DEFENSE CENTERS OF EXCELLENCE
For Psychological Health & Traumatic Brain Injury

Scientific Reviews of Recent Studies on the Treatment of Posttraumatic Stress Disorder

January 28, 2016; 1-2:30 p.m. (ET)

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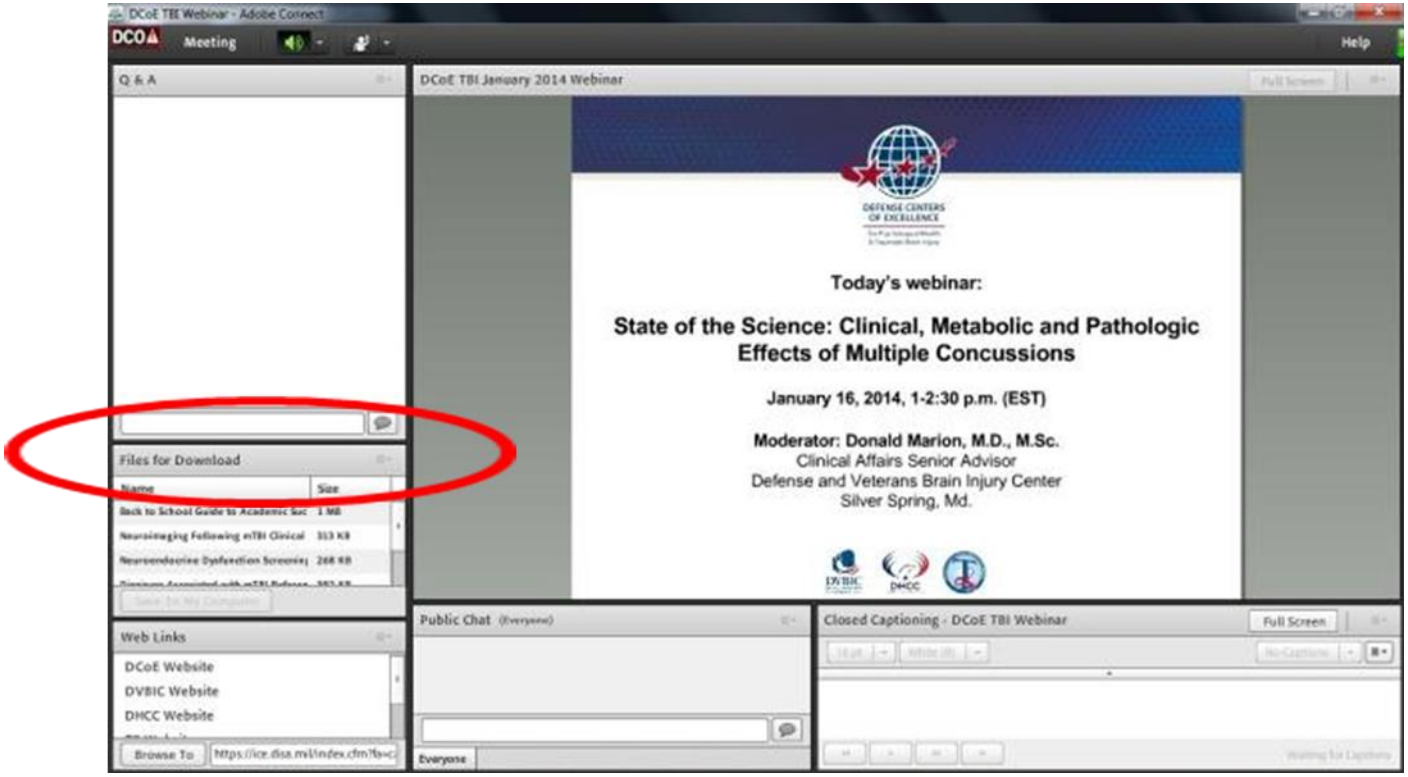
DVBIC
DHCC

Webinar Details

- Live closed captioning is available through Federal Relay Conference Captioning (see the “Closed Captioning” box)
- Webinar audio is not provided through Adobe Connect or Defense Connect Online
  - Dial: CONUS 888-455-0936; International 773-799-3736 Use participant pass code: 1825070
- Question-and-answer (Q&A) session
  - Submit questions via the Q&A box

Resources Available for Download

Today's presentation and resources are available for download in the "Files" box on the screen, or visit **dvbic.dcoe.mil/online-education**



Continuing Education Details

- DCoE's awarding of continuing education (CE) credit is limited in scope to health care providers who actively provide psychological health and traumatic brain injury care to active-duty U.S. service members, reservists, National Guardsmen, military veterans and/or their families.

- The authority for training of contractors is at the discretion of the chief contracting official.
  - Currently, only those contractors with scope of work or with commensurate contract language are permitted in this training.

Continuing Education Accreditation

- This continuing education activity is provided through collaboration between DCoE and Professional Education Services Group (PESG).

- Credit Designations include:
  - 1.5 AMA PRA Category 1 credits
  - 1.5 ACCME Non Physician CME credits
  - 1.5 ANCC Nursing contact hours
  - 1.5 CRCC
  - 1.5 APA Division 22 contact hours
  - 0.15 ASHA Intermediate level, Professional area
  - 1.5 CCM hours
  - 1.5 AANP contact hours
  - 1.5 AAPA Category 1 CME credit

Continuing Education Accreditation

Physicians
This activity has been planned and implemented in accordance with the essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME). Professional Education Services Group is accredited by the ACCME as a provider of continuing medical education for physicians. This activity has been approved for a maximum of 1.5 hours of *AMA PRA Category 1 Credits* ™. Physicians should only claim credit to the extent of their participation.

Nurses
Nurse CE is provided for this program through collaboration between DCOE and Professional Education Services Group (PESG). Professional Education Services Group is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. This activity provides a maximum of 1.5 contact hours of nurse CE credit.

Occupational Therapists
(ACCME Non Physician CME Credit) For the purpose of recertification, The National Board for Certification in Occupational Therapy (NBCOT) accepts certificates of participation for educational activities certified for AMA PRA Category 1 Credit ™ from organizations accredited by ACCME. Occupational Therapists may receive a maximum of 1.5 hours for completing this live
program.

Physical Therapists
Physical Therapists will be provided a certificate of participation for educational activities certified for AMA PRA Category 1 Credit ™. Physical Therapists may receive a maximum of 1.5 hours for completing this live program.

Continuing Education Accreditation

Psychologists
This Conference is approved for up to 1.5 hours of continuing education. APA Division 22 (Rehabilitation Psychology) is approved by the American Psychological Association to sponsor continuing education for psychologists. APA Division 22 maintains responsibility for this program and its content.

Physical Therapists
Physical Therapists will be provided a certificate of participation for educational activities certified for AMA PRA Category 1 Credit™. Physical Therapists may receive a maximum of 1.5 hours for completing this live program.

Psychologists
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Rehabilitation Counselors
The Commission on Rehabilitation Counselor Certification (CRCC) has pre-approved this activity for 1.5 clock hours of continuing education credit.

Speech-Language Professionals
This activity is approved for up to 0.15 ASHA CEUs (Intermediate level, Professional area)

Continuing Education Accreditation

Case Managers
This program has been pre-approved by The Commission for Case Manager Certification to provide continuing education credit to CCM® board certified case managers. The course is approved for up to 1.5 clock hours. PESG will also make available a General Participation Certificate to all other attendees completing the program evaluation.

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Professional Education Services Group is accredited by the American Academy of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider number: 031105. This course if offered for 1.5 contact hours (which includes 0 hours of pharmacology).

Physician Assistants
This Program has been reviewed and is approved for a maximum of 1.5 hours of AAPA Category 1 CME credit by the Physician Assistant Review Panel. Physician Assistants should claim only those hours actually spent participating in the CME activity. This Program has been planned in accordance with AAPA's CME Standards for Live Programs and for Commercial Support of Live Programs.

Other Professionals
Other professionals participating in this activity may obtain a General Participation Certificate indicating participation and the number of hours of continuing education credit.

Questions and Chat

- Throughout the webinar, you are welcome to submit technical or content-related questions via the Q&A pod located on the screen. **Please do not submit technical or content-related questions via the chat pod**.
- The Q&A pod is monitored during the webinar; questions will be forwarded to presenters for response during the Q&A session.
- Participants may chat with one another during the webinar using the chat pod.
- The chat function will remain open 10 minutes after the conclusion of the webinar.

Webinar Overview

The Department of Defense (DoD) and Department of Veterans Affairs (VA) collaborated with the Institute of Medicine (IOM) in a two-phased review of prevention, screening, diagnosis, treatment and rehabilitation of posttraumatic stress disorder (PTSD). Phase I assessed DoD and VA collaborative efforts as well as related research studies and clinical trials. In Phase II, IOM gathered additional data from site visits at military treatment facilities (MTFs) and VA facilities and from literature reviews. Using these methods, IOM examined PTSD management systems and identified components to assist DoD and VA in closing gaps in care, improving delivery of care and increasing quality of care. In addition, several MTFs provided valuable insights into evidence-based treatments in areas of psychotherapy and pharmacotherapy, as well as complementary and alternative therapies, such as acupuncture, art therapy and biofeedback.

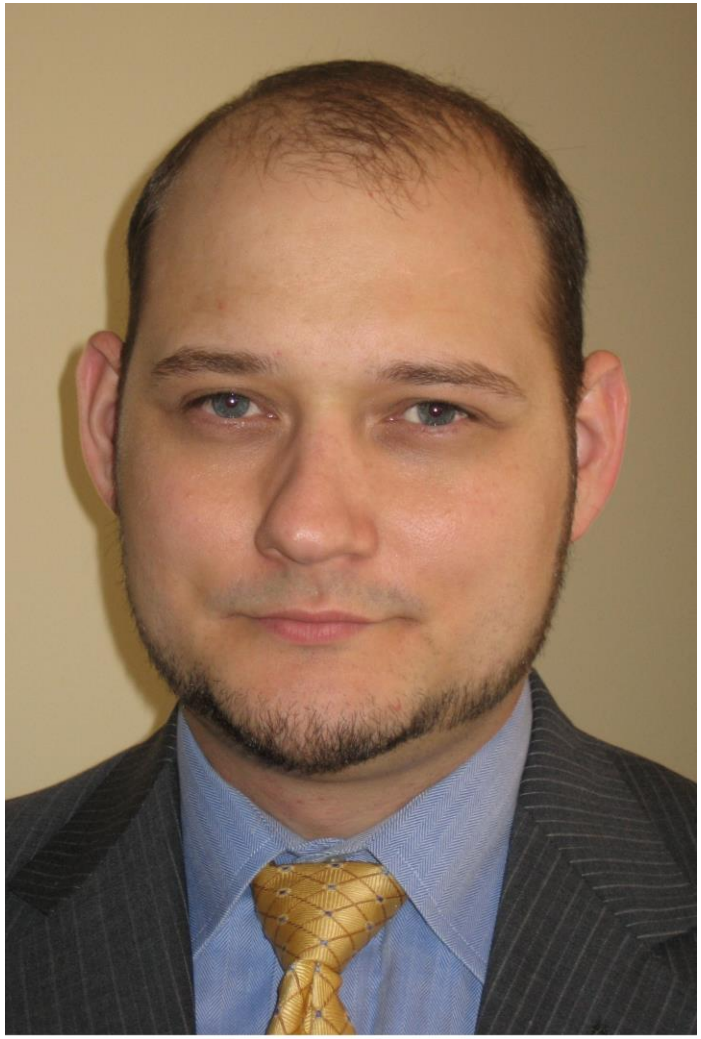
At the conclusion of this webinar, participants will be able to:

- Define the role of scientific reviews in the treatment of PTSD
- Examine current PTSD treatment guidelines
- Identify recent scientific reviews of PTSD treatment
- Incorporate new evidence into practice

Bradley E. Belsher, Ph.D.

- Dr. Bradley Belsher, Ph.D., is an employee of the Henry M. Jackson Foundation for the Advancement of Military Medicine. Dr. Belsher serves as a clinical research psychologist in the Research Directorate of the DoD Deployment Health Clinical Center (DHCC). He is licensed to practice as a clinical psychologist in the Commonwealth of Virginia.
- Dr. Belsher also holds an appointment as a Research Assistant Professor in the Department of Psychiatry at the Uniformed Services University of the Health Sciences.
- Dr. Belsher has significant experience implementing trauma-based interventions and supervising the delivery of these interventions.
- Prior to working at DHCC, Dr. Belsher trained in the Veterans Affairs where he was involved with several telehealth research projects aimed at improving care for veterans experiencing posttraumatic stress symptoms.
- Dr. Belsher is the author of numerous peer-reviewed publications, book chapters, and scholarly presentations.

Daniel P. Evatt, Ph.D.



- Clinical research psychologist who serves on the Research Directorate at the Deployment Health Clinical Center in Silver Spring, Maryland
- Has training and expertise in clinical trials research and experimental research in the domains of psychological health and substance abuse
- Trained at the Brown University Alpert Medical School and the Johns Hopkins University School of Medicine where he was involved in numerous psychopharmacology and substance abuse clinical trials and research studies
- Currently conducts health services research with a focus on PTSD, depression, and alcohol misuse management among active-duty service members
- Licensed psychologist in Maryland

Scientific Reviews of Recent Studies on the Treatment of Posttraumatic Stress Disorder

Dr. Bradley E. Belsher

Dr. Daniel P. Evatt

DHCC

Disclosures

- Dr. Evatt and Dr. Belsher have no relevant financial relationships to disclose.
- The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Army, or Air Force, the Department of Defense, nor the U.S. Government.
- The description of programs in this presentation is for descriptive purposes only and not intended to promote any individual program.

Introduction

The Institute of Medicine (IoM), in accordance with the 2010 National Defense Authorization Act (NDAA), recommends that DoD providers rely on Clinical Practice Guidelines (CPG) for the Management of Post-Traumatic Stress to inform the delivery of all PTSD treatments. However, limited data exists on whether mental health care providers in the MHS actually use the PTSD guideline and offer evidence-based treatments to their patients. *The 2010 VA/DoD Clinical Practice Guideline for the Management of Post-Traumatic* Stress was developed to assist facilities in implementing evidence-based care that is designed to promote maximum functionality and independence among service members receiving treatment for PTSD.

To promote evidence-based practice, providers, policymakers, and consumers must be informed on the best evidence that supports the optimal treatment of service members with PTSD.. This presentation will provide an overview on the evidence based practice (EBP) model and describe the current guidelines stated in the 2010 VA/DoD CPG on PTSD. The presenters will then describe more recent scientific research that has emerged on the management of PTSD since the 2010 CPG on the Treatment of Posttraumatic Stress Disorder.

Polling Question

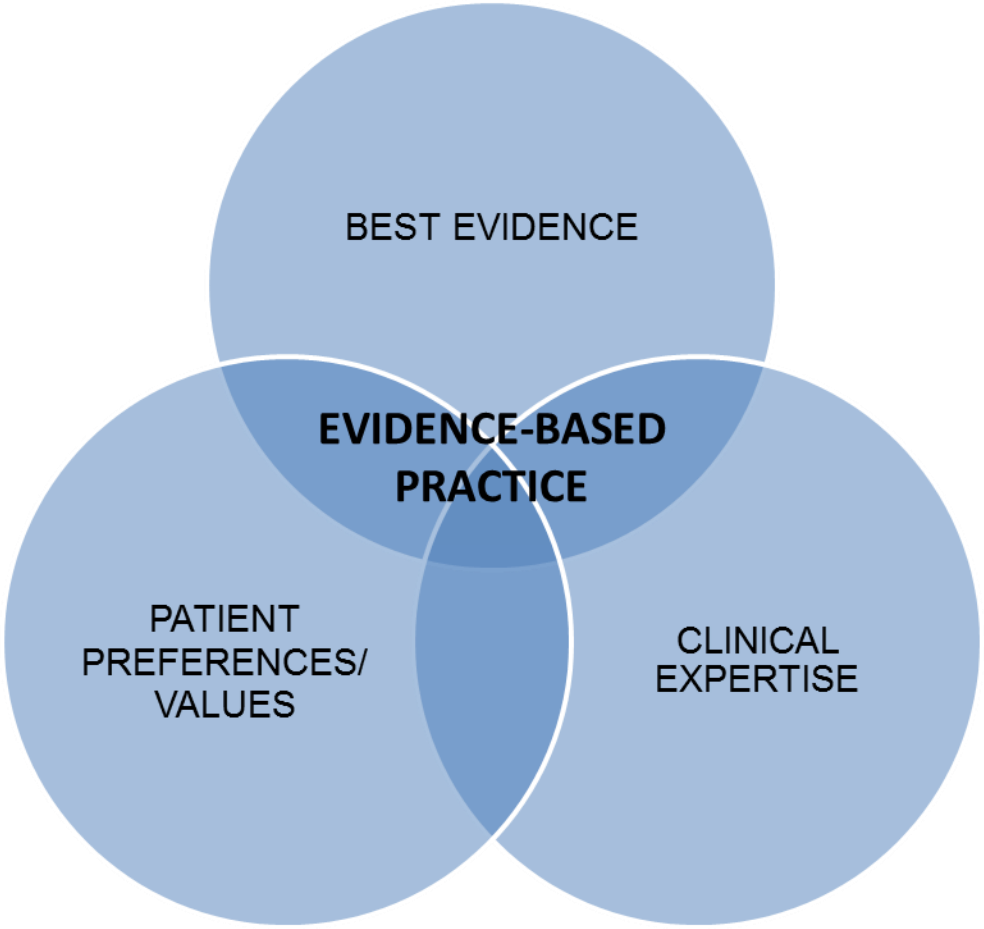
Question: What do you spend the majority of your professional time doing?

A. Direct Clinical Care
B. Administrative Support/Supervision
C. Conducting and Interpreting Research
D. Developing and Implementing Policy
E. Other

Scientific Reviews of Recent Studies on the Treatment of Posttraumatic Stress Disorder

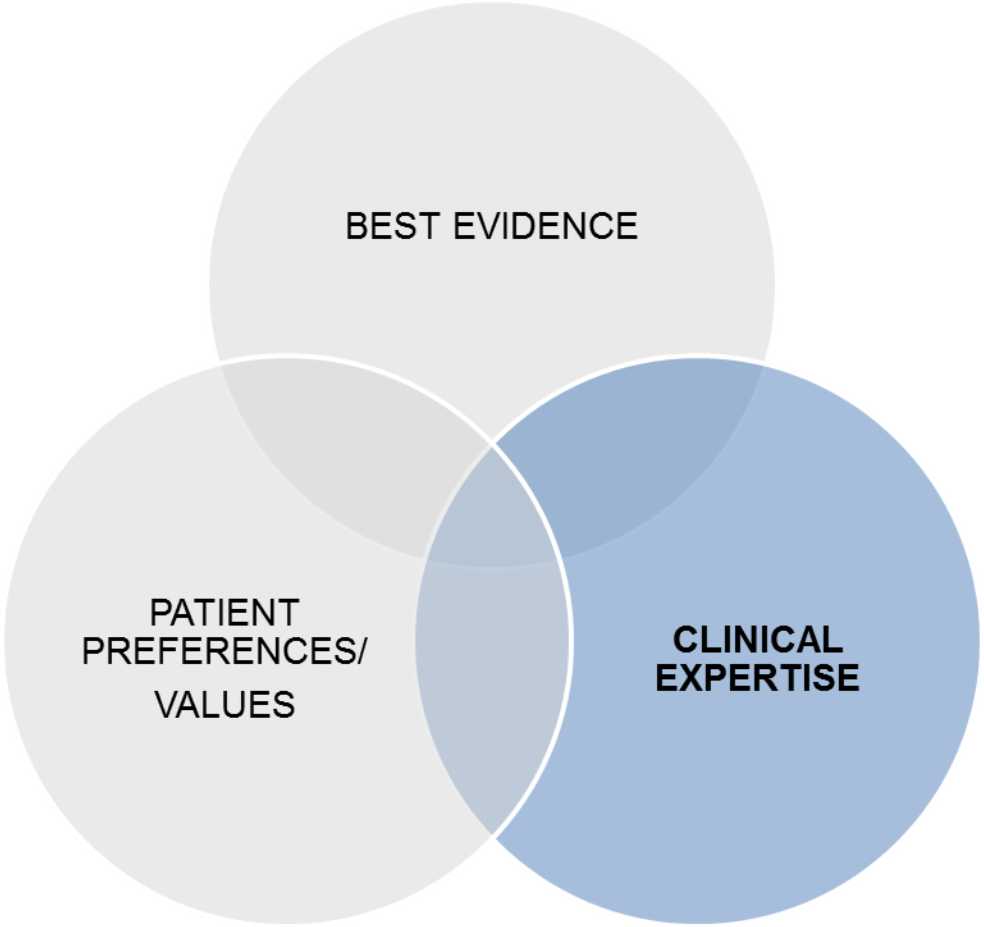
- Where does research fit into practice?

Evidence-Based Practice (EBP)

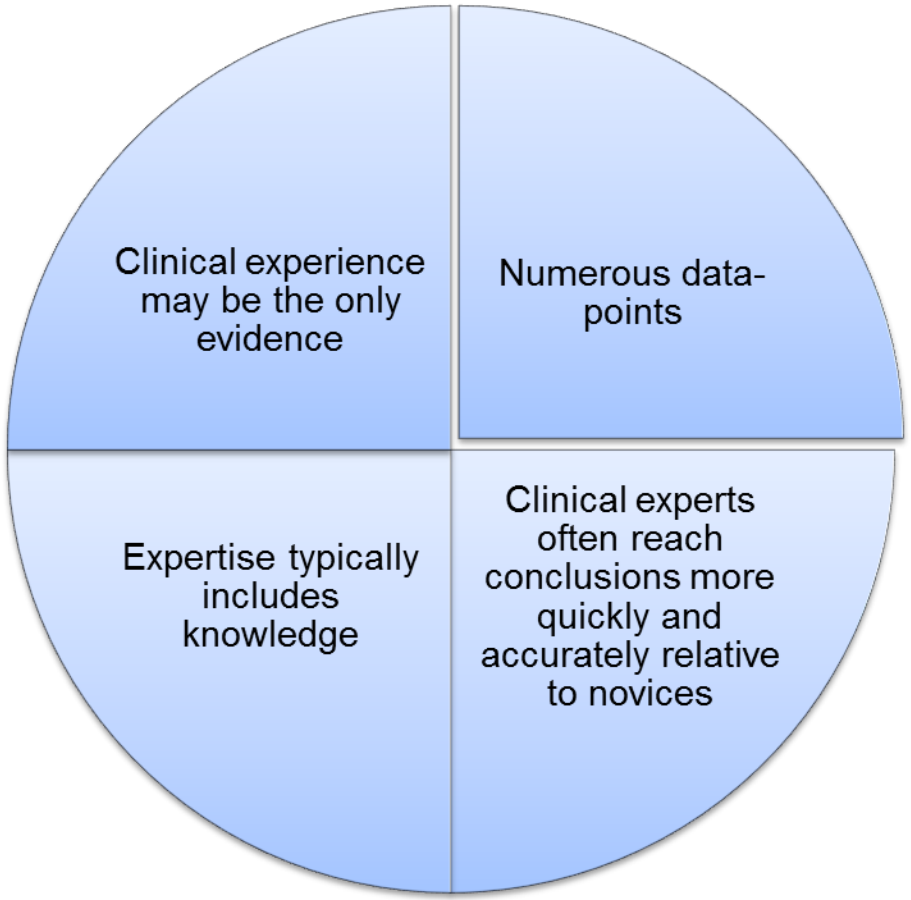


Institute of Medicine, 2001

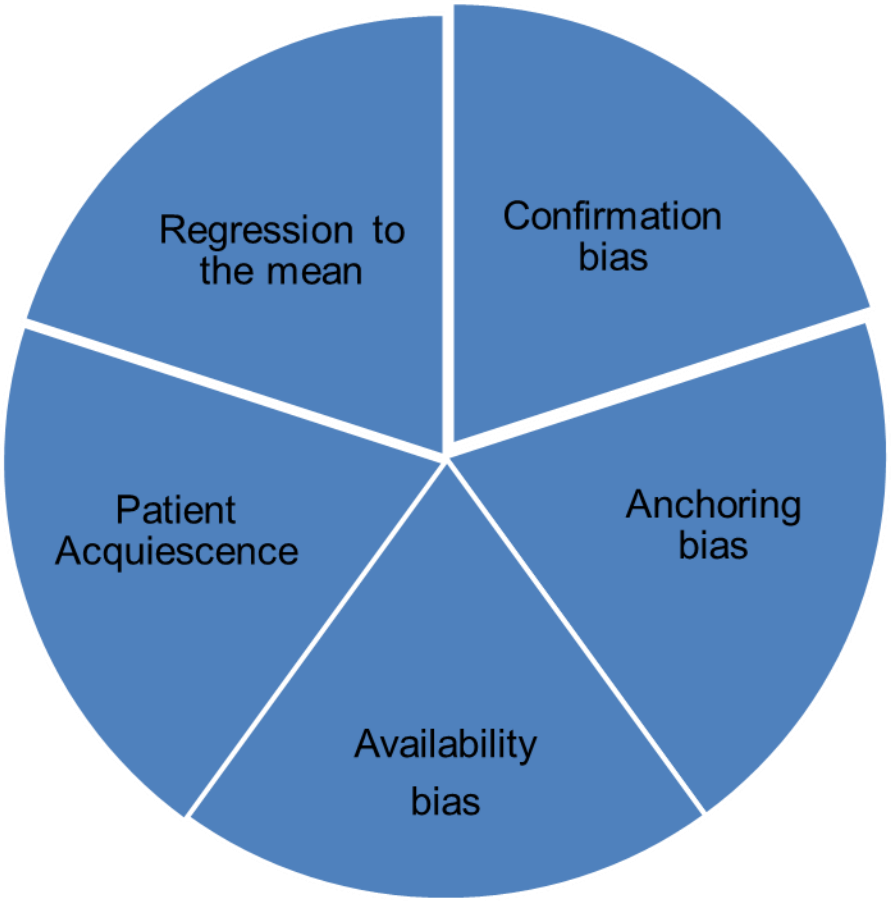
Clinical Expertise



Clinical Experience



Clinical Experience is Uncontrolled



Survey on Practitioner's Decision in Selection of Treatments

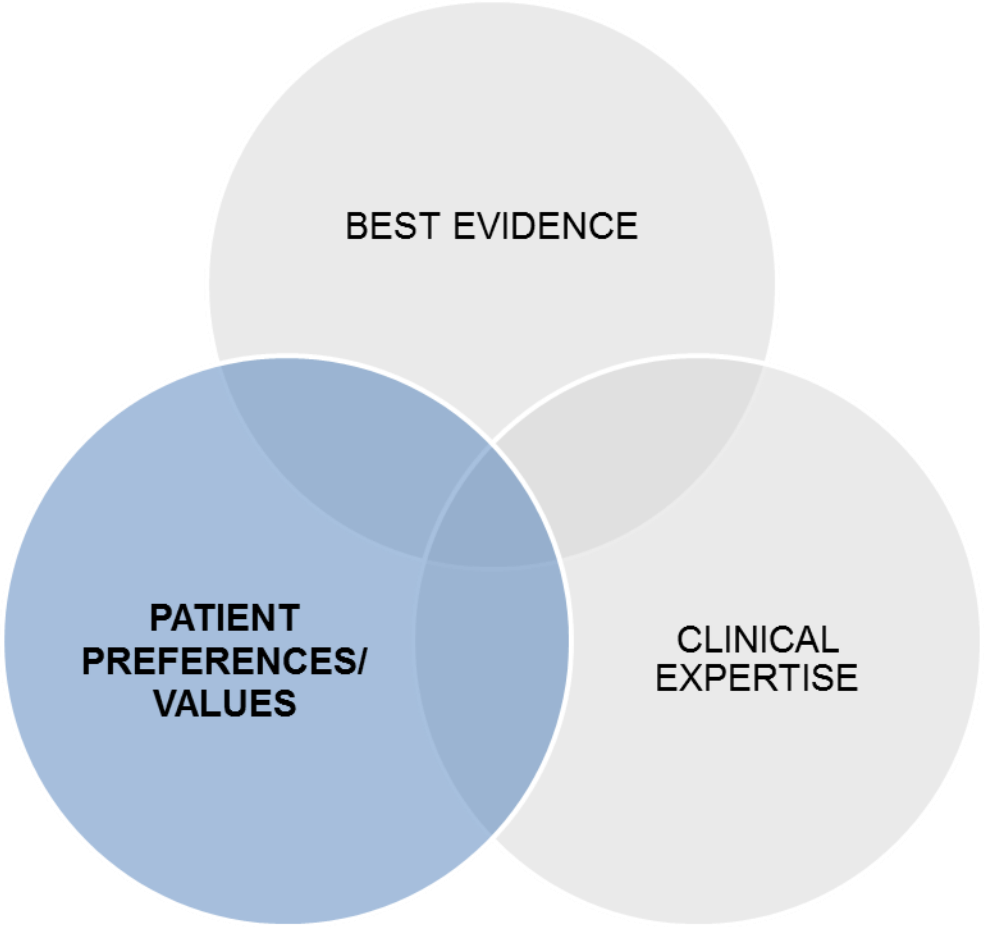
1. "Clinical experience with positive results that held up over time"
2. "Compatibility with theoretical orientation"
3. "Compatibility with personality"
4. "Clinical experience of fast, positive results with clients"
5. "Intervention emotionally resonated for you"
6. "Endorsement by respected professional"
7. "Your intuition"
8. "Colleagues' reports of success"
9. **"Favorable research in peer reviewed journals"**

Pignotti, 2009

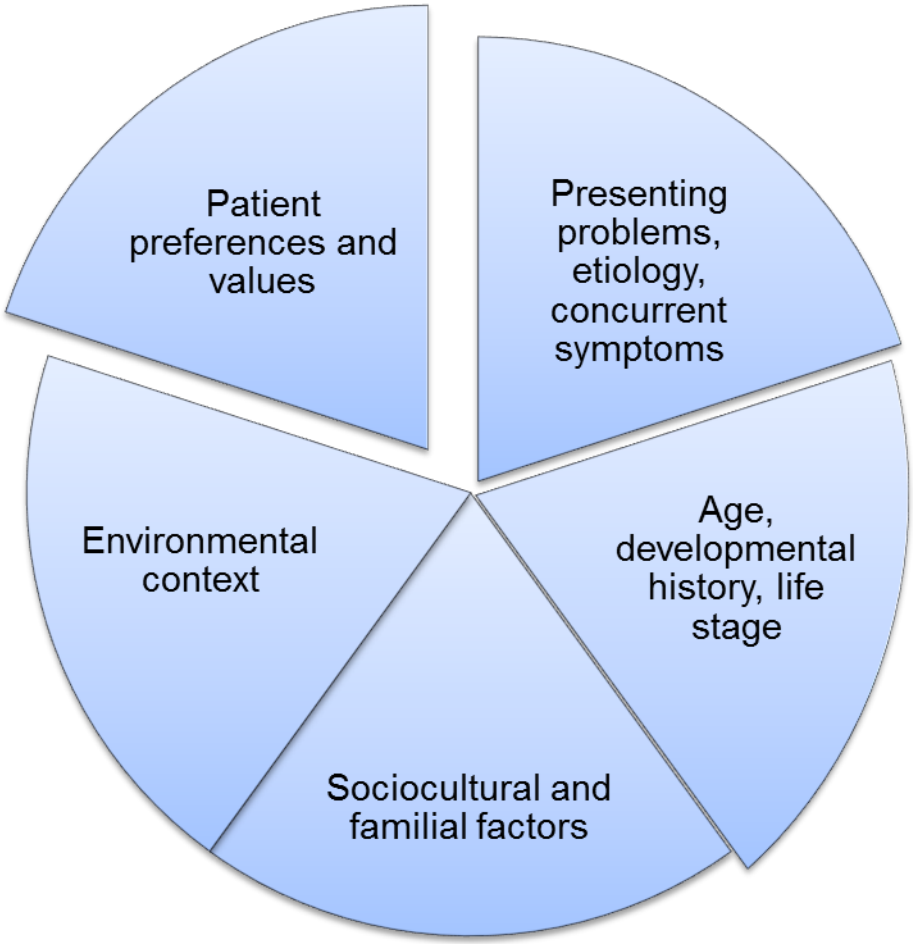
Clinical Scenario

- Provider
  - Believes the treatment works
  - Unknowingly rejects evidence that the treatment does not work
  - Has observed that many patients got better after receiving the treatment
- Patient
  - Expects the treatment to work
  - Came to see provider at peak symptom endorsement
  - Personally likes the provider

Evidence-Based Practice

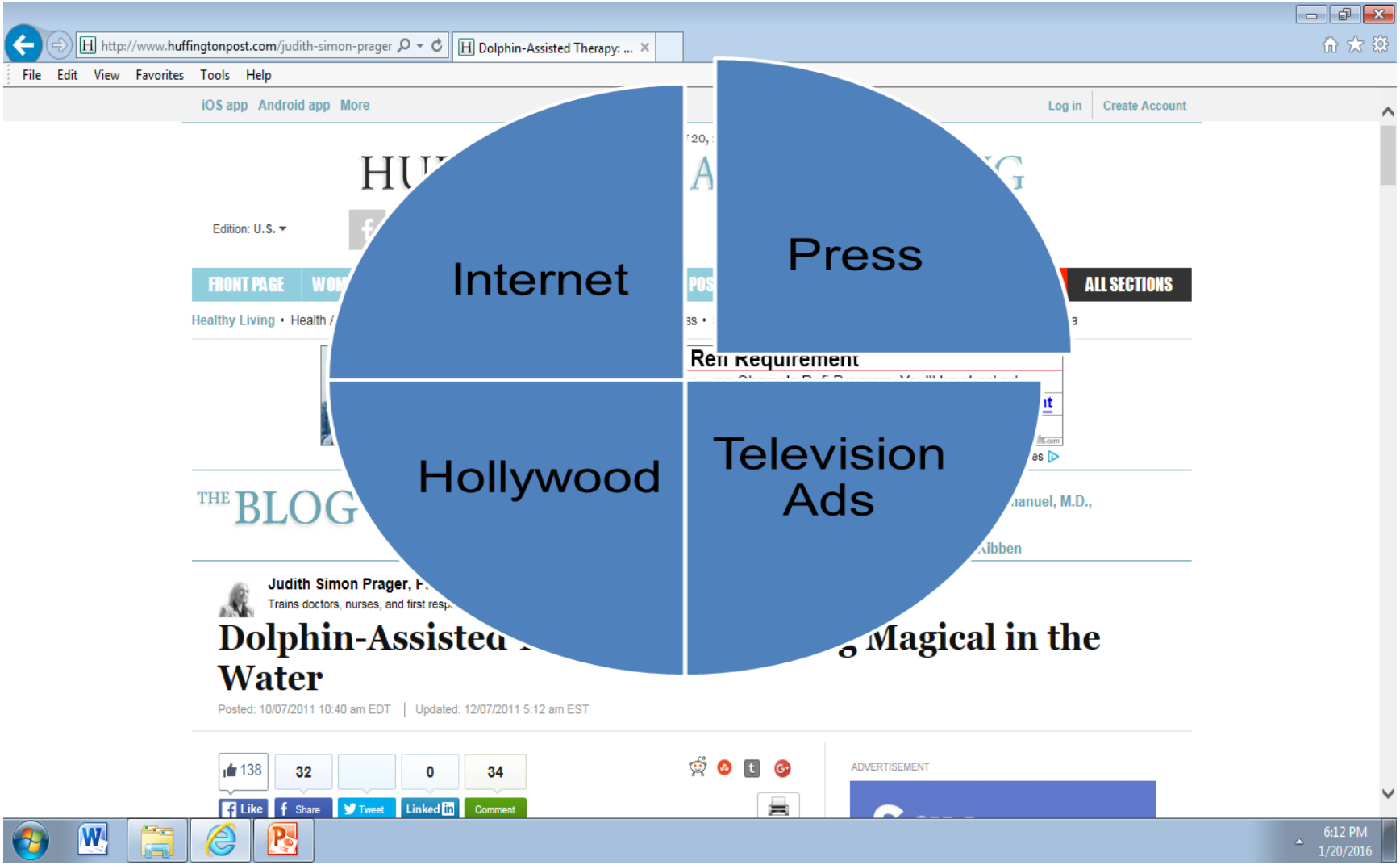


Patient Characteristics, Values, and Context

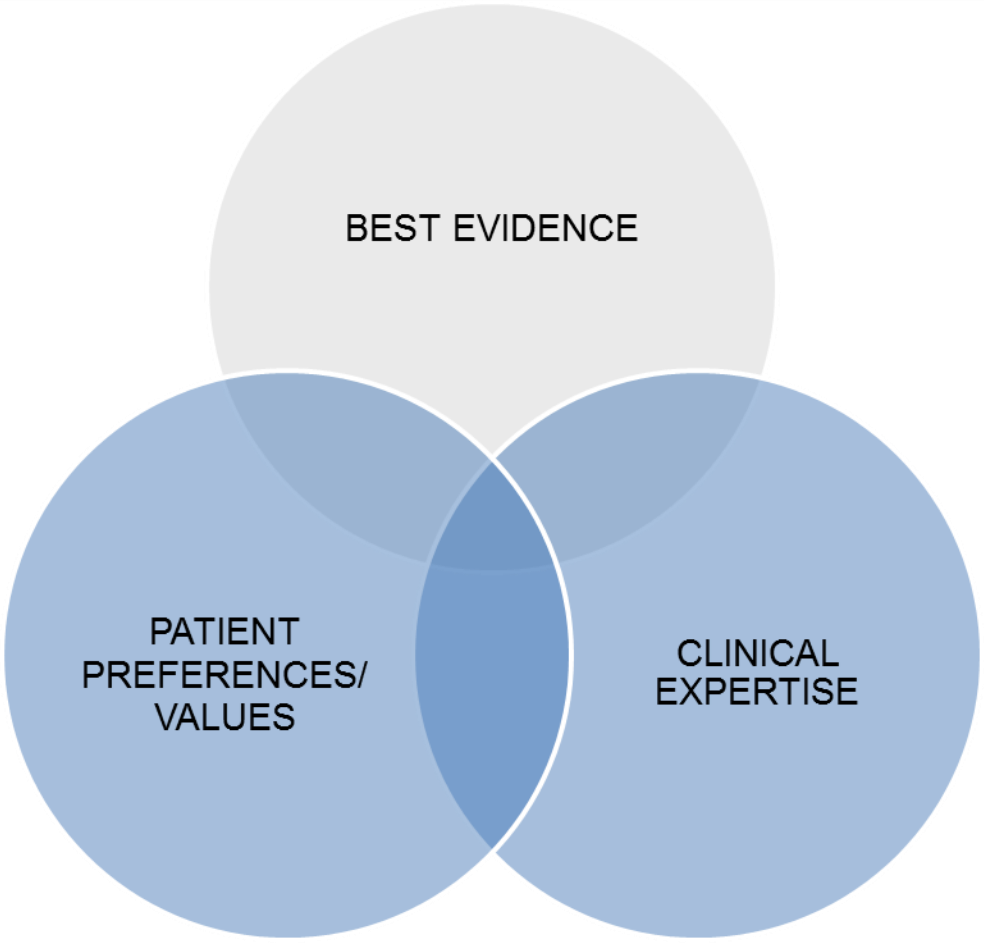


APA Presidential Task Force on Evidence-Based Practice, 2006

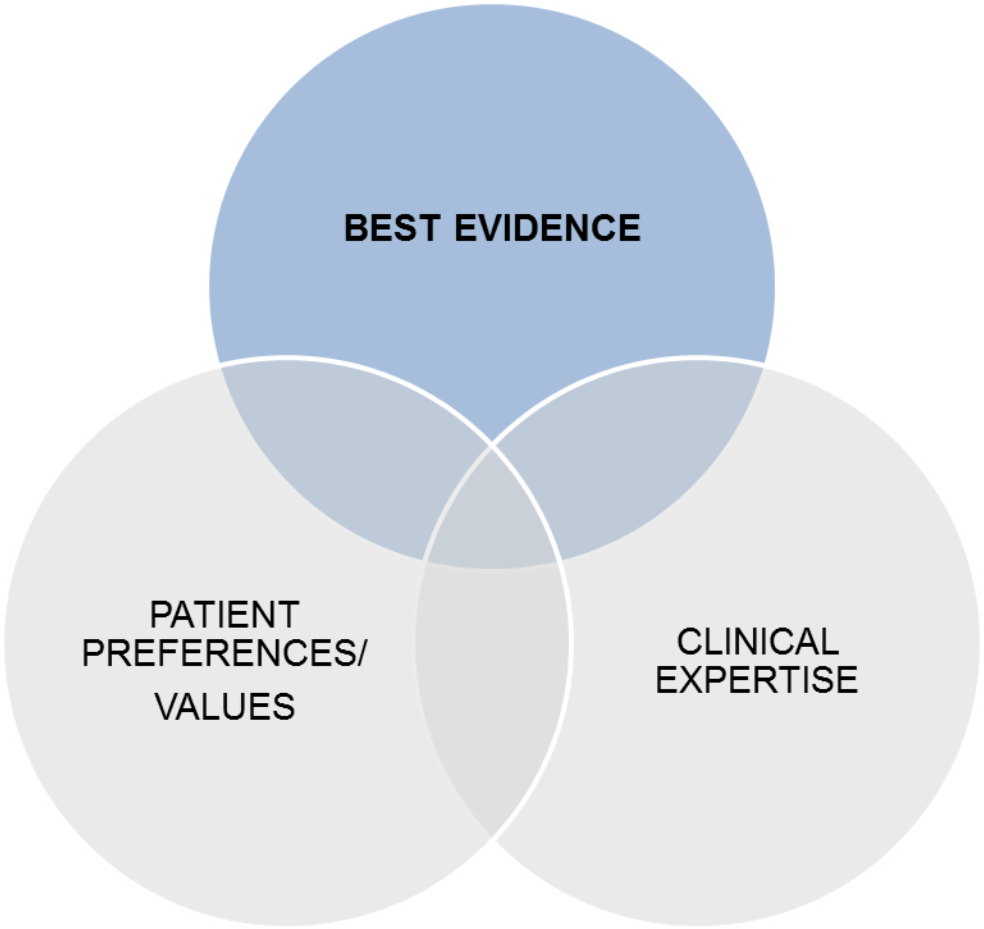
Patient Preferences



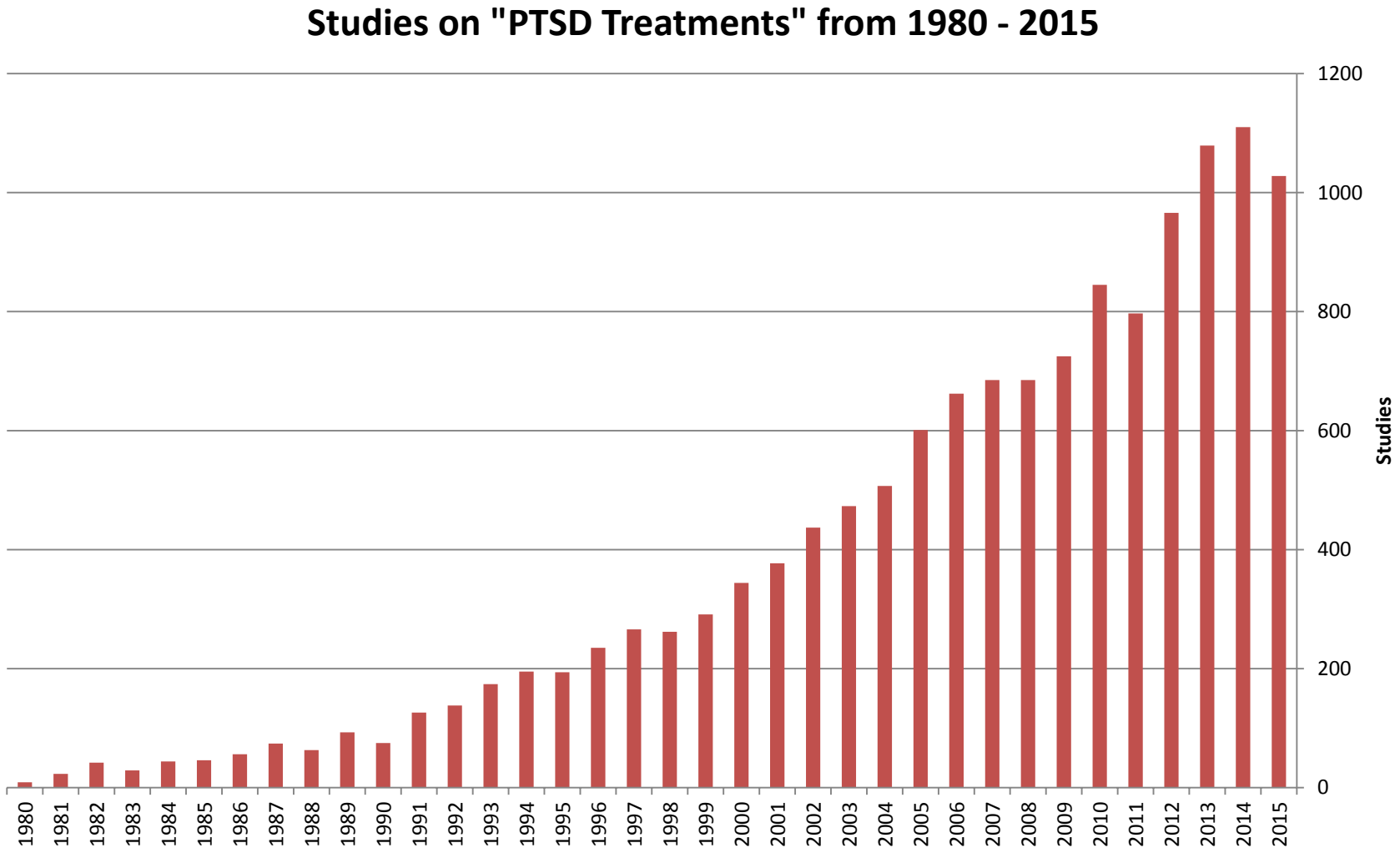
Without Evidence there is no EBP



Best Evidence



Evidence: What does the literature say?



Not all evidence is equal

Quality:

"[T]he extent to which all aspects of a study's design and conduct can be shown to protect against systematic bias, nonsystematic bias, and inferential error."

(Ip S, Kitsios GD, Chung M, et al. (2011). p 1)

Relevance of Peer-Reviewed Research

1. Informal discussions with a colleague
2. Workshops
3. Theoretical books
4. How-to books
5. **Research articles**

(Cohen, Sargent, & Sechrest, 1986).

Clinical Practice Guidelines (CPGs)

APA Presidential Task Force on Evidence-Based Practice, 2006

Clinical Practice Guidelines (CPGs)

- Guidelines are based on the best information available at the time of publication.
- Designed to provide information and assist in decision-making.
- Not intended to define a standard of care and should not be construed as one.
- Should not be interpreted as prescribing an exclusive course of management.

CPG Working Group

- VA/DOD health care clinicians recognized as experts in the topic or known for their contributions to the care of patients to be covered under the CPG.
- VA/DOD identifies clinical leaders to champion the CPG development process.
- The clinical leaders defined the scope of the CPG and identify a group of clinical experts from the VA and DOD to form the WG.
- Separate VA and DOD subgroups of the WG are convened to develop specific sections of the CPG.

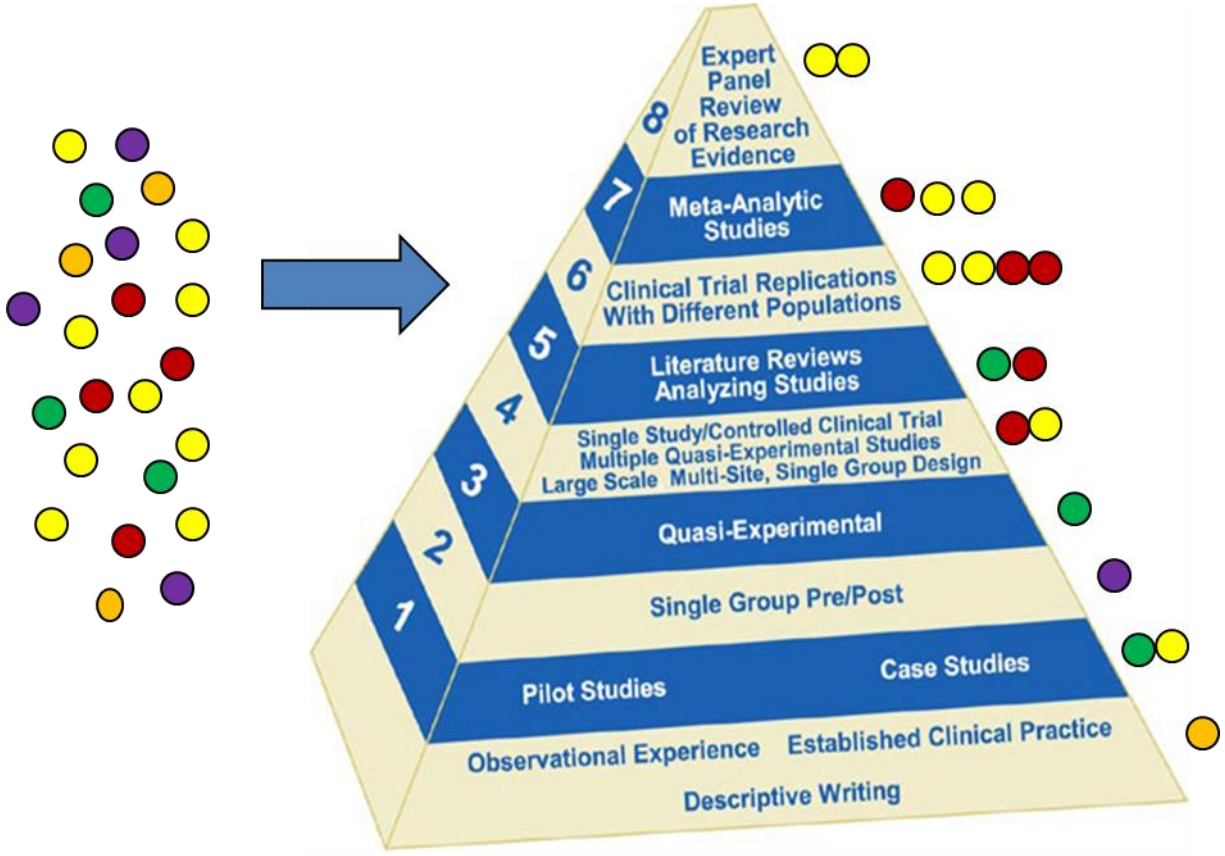
(Susskind, Ruzek & Friedman, 2012)

Selection of Evidence

- Designed to identify the best available evidence:

  - Published, **peer-reviewed RCTs**, **meta-analyses** and **systematic reviews** are considered to constitute the strongest level of evidence in support of guideline recommendations.

Selection of Evidence



PHASE 1: Literature Reviews of Existing Research

(SAMHSA Pyramid of Evidence Based Practice, Center for Substance Abuse Treatment, 2007)

PTSD CPGs

- Initial Search:
  - 59 systematic reviews/meta-analyses
  - 178 RCTs
  - 24 controlled trials (CT)
- A more detailed (full) search was conducted on each question, supplemented by hand searches and cross-referencing to search for relevant articles.

Quality of Evidence

- **Good**: Consistent results from a number of higher quality studies (RCTs and meta-analyses of RCTs) across a broad range of populations support, with a high degree of certainty, that the results of the studies are true.

- **Fair**: The results could be caused by true effects but a moderate risk of biases is present across some or all of the studies.

- **Poor**: Any conclusion is uncertain because of serious methodological shortcomings, sparse data, or inconsistent results.

Net Effect of the Intervention

- **Substantial**: More than a small relative impact on a frequent condition *or* a large impact on an infrequent condition.

- **Moderate**: A small relative impact on a frequent condition *or* a moderate impact on an infrequent condition

- **Small**: A negligible relative impact on a frequent condition *or* a small impact on an infrequent condition with a significant impact at the individual patient level.

- **Zero or Negative**: Negative or no impact on patients

US Preventative Service Task Force (USPSTF) Grade system

Evidence Rating System

SR	
A	A strong recommendation that clinicians provide the intervention to eligible patients. Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.
B	A recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.
C	No recommendation for or against the routine provision of the intervention is made. At least fair evidence was found that the intervention can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. At least fair evidence was found that the intervention is ineffective or that the harms outweigh benefits.
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms can not be determined.

SR = Strength of recommendation

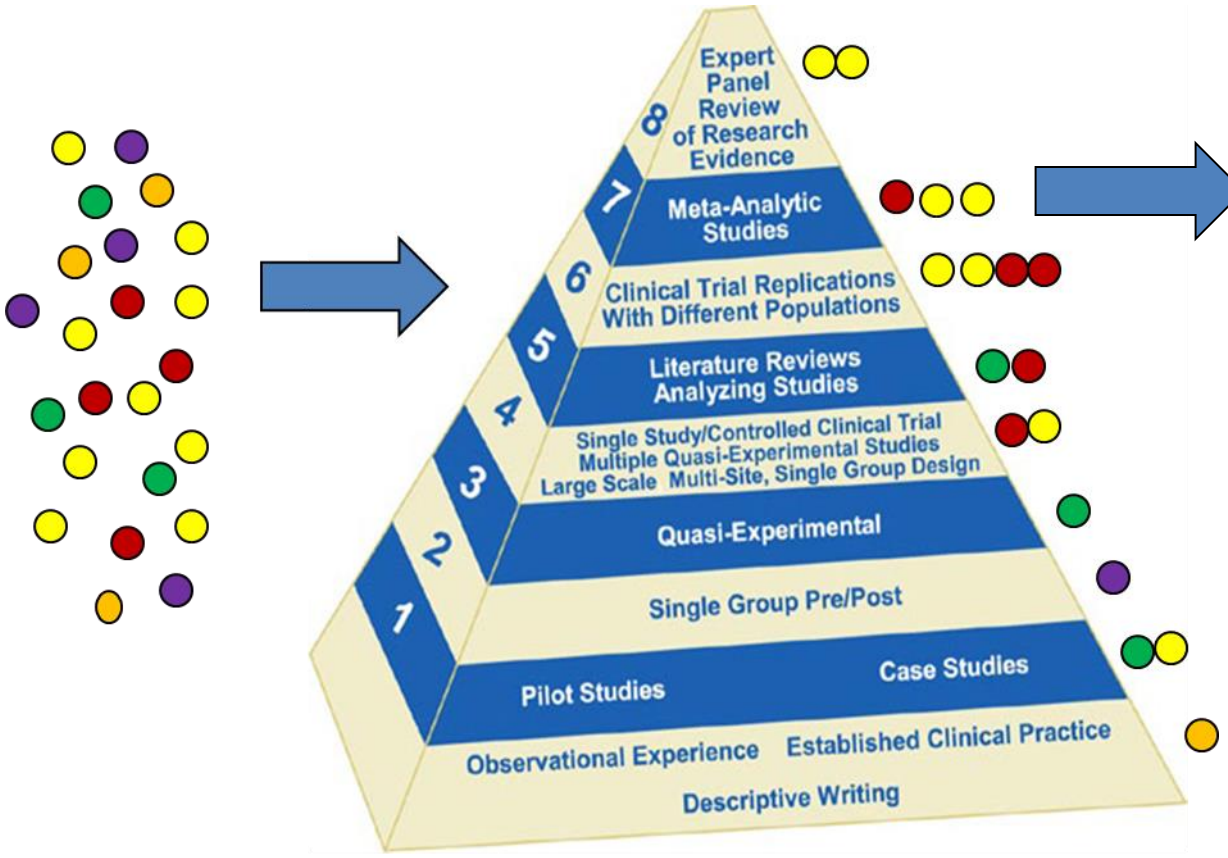
(VA/DoD, 2010)

Methodology Changes in Upcoming CPGs

Strength of Recommendation

- *Strong For*
- *Weak For*
- *Weak Against*
- *Strong Against*

CPG Development



PHASE 2
Grading the Evidence

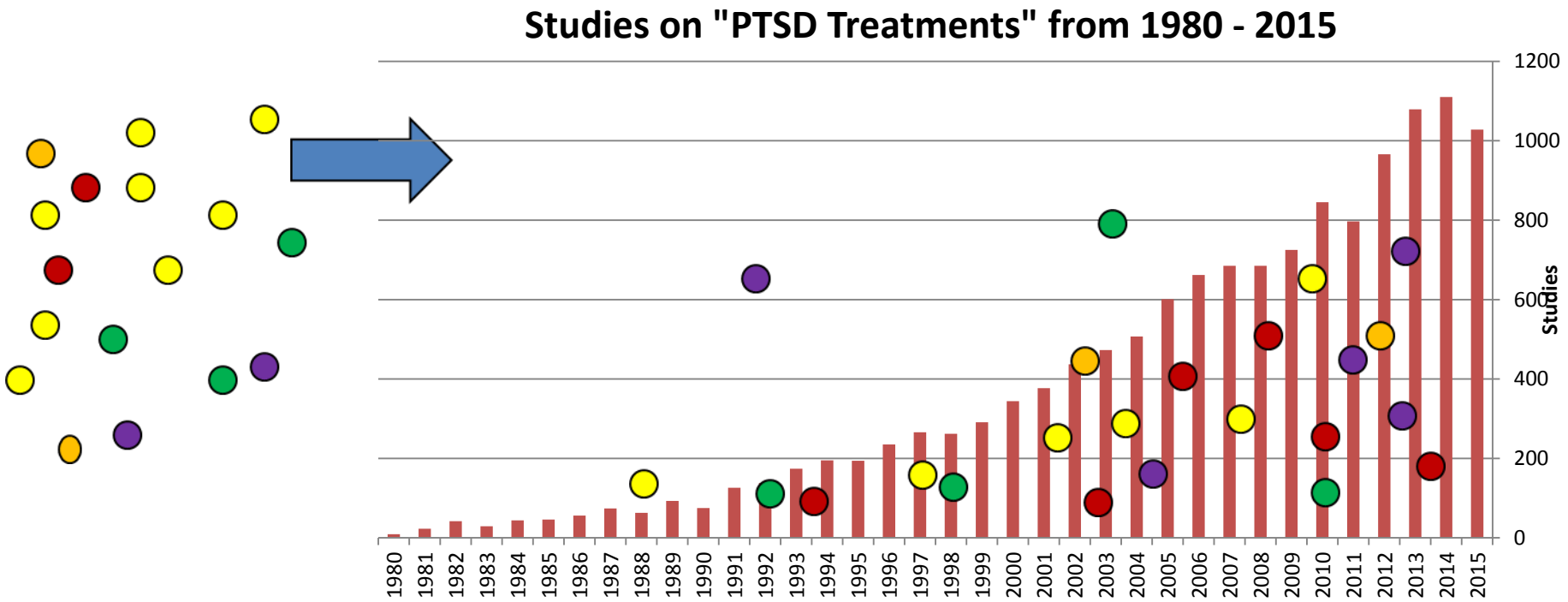
PHASE 3

Clinical Standards

PHASE 1: Literature Reviews of Existing Research

(SAMHSA Pyramid of Evidence Based Practice, Center for Substance Abuse Treatment, 2007)

Literature Search



2010 DoD/VA CPGs on PTSD

- Emphasizes a patient-centered approach that recommends the management and intervention shown to be effective in treating PTSD regardless of the treatment setting (e.g., primary care or mental health clinic).

- A key element of the CPG guides practitioners to develop collaborative interdisciplinary treatment plan; determine optimal setting for care.

- It may be helpful to coordinate care using a collaborative care approach based in primary care that includes care management.

(VA/DoD, 2010)

2010 CPGs on PTSD: Pharmacotherapy

Table I - 6 Pharmacotherapy Interventions for Treatment of PTSD

	Effect = Balance of Benefit and Harm			
SR	Significant	Some Benefit	Unknown	No Benefit
A	SSRIs SNRIs		-	-
B	-	Mirtazapine Prazosin (for sleep/nightmares) TCAs Nefazodone [Caution]* MAOIs (phenelzine) [Caution]*	-	-
C			Prazosin (for global PTSD)	
D	-	-	-	Benzodiazepines [Harm] Tiagabine Guanfacine Valproate Topiramate Risperidone
I	-	-	Atypical antipsychotic (Except risperidone, as adjunct) Atypical antipsychotic (monotherapy) Conventional antipsychotics Buspirone Non-benzodiazepine hypnotics Bupropion Trazodone (adjunctive) Gabapentin Lamotrigine Propranolol Clonidine	-

*SR = Strength of recommendation (see Appendix A); * Attention to drug to-drug and dietary interactions*

(VA/DoD, 2010)

2010 CPGs on PTSD: Psychotherapy

Table I-4 Psychotherapy Interventions for Treatment of PTSD

	Balance of Benefit and Harm			
SR	Significant Benefit	Some Benefit	Unknown Benefit	None
A	**Trauma-focused** psychotherapy that includes components of exposure and/or cognitive restructuring; or, **Stress inoculation** training			
C		Patient Education Imagery Rehearsal Therapy Psychodynamic Therapy Hypnosis Relaxation Techniques Group Therapy		
I		Family Therapy	WEB-Based CBT Acceptance and Commitment Therapy Dialectical Behavioral Therapy	

SR = Strength of Recommendation (see Appendix A)

(VA/DoD, 2010)

VA/DoD CPGs for PTSD

Strongly recommends that patients diagnosed with PTSD should be offered one of the evidence-based trauma-focused psychotherapeutic interventions that include components of exposure and/or cognitive restructuring

(VA/DoD, 2010, p.117)

Evidence-Based Practices for PTSD

- Cognitive Behavioral Therapy
  - Exposure Therapy
  - Cognitive Therapy
  - Stress Inoculation Training (SIT)
  - EMDR
  - Combination of CR and exposure therapy

- Medications
  - Sertraline (Zoloft)
  - Paroxetine (Paxil)

(VA/DOD, 2010)

Qualifying Statements

Variations in practice will inevitably and appropriately occur when providers take into account the needs of individual patients, available resources, and limitations that are unique to an institution or type of practice.

All current treatments have limitations—not all patients respond to them, patients drop out of treatment, or providers' comfort or experience in using a particular intervention is limited

(VA/DoD, 2010, title page)

Evidence-Based Practice

- The use of guidelines must always be in the context of a health care provider's clinical judgment in the care of a particular patient. For this reason, the guidelines may be viewed as an educational tool to provide information in shared decision making. (http://www.healthquality.va.gov/).

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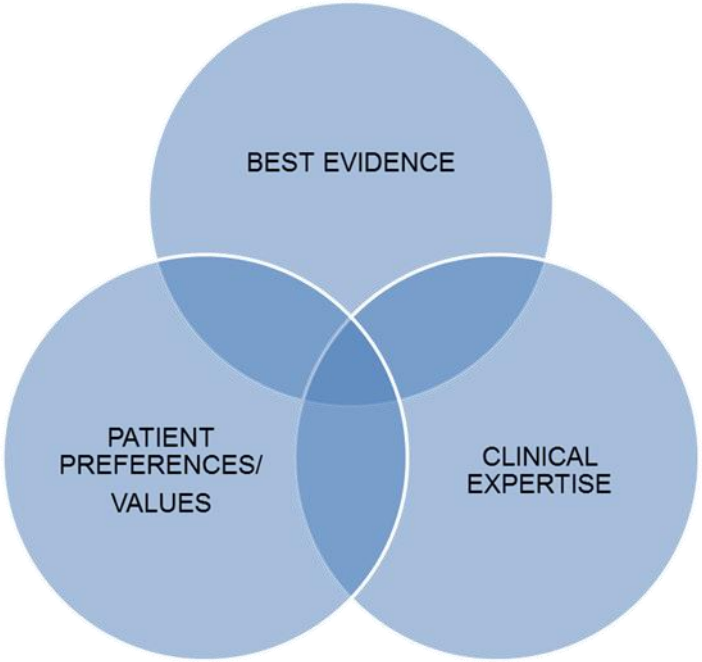
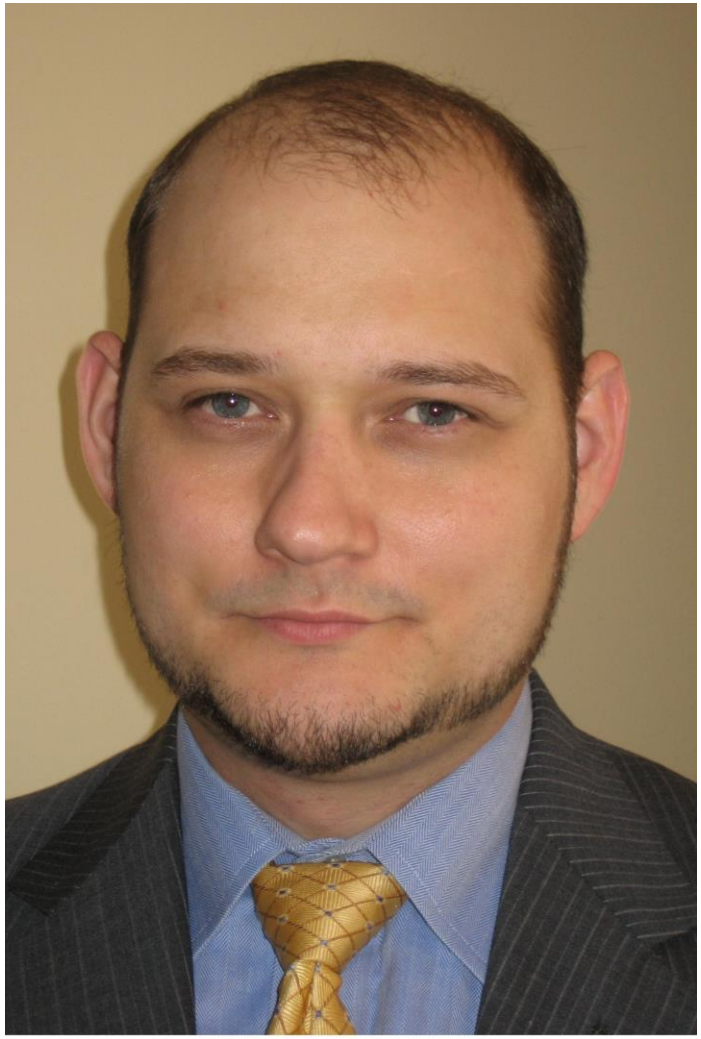


Daniel P. Evatt, Ph.D.



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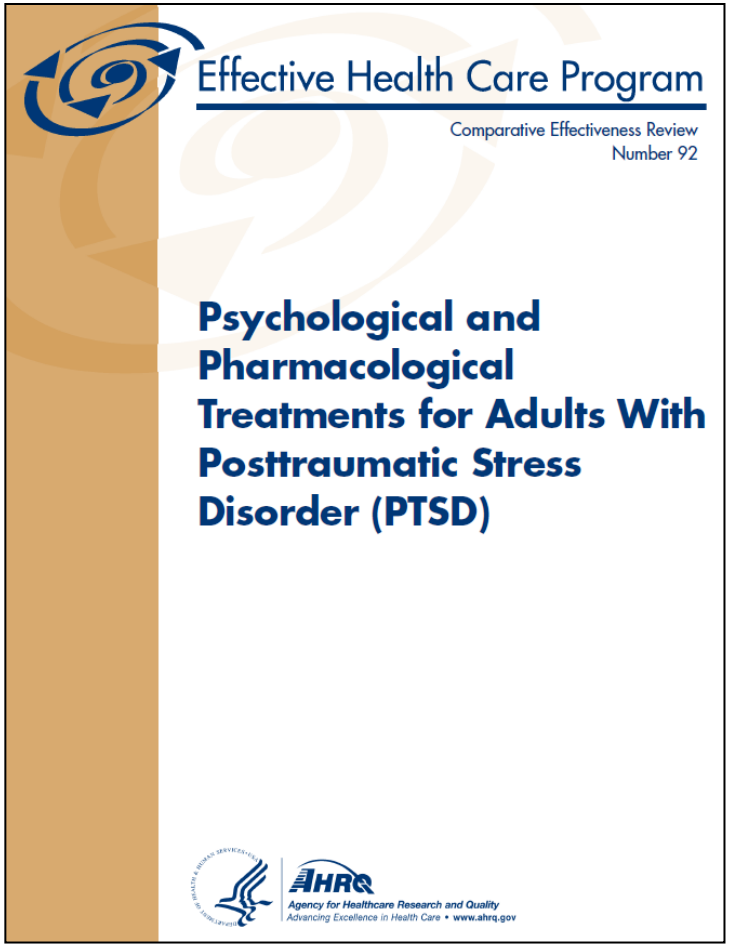
- Currently conducts health services research with a focus on PTSD, depression, and alcohol misuse management among active-duty service members
- Licensed psychologist in Maryland

Recent Scientific Reviews of PTSD Treatment

If CPGs are so good, why know the evidence?

- Knowledgeable practitioner
  - Scientist-practitioner/Scholar-practitioner/Bench-scientist
- Ongoing debates in the field
- Patient questions
- To know what we don't know!

AHRQ Comparative Effectiveness Review



(Jonas, Cusack, Forneris, et al. (2013)

Key Questions

KQ1: What is the comparative effectiveness of different psychological treatments for adults diagnosed with PTSD?

KQ2: What is the comparative effectiveness of different pharmacological treatments for adults diagnosed with PTSD?

KQ3: What is the comparative effectiveness of different psychological treatments versus pharmacological treatments for adults diagnosed with PTSD?

KQ4: How do combinations of psychological treatments and pharmacological treatments (e.g. CBT plus paroxetine) compare with either one alone (i.e. one psychological or one pharmacological treatment)?

KQ5: Are any of the treatment approaches for PTSD more effective than other approaches for victims of particular types of trauma?

KQ6: What adverse effects are associated with treatments for adults diagnosed with PTSD?

AHRQ Treatments Compared

Psychological Treatments
Brief Eclectic Psychotherapy
CBT (broadly defined; 5 types)
EMDR
Hypnosis or Hypnotherapy
Interpersonal Therapy
Psychodynamic Therapy

Pharmacological Treatments
SSRIs (6 types)
SNRIs (3 types)
Second-generation antidepressants (4 types)
Tricyclic antidepressants (3 types)
Alpha-blockers (i.e., prazosin)
Atypical antipsychotics (2 types)
Benzodiazepines (4 types)
Anticonvulsants/mood stabilizers (5 types)

Note:

Not all-inclusive list

Some specific exclusions (e.g., CAM)

AHRQ: Bias

- AHRQ has predefined criteria
  - (Viswanathan M, Ansari MT, Berkman ND, et al. 2012)
  - Two reviewers
- One a senior investigator
- 3rd resolved disputes
  - "Low, medium, or high risk"

Stanford Research Into the Impact of Tobacco Advertising
http://tobacco.stanford.edu/tobacco_main/images.php?token2=fm_st002.php&token1=fm_img0101.php&theme_file=fm_mt001.php&theme_name=Doctors%20Smoking&subtheme_name=20,679%20Physicians

Risk of Bias Assessment Categories

Criteria

- Was randomization adequate?
- Was allocation concealment adequate?
- Were groups similar at baseline?
- Were outcome assessors masked?
- Were care providers masked?
- Were patients masked?
- Was overall attrition 20% or higher?
- Was differential attrition 15% or higher?
- Did the study use intention-to-treat analysis?
- Did the study use adequate methods for handling missing data?
- Were outcome measures equal, valid, and reliable?
- Did study report adequate treatment fidelity (therapist adherence) based on measurement by independent raters?

Polling Question

Question: The 2013 AHRQ Comparative Effectiveness Review arrived at 123 studies eligible to be included in analyses. How many of the 123 studies were excluded from quantitative analysis because of a “High” risk of bias.

A. 3 (2.4%)
B. 14 (11%)
C. 26 (21%)
D. 43 (37%)
E. 63 (51%)

All Studies not Created Equally: Bias Examples

- Substantial dropout, limited description of randomization; study reported as double blind, but write up suggests VPA folks got a lot more blood draws/monitoring; also, study physician told by pharmacist to adjust doses, so not blind to treatment arm.
- Baseline characteristics not reported for important potential confounders in this small study (n=12) to allow for determination of potential selection bias (described as "non-significant difference", but given small sample size, almost any difference will be nonsignificant). In addition, unclear whether randomization or allocation concealment were adequate; unclear whether outcome assessors were masked. Instruments of uncertain validity used to assess outcomes.
- No masking; no reporting of handling of missing data; no reporting of attrition data; not sure if ITT or completers analysis.
- High overall and differential attrition; completers analysis; no approach to handling missing data; no assessment of treatment fidelity; in the two active treatment groups, about 31% and 43% did not complete treatment, respectively.

Review Procedures

- First determine efficacy
  - Placebo controlled studies for pharmacotherapies
  - Placebo, usual care, or wait-list control for psychotherapies
    - Next assessed head-to-head trials
    - Combined results
  - Meta-analysis when appropriate
  - Qualitative methods when meta-analysis not appropriate
    - Appropriate statistical methodology was applied

Key Question 1: Psychological Treatments

- CPT, Cognitive Therapy, CBT-Exposure, and CBT Mixed had “Moderate” or better evidence for BOTH reducing PTSD symptoms and loss of PTSD diagnosis.
- CBT-Exposure was the only treatment to have a “High” level of evidence for reducing PTSD symptoms.
- EMDR, Narrative Exposure Therapy, and Brief Eclectic Therapy had at least “Low” level of evidence for BOTH reducing PTSD symptoms and loss of PTSD diagnosis.
- Insufficient evidence to support Stress Innoculation Training, relaxation, Image Rehearsal Therapy, and trauma affect regulation.

CBT-Exposure Comparison

AHRQ Comparative Review			
Intervention	Outcome	Results Effect Size (95% CI)	Strength of Evidence
CBT-Exposure	PTSD symptoms	SMD, -1.27 (-1.54 to -1.00; 7 trials, N=387) WMD, -28.9 (-35.5 to -22.3; 4 trials, N=221)	High
CBT-Exposure	Loss of Diagnosis	0.66 (0.42 to 0.91; 3 trials, N=197); NNT, 2	Moderate

VA/DoD Clinical Practice Guidelines			
Intervention	Outcome	Quality of Evidence	Strength of Recommendation
Exposure-therapy	PTSD Treatment	Good	A

Key Point: Stress Inoculation Therapy (SIT)

AHRQ Comparative Review			
Intervention	Outcome	Quality of Evidence	Strength of Recommendation
Stress Inoculation Therapy	PTSD Treatment	Insufficient Evidence	Insufficient

VA/DoD Guidelines			
Intervention	Outcome	Quality of Evidence	Strength of Recommendation
Stress Inoculation Therapy	PTSD Treatment	Good	High (A)

Why?

Grade for SIT greater in VA/DoD guidelines relative to AHRQ review.

- VA/DoD guidelines included 4 trials.
- AHRQ included 1 trials (Foa et al., 1999) "The single trial of stress inoculation training suggests that it may be efficacious, but further research is needed to confirm or refute the findings".
  - Foa et al., 1991: Excluded for high risk of bias
  - Kilpatrick et al., 1982: Excluded b/c nonrandomized study that did not require PTSD diagnosis or use validated outcome measures.
- Conclusions?

Key Question 2: Pharmacological Treatments

- Evidence of moderate strength supporting the efficacy of Fluoxetine, Paroxetine, Sertraline, Topiramate, and Venlafaxine for improving PTSD symptoms.
- Most studies did not report loss of PTSD diagnosis outcome.
- Risperidone has some evidence of effectiveness.

Summary of Additional Findings

- AHRQ Statement: Indirect evidence would suggest that psychological treatments are more effective than pharmacological treatments (because effect sizes for reduction of PTSD symptoms are much larger in trials of the efficacious psychological treatments than in trials of the efficacious pharmacological treatments). However, conclusions based on naïve indirect comparisons can be flawed—primarily because it is difficult to determine how similar populations are across two somewhat different bodies of literature (i.e., studies of psychological treatments and pharmacological treatments).

- Overall, the review found insufficient evidence (often due to a lack of studies) for greater relative effectiveness of psychotherapy vs pharmacotherapy or any combination.

- Insufficient evidence also found based on type of trauma or adverse events

Efficacy of recommended treatments for veterans with PTSD: A metaregression analysis

Clinical Psychology Review 40 (2015) 184–194

Contents lists available at ScienceDirect

Clinical Psychology Review

The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis

Joris F.G. Haagen [a,*], Geert E. Smid [c], Jeroen W. Knipscheer [a,c], Rolf J. Kleber [a,b]

HIGHLIGHTS

- Veterans with PTSD benefit less from psychotherapy than other populations.
- We performed meta-analyses to identify psychotherapy efficacy predictors.
- Group-only therapy formats should not be used to treat PTSD.
- Exposure therapy and CPT are preferred above SMT and EMDR.
- Patients with low and high PTSD symptom severity levels risk lower treatment gains.

ARTICLE INFO

ABSTRACT

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2. Method
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   - 2.3. Data extraction
   - 2.4. Methodological quality
   - 2.5. Statistical analysis
3. Results
   - 3.1. Univariate predictors
   - 3.2. Multivariate predictors
   - 3.3. Heterogeneity, publication bias and sensitivity analysis

(Haagen, Smid, Knipscheer, & Kleber, 2015)

Purpose

Compared EMDR, exposure, cognitive, cognitive, restructuring, cognitive processing, trauma-focused cognitive behavioural, and stress management therapies for treatment of PTSD.

Method

Conducted systematic literature search and identified 57 studies; calculated pooled effect sizes and compared effect sizes in overall model; statistically examined heterogeneity and bias.

Findings:

- ET and CPT were the strongest and most reliable intervention predictors
- Stress management therapies (e.g., Stress inoculation therapy) performed worse; mixed findings with EMDR although comparable after controlling for treatment allocation.
- Individual and combination performed much better than group therapy.
- Number of trauma-focused treatment sessions positively predicted outcome.
- Lower treatment gains found in “high” or “low” PTSD severity groups relative to “moderate” PTSD severity group.

(Haagan et al., 2015)

Efficacy of recommended treatments for veterans with PTSD: A metaregression analysis

BJPsych | The British Journal of Psychiatry (2005) 208, 93–100. doi: 10.1192/bjp.bp.114.148551

Review article

Pharmacotherapy for post-traumatic stress disorder: systematic review and meta-analysis

Mathew Hoskins, Jennifer Pearce, Andrew Bethell, Liliya Dankova, Corrado Barbui, Wietse A. Tol, Mark van Ommeren, Joop de Jong, Soraye Seedat, Henhui Chen and Jonathan I. Bisson

Background
Pharmacological treatment is widely used for post-traumatic stress disorder (PTSD) despite questions over its efficacy.

Aims
To determine the efficacy of all types of pharmacotherapy, as monotherapy, in reducing symptoms of PTSD, and to assess acceptability.

Method
A systematic review and meta-analysis of randomised controlled trials was undertaken; 51 studies were included.

Results
Selective serotonin reuptake inhibitors were found to be statistically superior to placebo in reduction of PTSD symptoms but the effect size was small (standardised mean difference −0.23, 95% CI −0.33 to −0.12). For individual pharmacological agents compared with placebo in two or more trials, we found small statistically significant evidence of efficacy for fluoxetine, paroxetine and venlafaxine.

Conclusions
Some drugs have a small positive impact on PTSD symptoms and are acceptable. Fluoxetine, paroxetine and venlafaxine may be considered as potential treatments for the disorder. For most drugs there is inadequate evidence regarding efficacy for PTSD, pointing to the need for more research in this area.

Declaration of Interest
None.

Post-traumatic stress disorder (PTSD) is a common mental disorder with an estimated prevalence of 15.4% in the most robust epidemiological studies (those using diagnostic interviews and random samples) of conflict-affected populations,[1] and a 12-month prevalence across the world of 3–4%.[2] The disorder may occur in people of any age who have been exposed to one or more exceptionally threatening or horrifying events. Characteristic symptoms include re-experiencing, avoidance and hypervigilance.[3,4] The disorder is associated with substantial comorbidity, such as depression, anxiety and substance misuse,[5] and significant economic burden.[6] Previous meta-analyses of pharmacological treatment of PTSD have been inconsistent. The UK's National Institute for Health and Care Excellence (NICE) guidelines found that only paroxetine, mirtazapine, amitriptyline and phenelzine were significantly superior to placebo.[7] Owing to the relatively small effect sizes and sample sizes, none of these drugs was included as a first-line treatment for PTSD; all were recommended as second-line treatment after the initiation of trauma-focused psychological treatment. The guidelines of the Australian Centre for Posttraumatic Mental Health (ACPMH), consistent with NICE, recommended that pharmacological interventions should not be used in preference to trauma-focused psychological treatment.[8] Other reviews have been more positive about pharmacological treatment, grouping selective serotonin reuptake inhibitors (SSRIs) together and rating them as equivalent to trauma-focused psychological treatments.[9,10] A Cochrane review reported strong benefits,[11] but the Institute of Medicine found inadequate evidence to determine the efficacy of pharmacological treatment for PTSD.[12] There are, however, major differences between the methodological quality of these reviews, making direct comparison problematic.[13] Given the inconsistent findings of previous meta-analyses and the increasing number of randomised controlled trials (RCTs) of pharmacological treatments, the World Health Organization (WHO) commissioned an update of the information obtained by the most methodologically robust systematic reviews published to date: those by NICE, ACPMH and the Cochrane Collaboration.[7,8,11] We reviewed RCTs that assessed the efficacy of pharmacological treatment compared with placebo control groups at reducing traumatic stress symptoms in individuals experiencing PTSD.

Method

All double-blind, randomised, placebo-controlled and comparative trials of the pharmacological treatment of PTSD completed from October 2005 (to ensure all eligible trials not published at the time of the NICE, Cochrane and ACPMH searches would be included) were considered in our primary and additional searches, covering 15 separate databases. Trials completed before October 2005 that were included in the NICE, Cochrane and ACPMH reviews were also considered. Published and unpublished abstracts and reports were sought out in any language. Studies were not excluded on the basis of differences between them such as sample size and duration. Pharmacotherapy trials in which there was ongoing or newly initiated trauma-focused psychotherapy or where the experimental medication served as an augmentation agent to ongoing pharmacotherapy were excluded. Pharmacotherapy trials in which there was ongoing supportive counselling were allowed provided it was not initiated during the course of the treatment, on the basis that this is common in trials and the limited evidence for supportive counselling.[14] Open label trials were not considered. Our review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist and reporting guidance.[15]

Participants

All studies of participants with PTSD according to ICD or DSM criteria were eligible.[3,4] There was no restriction on the basis of onset, duration or severity of PTSD symptoms, or on the presence of comorbid disorders, trauma type, age or gender of participants.

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Hoskins, et al., 2015

Purpose

Determine efficacy of all types of pharmacotherapy for improving PTSD symptoms .

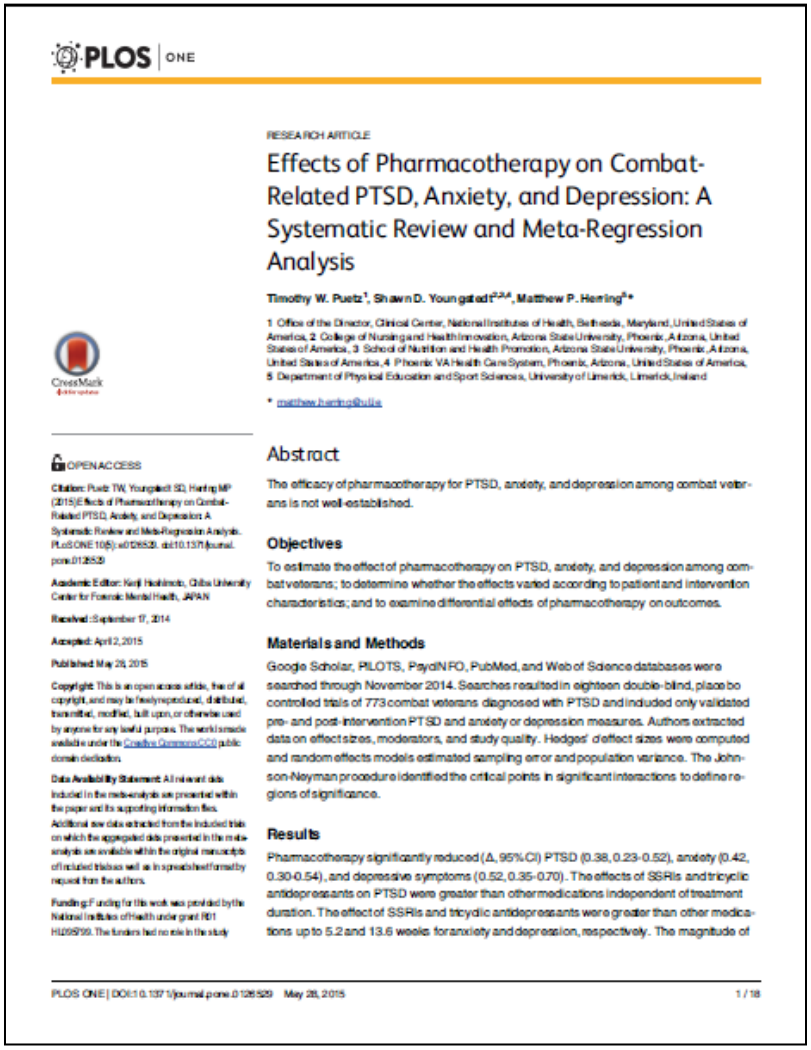
Method

Conducted systematic literature review of pharmacological treatments for adults with PTSD compared to placebo or other medications. Assessed bias; included 51 studies; conducted fixed/random effects model depending on heterogeneity; drugs analyzed at the individual level and then at class level when possible.

Findings: Hoskins et al., 2015

- Small positive effect of SSRI group on PTSD symptoms
- Sufficient evidence for individual effects for paroxetine, fluoxetine, and venlafaxine.
- No differences observed in combat related versus non-combat related trauma.
- Effect sizes lower than typically seen in trauma focused therapies, but caution with conclusions:
  - Different comparisons: placebo versus TAU
  - Pharmacotherapies often used by patients in therapy trials
- Insufficient evidence for other drugs (e.g., Brofaromine, Sertraline, Olanzapine, or Topiramate).
  - More research needed

Effects of Pharmacotherapy on Combat-Related PTSD, Anxiety, and Depression: A Systematic Review and Meta-Regression Analysis



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RESEARCH ARTICLE

Effects of Pharmacotherapy on Combat-Related PTSD, Anxiety, and Depression: A Systematic Review and Meta-Regression Analysis

Timothy W. Puetz[1], Shawn D. Youngstedt[2,3,4], Matthew P. Herring[5]*

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Abstract

The efficacy of pharmacotherapy for PTSD, anxiety, and depression among combat veterans is not well-established.

Objectives

To estimate the effect of pharmacotherapy on PTSD, anxiety, and depression among combat veterans; to determine whether the effects varied according to patient and intervention characteristics; and to examine differential effects of pharmacotherapy on outcomes.

Materials and Methods

Google Scholar, PILOTS, PsycINFO, PubMed, and Web of Science databases were searched through November 2014. Searches resulted in eighteen double-blind, placebo controlled trials of 773 combat veterans diagnosed with PTSD and included only validated pre- and post-intervention PTSD and anxiety or depression measures. Authors extracted data on effect sizes, moderators, and study quality. Hedges' d effect sizes were computed and random effects models estimated sampling error and population variance. The Johnson-Neyman procedure identified the critical points in significant interactions to define regions of significance.

Results

Pharmacotherapy significantly reduced (Δ, 95% CI) PTSD (0.38, 0.23-0.52), anxiety (0.42, 0.30-0.54), and depressive symptoms (0.52, 0.35-0.70). The effects of SSRIs and tricyclic antidepressants on PTSD were greater than other medications independent of treatment duration. The effect of SSRIs and tricyclic antidepressants were greater than other medications up to 5.2 and 13.6 weeks for anxiety and depression, respectively. The magnitude of

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Data Availability Statement: All relevant data included in the meta-analysis are presented within the paper and its supporting information files. Additional raw data extracted from the included trials on which the aggregated data presented in the meta-analysis are available within the original manuscripts of included trials as well as in spreadsheet format by request from the authors.

Funding: Funding for this work was provided by the National Institutes of Health under grant R01 HL095799. The funders had no role in the study

(Puetz, Youngstedt, & Herring, 2014)

Purpose

Determine efficacy of all pharmacotherapies for combat-related PTSD.

Method

Reviewed RCTs of pharmacological treatments for combat Veterans diagnosed with PTSD; arrived at 18 studies used in meta-analysis; calculated effect sizes; assessed study quality but did not weight results based on quality

Findings:

- Overall, pharmacotherapy improved PTSD.
- Improvements greatest in SSRIs and TCAs.
- Pharmacotherapy significantly improved comorbid depression and anxiety.
- SSRIs and TCAs only more effective for depression up to about 3.5 months:
  - Suggests SSRIs/TCAs addressing depression directly + indirectly
- SSRIs and TCAs only more effective for depression up to 5 weeks; after 11 weeks other pharmacotherapies more effective
  - Suggests SSRIs/TCAs addressing anxiety indirectly, but perhaps not as well directly

(Puetz et al., 2015)

Recent Notable RCTs

- Structure Approach Therapy: Reduce PTSD symptoms + relationship distress:
  - RCT found that SAT produced greater improvements in PTSD and relationship outcomes (Sautter et al., 2015)

- Mindfulness Based Stress Reduction (MBSR) produced greater reduction in PTSD symptoms (Polusny et al., 2015):
  - Differences modest; at 2 month follow-up, no difference in diagnosis.

- Telemedicine based collaborative care improves PTSD care (Fortney et al., 2015):
  - Received more treatment (CPT).
  - Improved PTSD symptoms at one year.

Future Research Directions

- Trauma population is heterogeneous and collaborating with patients on structure and outcomes is critical (Cloitre, 2015).

- PTSD symptoms heterogeneous with numerous potential biomarkers; several promising biomarkers emerging for identification, treatment, and disease progression (Michopoulos et al., 2015; Rasmusson & Abdallah, 2015).

- Focus on commonalities (Schnyder et al., 2015) and most effective components of interventions.
  - Is branding good?

Incorporating New Evidence: Limitations

- Impossible for single clinician to synthesize field.
- Contrasting evidence.
- Our own bias.
- **Primary concern is deviating from best evidence before the field is settled.**
  - Opportunity cost of using unsettled approaches in lieu of first line treatments.

When New Evidence is Relevant

- **When new VA/DoD CPGs arrive.**
  - Also consider other authoritative bodies.
- Evidence addresses important factors not addressed in existing guidelines:
  - Comparisons between two first line treatments.
  - Findings in areas with insufficient existing evidence.
  - Additional information on treatment delivery or context.
- Large shift in evidence (typically based on authoritative systematic reviews) between CPG publications that is acknowledged by the field.

When to Wait for More Evidence

- As a general rule, defer to CPGs or other authoritative bodies.
- When evidence is mixed.
- Paradigm shifting findings typically require an abundance of evidence:
  - *No testimony is sufficient to establish a miracle, unless the testimony be of such a kind, that its falsehood would be more miraculous than the fact which it endeavors to establish*
  - David Hume – 1748
- When we already have good evidence for an approach!

PTSD Research Resources

- National Center for PTSD
- www.pstd.va.gov
- ClinicalTrials.gov
- Institute of Medicine iom.edu
- National Institute of Mental Health (NIMH) www.nimh.nih.gov
- International Society for Traumatic Stress Studies istss.org

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