case-control studies	Recall bias and potentially confounded by tobacco use.
Transitional Cell Cancer	<u>Insufficient evidence</u> of an increased risk among those with >40 joint years.	- 1 High ROB case-control study (52 cases)	Small and methodologically limited.



Other Harms Associated with Cannabis Use

- Motor Vehicle Accidents (MVA)
 - Moderate strength evidence that acute cannabis intoxication is associated with increase in collision risk. (Rogeberg et al., 2016)
 - (OR 1.35; 95% CI = 1.15 - 1.61)
- Emerging Harms
 - Cannabis hyperemesis syndrome
 - Exposure to contaminants
 - Exposure to infectious diseases



Summary: Chronic Pain

- Cannabis (nabiximols) may improve pain, spasticity, and sleep in patients with multiple sclerosis (Low SOE).
- Insufficient data on other secondary outcomes.
- Insufficient data for other chronic pain patient populations.
- Insufficient data on non-nabiximols preparations or other routes of administration for pain.



Summary: PTSD

- Insufficient evidence from two observational studies to draw conclusions about the effectiveness of cannabis in patients with PTSD
- 7 ongoing studies of cannabis to treat PTSD
- No studies of harms of cannabis in patients with PTSD
- Increased risk of some harms in a general population that are potentially relevant for patients with PTSD including cognitive functioning and mental health effects



Summary: Harms

- Cannabis use may be associated with:
 - Increased risk of mental health adverse effects in a general population.
 - Psychosis, mania, suicide related behaviors
 - Strength of evidence on its long term and physical effects is low and inconsistent.



Limitations

- OF EVIDENCE BASE:
 - Few methodologically rigorous trials.
 - Limited or no trials available on musculoskeletal pain, cancer pain, and other pain conditions.
 - Cannabis formulations studied in trials may not reflect what is available in dispensaries.
 - Applicability to heavy users or older, chronically ill populations is limited.
 - Short follow-up duration.
- OF OUR SYSTEMATIC REVIEW:
 - Relied on existing high quality systematic reviews when available.
 - Excluded studies of synthetic, prescription cannabinoids.



Discussion

- Recent cannabis related reviews
- Evidence-based treatment for chronic pain
 - Considerations related to cannabis use and opioid epidemic
- Cannabis Use Disorder diagnosis and treatment
- Evidence-based treatment for PTSD
 - Considerations related to the possibility of mental health and cognitive functioning adverse effects
 - Weighing risks and benefits with patients and discussing alternative evidence-based options



Other Recent Reviews

- Recent systematic reviews:
 - Non-significant trend towards benefit of pain reduction (low to moderate SOE) (Whiting et al., 2015)
 - Insufficient to low SOE for benefit (Butler et al., 2015)
- National Academies of Science, Engineering, and Medicine
 - “There is substantial evidence that cannabis is effective for the treatment of chronic pain in adults.”



Chronic Pain Treatment

- Effective non-pharmacologic therapies: exercise, cognitive behavioral therapy (CBT), interventional procedures
- Effective non-opioid medications: acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antidepressants

(Dowell et al., 2016)



Clinical Practice Recommendations



RESEARCH
EDUCATION
TREATMENT
ADVOCACY



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Focus Article

Cannabis in Pain Treatment: Clinical and Research Considerations

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Clinical Practice Recommendations for Pain

- Awareness of federal, state, and institutional policies and laws.
- Establish goals of care for cannabis use.
- Screen for signs of misuse, abuse, and addiction.
- Counsel patients on harms and risks.
- Advise on routes of administration.
- Continually monitor cannabis use/utility, functional status, symptom severity, and use of other medications/substances.
 - Consider use of urine drug tests.
- Monitor for other harms (i.e. MVA, falls).
- Advise on discontinuation or referral to substance use treatment.

Savage et al., 2016



Cannabis Use Disorder

- DSM 5 Criteria for Cannabis Use Disorder (CUD)
- CUD treatment
 - No FDA approved medications to treat CUD
 - Contingency Management, Motivational Enhancement Therapy, Cognitive Behavioral Therapy



PTSD Treatment Considerations

- Possible harms of cannabis use particularly salient for patients with PTSD
- Other evidence-based treatments for PTSD
 - VA/DoD Clinical Practice Guideline for PTSD
- Patient and provider resources available at the National Center for PTSD website:
<https://www.ptsd.va.gov/>
- Currently, the evidence base is insufficient



Discussants

- Karen Drexler, MD, Deputy National Mental Health Program Director
- Paula Schnurr, PhD, Executive Director of the National Center for PTSD
- John Williams, MD, Director of the Durham VA ESP



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