DEFENSE CENTERS OF EXCELLENCE
For Psychological Health & Traumatic Brain Injury

Using Meta-analysis to Determine the Most Effective Treatments for Posttraumatic Stress Disorder

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Webinar Details

- Live closed captioning is available through Federal Relay Conference Captioning (see the “Closed Captioning” box)
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- Question-and-answer (Q&A) session
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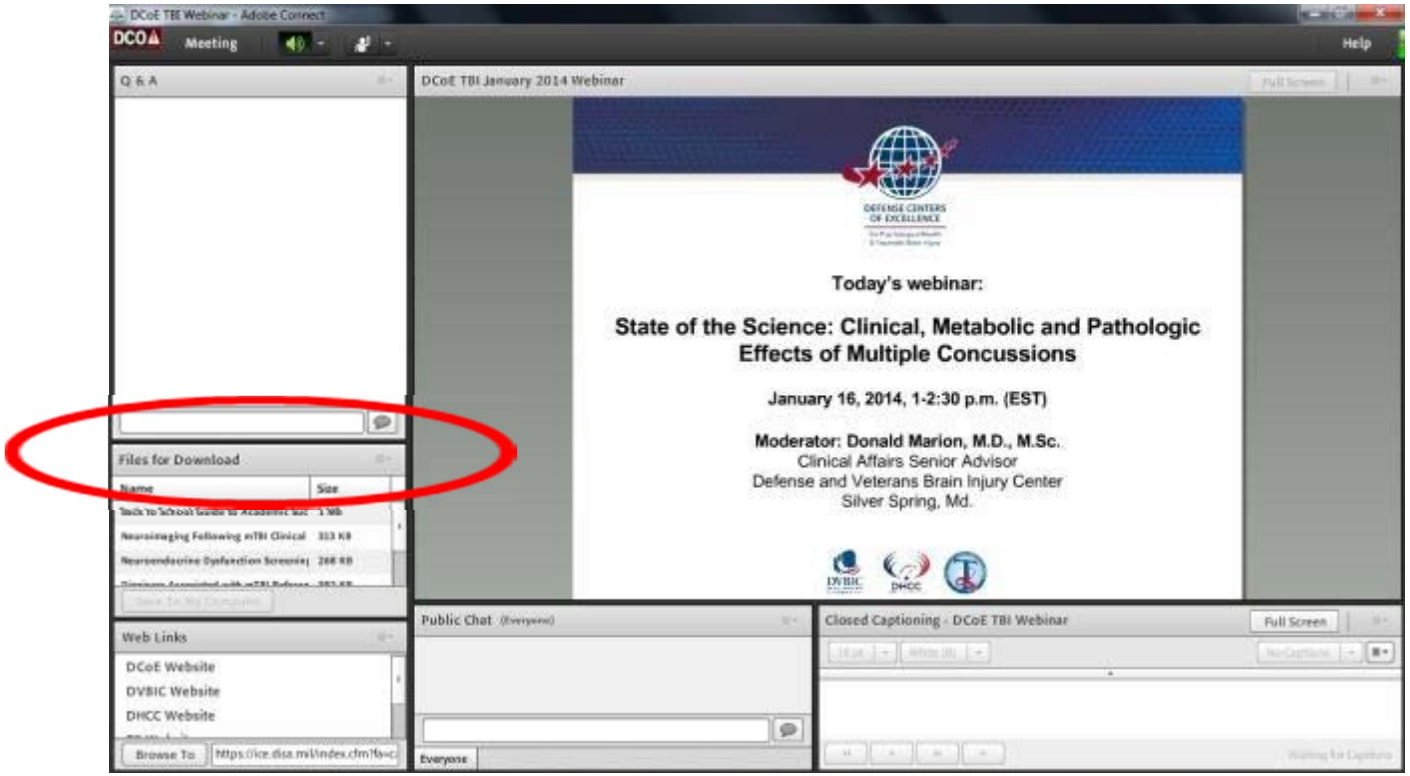

Continuing Education Details

- 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.

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- Credit Designations include:
  - 1.5 AMA PRA Category 1 credits
  - 1.5 ANCC nursing contact hours
  - 1.5 APA Division 22 contact hours
  - 1.5 ACCME AMA PRA Category 1 credits
  - 1.5 CRCC continuing hours
  - 0.15 ASHA, Intermediate level continuing hours

Continuing Education Accreditation

Physicians
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- The online CE evaluation will be open through **Thursday, November 5, 2015**.

Questions and Chat

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- 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.

Summary and Learning Objectives

This webinar will review the current guidelines for the treatment of posttraumatic stress disorder (PTSD) at all points in the treatment continuum. It will highlight the significant areas where current major guidelines (VA/DoD, WHO, NICE, APA and ISTSS) are not in agreement including medications versus therapy, individual medications and behavioral therapies. The presenter will discuss variances in the evaluation of data that resulted in these differences and will review an evaluation of current studies in the form of four meta-analyses looking at more than17,000 citations for best evidence-based treatment.

Webinar participants will be able to:

- Restate the current guidelines for the treatment of PTSD
- Differentiate between the current evidence for medication versus behavioral therapy as evidence-based treatment
- Identify medications with the best evidence supporting their use for PTSD
- Compare behavioral therapies with the best evidence supporting their use for PTSD

Dr. Jonathan P. Wolf

- Dr. Wolf is an Attending Psychiatrist at Walter Reed National Military Medical Center (WRNMMC), National Intrepid Center of Excellence. He is one of two attending psychiatrists on an integrated outpatient program treating service members with both acute and longstanding co-occurring neuropsychiatric issues.

- He has professional and technical oversight and direction of licensed and non-licensed healthcare providers, enlisted active duty personnel, reserve officers, nursing staff, psychiatric residents, interns, and medical students as well as leadership of multidisciplinary treatment team including psychiatry, occupational and physical therapy.

- Dr. Wolf is the lead attending on cases involving substance abuse/addictions and provides diagnostic evaluation of patients based upon laboratory and clinical findings, referral of patients to appropriate specialty clinics.

- His work includes collaboration with inpatient and outpatient physicians in other medical specialties on cases involving complicated and multifaceted problems. Dr. Wolf also provides oversight on research projects involving psychopharmacology and exposure treatment for posttraumatic stress disorder.

Using Meta-analysis to Determine the most Effective Treatments for Posttraumatic Stress Disorder

Dr. Jonathan Wolf, MD

Disclosure Information

We 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.

Learning Objectives

- Restate the current guidelines for the treatment of PTSD.
- Differentiate between the current evidence for medication vs. behavioral therapy as evidence-based treatment.
- Identify medications with best evidence supporting their use for PTSD.
- Compare behavioral therapies with the best evidence for support of their use for PTSD.

PTSD Criteria IV vs. V

- Diagnostic criteria for PSTD underwent modification with publication of DSM V in 2012.

- The majority of the studies reviewed and guidelines referenced utilized DSM IV criteria.

- The conclusions drawn from this presentation apply most directly to patients meeting DSM IV criteria for PTSD.

Outline

1. Background
2. Details of the meta – analysis
3. Brief discussion of translation to clinical practice

Background

Background

- Since September 11th 2001 American troops have deployed more than 3.3 million times.
- More than 2 million service members have deployed, 793,000 service members have deployed more than once. 400,000 service members have deployed 3 or more times.
- As of September 2012 1.6 million service members involved in the global war on terror had transitioned to veteran status.
- These service members will be transitioning their care from the DoD system to the VA and civilian providers.

Background

- Clinicians looking for expert guidance to treat returning service members with PTSD may find themselves confused.
- Current major guidelines are contradictory despite drawing from a common pool of studies.
- Currently no consensus exists on first line medications for PTSD or even if medications should be considered as first line treatment at all.

Major Guidelines Referenced

- Veteran's Administration/Department of Defense (2010)
- UK National Institute for Health and Clinical Evidence Guidelines (2005)
- American Psychiatric Association Practice Guideline for the Treatment of Patients with ASD and PTSD (2004)
- International Society For Traumatic Stress Studies (2008 and 2012 guidelines)
- World Health Organization (2013)
- Australian Centre for Posttraumatic Mental Health (2013)

Medications vs Behavioral Therapy for 1st Line Treatment?

	VA/DoD	NICE	APA	ISTSS	WHO	ACPMH
Recommend First Line Treatment	Medication or Therapy	Therapy	Medications or Therapy	Medications or Therapy	Therapy	Therapy

	Va/DoD	NICE	APA	ISTSS	WHO	ACPMH
First Line Medications	SSRIs , SNRIs	Mirtazapine, Amitriptyline, Phenelzine, Paroxetine	SSRIs	SSRI (Fluoxetine, Paroxetine, Sertraline), SNRI (Venlafaxine), TCAs, Mirtazapine, Nefazodone, Phenelzine, Prazosin	SSRI's, TCA's	SSRI'S
Second Line Medications	Mirtazapine Prazosin (for sleep) TCAs Nefazodone MAOI's	Hypnotics for sleep, "different classes of antidepressants " or adjunctive olanzapine for treatment refractory cases.	TCA's MAOIs	Bupropion Trazodone	None	TCA's

Recommended Behavioral Therapies

	VA/DoD	NICE	APA	ISTSS	WHO	ACPMH
First Line Behavioral Therapy	Cognitive Therapy (CT), Exposure, Stress Inoculation Training (SIT), EMDR (Eye Movement Desensitization Training)	TFCBT (Trauma Focused Cognitive Behavioral Therapy)	TFCBT	Exposure, CPT (Cognitive Processing Therapy), CT SIT EMDR	CBT, EMDR	TFCBT, EMDR
Second Line Behavioral Therapy	IRT (Image Rehearsal Therapy), Psychodynamic Therapy			Psychodynamic	Group CBT, Stress Management	

Summary of Guidelines

- Three of five guidelines recommended behavioral therapy as superior to all psychopharmacological interventions. Three out of five considered therapy and medications to be equivalent therapy.

- Medication recommendations were also inconsistent. Some guidelines recommended all agents of a particular class (SSRI's); some guidelines evaluated individual agents. Some medications given first line recommendation under one guideline were contraindicated by others. Paroxetine was the sole medication to be recommended as a first line medication by all guidelines.

- Greater consensus existed with regard to behavioral therapy recommendations with exposure based therapy and CBT approaches held superior to others, although there was some variability.

Summary of Guidelines

- Differences in guidelines result from fundamental differences in the evaluation and collection of data:
  - Collection of data was idiopathic in construction of the majority of guidelines
  - VA/DoD and ISTSS valued the number of positive trials regardless of effect size, where NICE and the Australian Centre considered positive effect sizes lower than 0.5 to be negative.
  - ISTSS valued uncontrolled data more than VA/DoD; NICE ignored uncontrolled data altogether

Summary of Guidelines

- Narrative Review - traditional literature reviews in which the selection of items reviewed, the quality assessments, the data extraction and the conclusions and the extent to which different studies come to the same conclusion, are subjective, using implicit criteria, and are biased in unsystematic ways. Narrative reviews are by their nature unreplicable.

- Systematic Review – a literature review using defined criteria to search for all relevant data to answer a research question

- Meta analysis – a systemic review that additionally uses statistical methods to evaluate data from the review.

Organization	Standardization of Data Collection?	Standardization of Data Evaluation?
DoD/VA	No	No
NICE	Yes	+/-
APA	No	No
ISTSS	No	No
WHO	No	No
ACPMH	+/-	Yes

Why Meta – Analysis?

- Transparency –
- In collection of data:
- Systematic collection of data results in largest possible data pool and eliminates bias.
- In evaluation of data:
- Allows readers to evaluate criteria by which conclusions are drawn
- Indicates level of evidence required in future studies to alter clinical practice

Why Meta-analysis for PTSD?

- The experts have not reached consensus
- The data is still evolving

Meta-Analysis

- We completed a set of four meta-analyses that were designed to provide rigorous, transparent, and valid comparisons of medication and psychotherapy performance against control conditions and between pre/post-treatment conditions using gold-standard PTSD outcome measures and methodology.

Criteria

- RCTs with ≥8 weeks of medication or ≥8 sessions of psychotherapy involving active control conditions, such as placebo, alternative medication, supportive psychotherapy, biofeedback, or relaxation training.
- Clinician-Administered PTSD Scale(CAPS), Short PTSD Rating Interview (SPRINT), or PTSD Symptom Scale-Interview (PSS-I) were required outcome measures.
- Effect size was evaluated to allow for the comparison of one intervention vs an alternative.
- Studies were grouped by duration to allow observation of effect trends.

The Questions

- Should medications and psychotherapy be considered equivalent first line treatments (DoD/VA, APA, ISTSS) or is psychotherapy superior (NICE, WHO, Australia)?

- Among individual medications, which should be considered first line?

- Among psychotherapies, which should be considered first line? Or are they equivalent?

Details of the Meta-Analysis

Methods

- Medline (1900 – June 2014), EMBASE (1860 – June 2014), PILOTS, Cochrane Central Register of Controlled Trials, and PsycINFO (1806-June 2014) and Global Health Library searched without language restrictions.
- Searches involved combinations of PTSD and generic medication names, psychotherapy names and/or abbreviations.
- After recovery of articles bibliographies of included studies were reviewed and search was supplemented by citations.

Inclusion Criteria

- Published and unpublished data were included.
- Data were evaluated only from randomized adult clinical trials using active control conditions and intention-to-treat designs.
- For medications placebo control was required; psychotherapy controls included supportive psychotherapy, treatment as usual, biofeedback, and relaxation training.
- We defined 8 weeks of medication or 8 psychotherapy sessions as the minimum length required for inclusion based upon standards often used in health services research.

Inclusion Criteria

- PTSD diagnosis by DSM – III- R or DSM – IV-TR criteria prior to treatment initiation was required.

- Trials with 100% prevalence of a co-morbid condition such as borderline personality disorder, primary thought disorder or substance use disorder were excluded as it was felt these represented primary study outcomes. Many included studies contained high rates of co-morbid conditions as typical of PTSD populations.

- Gold standard outcome measures were required: CAPS, SPRINT or PSS-I.

Inclusion Criteria: Medications

- For Medications:
- All studies examining anti-depressants and prazosin were included based upon performance in controlled trials.
- Trials of benzodiazepines were excluded due to limitations in trial design and/or overall evidence of harm.
- Adjunctive and monoagent SGA's were evaluated.
- Monoagent trials of mood stabilizers were evaluated and largely failed separate from placebo.

Inclusion Criteria: Psychotherapy

- Psychotherapies considered were CBT, CPT, DBT, EMDR, PE and SIT.
- Psychotherapy sessions were required to be individual, face-to- face, manualized and >45 minutes in duration.
- For purposes of generalizability, therapies deviating from traditional manualized approaches were excluded.
- Concomitant medication use was allowed provided medication types and percentages were similar for psychotherapy and control groups.

Study Selection and Data Abstraction

- Studies were reviewed by two-stage selection.
- Stage one, one author independently reviewed titles and abstracts to select full text articles.
- In stage two, both the first author and a co-author independently applied inclusion/exclusion criteria. Inter-rater agreement was >95%.

Statistical Analysis

- Due to differences between CAPS, SPRINT, and PSS-I effect sizes were pooled across studies to determine overall effect size for each medication or psychotherapy at each time grouping.

- By convention effect sizes >0.8 were considered large, those between 0.8 and 0.6 moderate, and those between 0.5 and 0.2 small.

Statistical Analysis

- Outcomes were grouped by time (8-12 weeks, 15-27 weeks, and 34+ weeks).
- 67% of studies ended, re-randomized and/or recorded outcomes at 8,12,24 or 36 weeks.
- Selected ranges allowed for capture of re-randomization and measurements occurring around these times.
- End points beyond 34 weeks were variable; to avoid arbitrary creation of different groupings, end points beyond 34 weeks were grouped together.

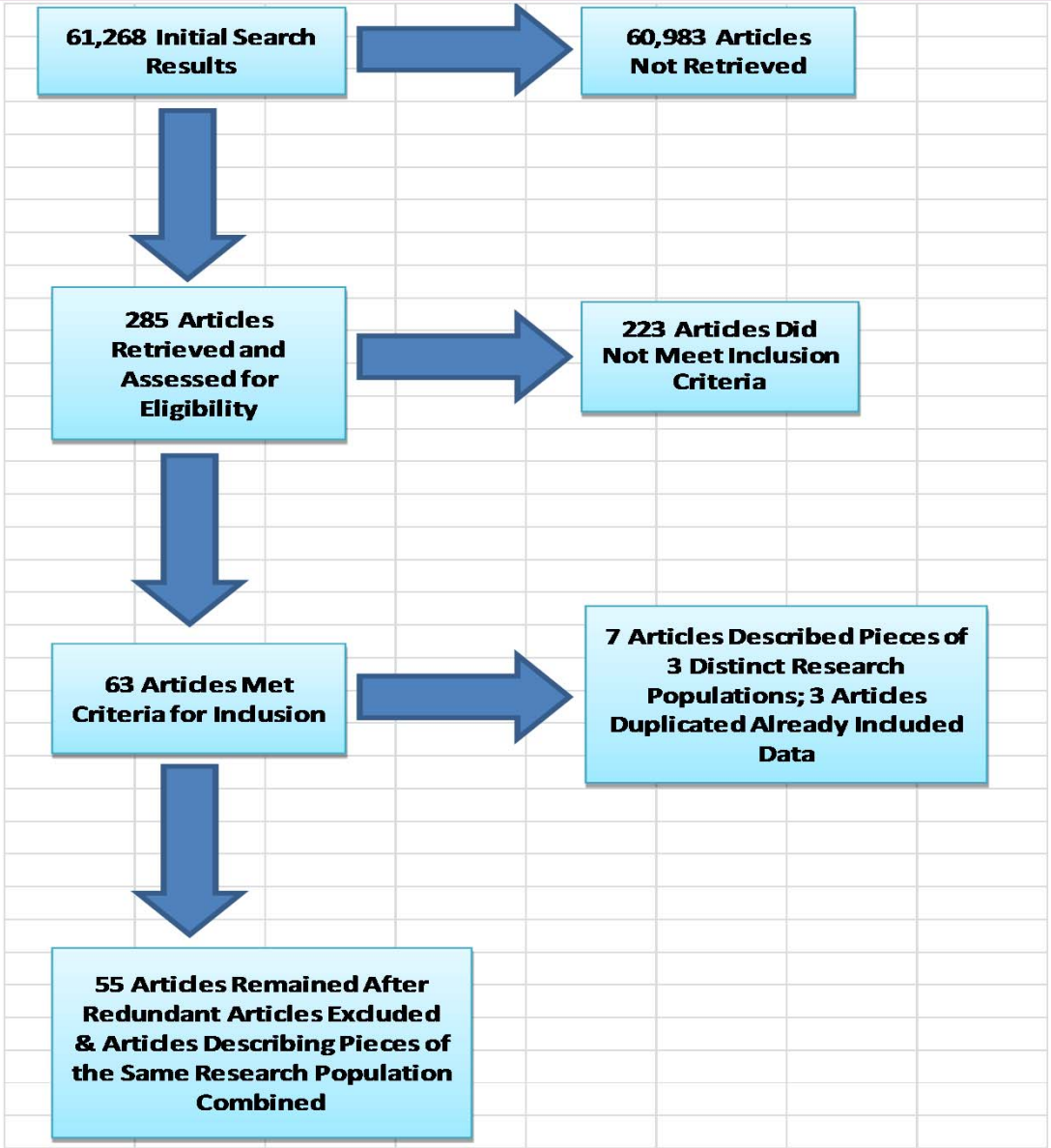
Statistical Analysis

- For studies involving the same research population treatment groups and control groups were pooled for each time period. Studies with multiple arms measured against a single control were analyzed as separate studies.

- When studies transitioned from controlled to uncontrolled or vice versa uncontrolled data points were excluded.

- Data points were also excluded if re-randomization involved the exclusion of treatment-responders or non-responders.

Results


61,268 Initial Search Results
60,983 Articles Not Retrieved
285 Articles Retrieved and Assessed for Eligibility
223 Articles Did Not Meet Inclusion Criteria
63 Articles Met Criteria for Inclusion
7 Articles Described Pieces of 3 Distinct Research Populations; 3 Articles Duplicated Already Included Data
55 Articles Remained After Redundant Articles Excluded & Articles Describing Pieces of the Same Research Population Combined

Results

- A total of 6,313 participants were enrolled in all trials.
- Average duration was 18 weeks (8-104) with average medication study running 17 week and average therapy treatment lasting 10 sessions.
- A mean of 115 participants (10-551) took part in each study.
- Forty-nine percent of the participants were women (0%-100%)
- Average percentage of veteran/combat trauma was 40% (40% med/24% PT)
- Dropout average was 29% (0-79%)
- Average baseline CAPS was 77 (80 med/72 PT), Average SPRINT for medications was 17, and average baseline PSS-I for psychotherapy was 31.
- Average percentage of MDD at initiation was 41% (0-86%)

Intervention	Author / Year	N	% Vet/Combat	% Women	Mean Age	% Depression	Mean Dose / # Sessions
Aripiprazole	Naylor (2015)	16	100	31	34	86	10mg
Brofaromine	Baker (1995)	118	60	19	44	Uncertain	Uncertain
Brofaromine	Katz (1995)	45	18	24	39	0	Uncertain
Bupropion	Becker (2007)	28	50	21	50	Uncertain	300mg
CPT	Suris (2013)	86	0	85	46	Uncertain	10 sessions
Divalproex	Davis (2008)	85	100	Uncertain	55	Uncertain	2309mg
Divalproex	Hamner (2009)	29	100	3	52	69	1196mg
EMDR	Carlson (1998)	35	100	0	48	Uncertain	Uncertain
EMDR, PE, PE/CR	Taylor (2003)	60	0	75	37	42	8 sessions
Fluoxetine	Davidson (2005)	123	32	50	44	Uncertain	49mg
Fluoxetine	Martenyi (2007)	411	5	72	41	Uncertain	30mg
Fluoxetine	Martenyi (2002), Martenyi (2002)	301	31	19	38	0	57mg
Fluoxetine	Martenyi (2006)	144	100	1	36	0	65mg
Fluoxetine	van der Kolk (2007)	59	0	83	36	Uncertain	30mg
Guanfacine	Davis (2008)	35	100	6	53	57	2mg
Guanfacine	Neylan (2006)	56	100	Uncertain	Uncertain	Uncertain	2mg
IE, IE/CR	Bryant (2003)	58	0	52	35	Uncertain	Uncertain
Mirtazapine	Davidson (2003)	29	14	50	47	73	39mg
Nefazodone	Davis (2004)	41	98	2	54	39	435mg
Olanzapine	Butterfield (2001)	15	60	93	43	53	14mg
Olanzapine	Carey (2012)	28	0	61	41	0	9mg
Olanzapine	Stein (2002)	21	100	0	53	Uncertain	15mg
Paroxetine	GlaxoSmithKline (2001)	263	0	66	43	0	Uncertain
Paroxetine	Marshall (2001)	551	8	67	42	45	30mg
Paroxetine	Marshall (2007)	52	0	67	40	63	Uncertain
Paroxetine	Schneier (2012)	37	0	54	50	66*	32mg
Paroxetine	Tucker (2000)	323	7	66	41	35	28mg
Paroxetine	Fani (2009)	18	Uncertain	56	41	Uncertain	Uncertain
Paroxetine	Fani (2011)	13	8	54	40	85	Uncertain
PE	Schnurr (2007)	284	100	100	45	64*	9 sessions
PE	Rauch (2014)	30	100	8	32	47	11 sessions
PE, IPT	Markowitz (2015)	110	0	77	40	50	8 PE / 13 IPT
PE, PE/CR	Marks (1998)	87	3	36	38	49	Uncertain
PE, SIT	Foa (1991)	45	0	100	32	Uncertain	Uncertain
Prazosin	Raskind (2007)	38	100	5	56	Uncertain	13mg
Prazosin	Raskind (2013)	67	100	15	30	34	20mg men / 9mg women
Prazosin	Raskind (2003)	10	100	0	53	Uncertain	10mg
Risperidone	Padala (2006)	20	0	100	41	Uncertain	3mg
Risperidone	Reich (2004)	21	0	100	28	62	1mg
Risperidone	Bartzokis (2004)	65	100	0	52	Uncertain	3mg
Risperidone	Krystal (2011)	296	100	3	54	70	3mg
Risperidone	Rothbaum (2008)	20	0	80	34	80	2mg
Sertraline	Brady (2000), Davidson (2001), Davidson (2001)	385	5	76	38	37	139mg
Sertraline	Friedman (2007)	169	100	20	46	0	135mg
Sertraline	Zohar (2002)	42	100	12	40	0	120mg
Sertraline, Citalopram	Tucker (2003)	58	3	74	39	78	sert 134mg / cit 36mg
Sertraline, Venlafaxine	Davidson (2006)	531	9	Uncertain	Uncertain	0	sert 110mg / ven 164mg
TF-CBT	Blanchard (2003), Blanchard (2003)	98	0	73	40	49	10 sessions
TF-CBT	McDonaugh (2005)	74	0	100	40	Uncertain	Uncertain
TF-CBT	Ehlers (2014)	121	0	59	39	36	12 sessions
Tiagabine	Connor (2005)	26	4	73	41	Uncertain	11mg
Tiagabine	Davidson (2007)	232	9	66	43	38	11mg
Topiramate	Tucker (2007)	40	0	79	42	61	150mg
Topiramate	Yeh (2011)	35	0	68	40	13	103mg
Venlafaxine	Davidson (2006)	329	12	54	41	0	182mg

Quality of Ratings

- Quality varied among studies with most having important limitations in design, reporting or both.
- Psychotherapy trials were generally better designed, executed and reported than medication studies. However, double-blinding was not possible for psychotherapy studies and it is unlikely that non-specific placebo effects were fully controlled for.
- Randomization and blinding success were questionable in some medication studies where groups differed significantly in adverse effects and attrition due to those effects.

Bias Risk	Intervention	Author / Year	Drop Out	Adherence	Sequence Generation	Allocation Concealment	Industry Support	Selective Reporting
VERY LOW	CPT	Suris (2013)	28%	Yes	Yes	Yes	No	No
VERY LOW	IE, IE/CR	Bryant (2003)	22%	Yes	Yes	Yes	No	No
VERY LOW	PE, PE/CR	Marks (1998)	60%	Yes	Yes	Yes	No	Yes
VERY LOW	PE	Schnurr (2007)	29%	Yes	Yes	Yes	No	No
VERY LOW	PE	Markowitz (2015)	25%	Yes	Yes	Yes	No	No
VERY LOW	TF-CBT	Ehlers (2014)	3%	Yes	Yes	Yes	No	No
VERY LOW	Topiramate	Yeh (2011)	26%	Yes	Yes	Yes	No	No
LOW	TF-CBT	Blanchard (2003), Blanchard (2003)	20%	Yes	Uncertain	Yes	No	Yes
LOW	TF-CBT	McDonaugh (2005)	23%	Yes	Uncertain	Yes	No	Yes
LOW	EMDR	Carlson (1998)	3%	Yes	Uncertain	Yes	No	Yes
LOW	EMDR, PE	Taylor (2003)	35%	Yes	Uncertain	Yes	No	Yes
LOW	Fluoxetine	Martenyi (2002), Martenyi (2002)	61%	Yes	Yes	Yes	Yes	No
LOW	Fluoxetine	Martenyi (2006)	67%	No	Yes	Yes	No	Yes
LOW	PE, SIT	Foa (1991)	18%	Yes	Uncertain	Yes	No	Yes
LOW	Prazosin	Raskind (2007)	18%	Uncertain	Yes	Yes	No	Yes
LOW	Divalproex	Davis (2008)	20%	Uncertain	Yes	Yes	No	Yes
MODERATE	Fluoxetine	van der Kolk (2007)	34%	Uncertain	Uncertain	Yes	No	Yes
MODERATE	Paroxetine	Schneier (2012)	41%	Uncertain	Uncertain	Yes	No	Yes
MODERATE	PE	Rauch (2014)	28%	Uncertain	Uncertain	Yes	No	Yes
MODERATE	Divalproex	Hamner (2009)	48%	Yes	Uncertain	Yes	Yes	Yes
MODERATE	Guanfacine	Neylan (2006)	10%	Yes	Uncertain	Yes	No	Yes
HIGH	Brofaromine	Baker (1995)	30%	Uncertain	Uncertain	Uncertain	Yes	Yes
HIGH	Brofaromine	Katz (1995)	27%	Uncertain	Uncertain	Uncertain	Yes	Yes
HIGH	Bupropion	Becker (2007)	23%	Uncertain	Uncertain	Uncertain	Yes	Yes
HIGH	Fluoxetine	Davidson (2005)	44%	Yes	Unclear	Uncertain	Yes	Yes
HIGH	Mirtazapine	Davidson (2003)	31%	Uncertain	Uncertain	Uncertain	No	Yes
HIGH	Nefazodone	Davis (2004)	44%	Uncertain	Uncertain	Yes	Yes	Yes
HIGH	Paroxetine	Marshall (2007)	42%	Uncertain	Uncertain	Yes	Yes	Yes
HIGH	Prazosin	Raskind (2013)	39%	Uncertain	Uncertain	Uncertain	No	Yes
HIGH	Prazosin	Raskind (2003)	0%	Uncertain	Uncertain	Uncertain	No	Yes
HIGH	Sertraline	Brady (2000), Davidson (2001), Davidson (2001)	79%	Yes	Uncertain	Uncertain	Yes	Yes
HIGH	Sertraline	Friedman (2007)	24%	Uncertain	Yes	Uncertain	Yes	Yes
HIGH	Sertraline	Zohar (2002)	26%	Yes	Uncertain	Uncertain	Yes	Yes
HIGH	Olanzapine	Carey (2012)	29%	Uncertain	Yes	Uncertain	Yes	Yes
HIGH	Topiramate	Tucker (2007)	5%	Uncertain	Yes	Uncertain	Yes	Yes
HIGH	Aripiprazole	Naylor (2015)	25%	Uncertain	Uncertain	Uncertain	No	Yes
HIGH	Guanfacine	Davis (2008)	19%	Uncertain	Uncertain	Uncertain	No	Yes
VERY HIGH	Fluoxetine	Martenyi (2007)	12%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Paroxetine	GlaxoSmithKline (2001)	51%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Paroxetine	Marshall (2001)	37%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Paroxetine	Tucker (2000)	39%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Sertraline, Citalopram	Tucker (2003)	24%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Sertraline, Venlafaxine	Davidson (2006)	34%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Venlafaxine	Davidson (2006)	32%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Olanzapine	Butterfield (2001)	27%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Tiagabine	Connor (2005)	50%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Tiagabine	Davidson (2007)	61%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Paroxetine	Fani (2009)	44%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Paroxetine	Fani (2011)	0%	Insufficient	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Risperidone	Padala (2006)	0%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Risperidone	Reich (2004)	0%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Olanzapine	Stein (2002)	10%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Risperidone	Bartzokis (2004)	26%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Risperidone	Krystal (2011)	17%	Uncertain	Uncertain	Uncertain	Yes	Yes
VERY HIGH	Risperidone	Rothbaum (2008)	44%	Uncertain	Uncertain	Uncertain	Yes	Yes

Effects of Medication vs Placebo

- Effect sizes for most medications when compared against placebo were small.
- Nefazodone and Venlafaxine both displayed large effects at 8-12 weeks. Fluoxetine, Paroxetine and Sertraline all displayed small effects during this period.
- At 15-24 weeks Prazosin displayed a large effect, venlafaxine's effect is still statistically significant, but small. Paroxetine's effect was non significant.
- At 34+ weeks, sertraline demonstrated a large effect. Effects from brofaromine, fluoxetine and paroxetine were non-significant.

Medication Effects on Pre- to Post- Treatment

- Medication within group effects were generally much larger than effect sizes compared to control conditions

- Effects at 8-12 weeks were large for Brofaromine, Bupropion, Citalopram, Fluoxetine, Nefazodone, Mirtazepine, Paroxetine, Sertraline, Venlafaxine. Prazosin was non significant at 8-12 weeks

- Effects were large for paroxetine, prazosin and venlafaxine at 15-24 weeks

- At 34+ weeks effects were large for brofaromine, fluoxetine and sertraline

Effects of Psychotherapy Versus Control Conditions

- Overall effect sizes were large for TFP's. Non-TFP's effect sizes remained small to moderate.
- Effects at 8-12 weeks were large for EMDR, PE and SIT. Effects were moderate for CPT. CBT and PE/CR effects were non-significant.
- At 15-24 weeks CPT and PE demonstrated large effects, CBT demonstrated a moderate effect. Both PE/CR and SIT were non significant.
- At 34+ weeks PE and PE/CR had large effects, CPT was moderate. CBT and EMDR effects were non-significant.

Psychotherapy Effects on Pre- to Post-Treatment

- Overall effect sizes were large for TFPs, non-TFPs, and individual psychotherapies were all large.

MONO-AGENT PHARMACOTHERAPY						
	8-12 Wk Pre/Post	14-27 Wk Pre/Post	34+ Wk Pre/Post	8-12 Wk vs. Control	14-27 Wk vs. Control	34+ Wk vs. Control
Brofaromine	-1.30 (-1.62 to -0.98)		-1.53 (-2.14 to -0.92)	-0.07 (-0.37 to 0.22)		-0.60 (-1.20 to 0.00)
Bupropion	-1.11 (-1.88 to -0.34)			-0.22 (-1.12 to 0.68)		
Citalopram	-1.54 (-2.17 to -0.91)			0.18 (-0.56 to 0.91)		
Divalproex	-0.69 (-1.14 to -0.25)			-0.03 (-0.46 to 0.41)		
Fluoxetine	-1.46 (-1.57 to -1.34)		-2.60 (-2.88 to -2.32)	-0.23 (0.39 to -0.07)		-0.10 (-0.35 to 0.15)
Mirtazapine	-1.23 (-1.97 to -0.50)			-0.81 (-1.65 to 0.02)		
Nefazodone	-0.86 (-1.43 to -0.30)			-1.32 (-2.02 to -0.63)		
Olanzapine	-2.00 (-2.69 to -1.31)			-0.72 (-1.36 to -0.09)		
Paroxetine	-1.35 (-1.49 to -1.22)	-1.67 (-2.47 to -0.86)	Missing data	-0.36 (-0.49 to -0.28)	0.09 (-0.67 to 0.86)	-0.08 (-0.38 to 0.21)
Risperidone	-1.35 (-2.00 to -0.71)			-0.48 (-1.1 to 0.14)		
Sertraline	-1.49 (-1.64 to -1.34)		-2.34 (-2.73 to -1.96)	-0.51 (-0.64 to -0.38)		-1.46 (-1.91 to -1.01)
Tiagabine	-2.47 (-2.81 to -2.12)	-3.28 (-4.33 to -2.23)		0.02 (-0.24 to 0.28)	0.11 (-0.82 to 1.04)	
Topiramate	-2.12 (-2.70 to -1.54)			-0.34 (-0.82 to 0.14)		
Venlafaxine	-3.78 (-4.12 to -3.43)	-2.45 (-2.74 to -2.16)		-1.78 (-2.01 to -1.52)	-0.32 (-0.54 to -0.10)	
PSYCHOTHERAPY						
CPT	-6.71 (-7.70 to -5.72)	-7.20 (-8.25 to -6.15)	-8.61 (-9.84 to -7.38)	-1.08 (-1.54 to -0.62)	-1.22 (-1.69 to -0.75)	-0.57 (-1.01 to -0.13)
EMDR	-2.06 (-2.72 to -1.41)		-2.12 (-3.28 to -0.96)	-0.87 (-1.42 to -0.32)		-1.12 (-2.41 to 0.16)
IPT	-0.95 (-1.42 to -0.48)	-1.42 (-1.93 to -0.92)		-0.15 (-0.67 to 0.37)	-0.25 (-0.77 to 0.27)	
PE / IE	-2.57 (-2.83 to -2.31)	-3.72 (-4.09 to -3.35)	-4.38 (-4.80 to -3.96)	-1.01 (-1.20 to -0.83)	-1.03 (-1.24 to -0.82)	-0.80 (-1.03 to -0.57)
PE / CR	-1.54 (-2.05 to -1.03)	-2.37 (-3.27 to -1.47)	-2.49 (-3.12 to -1.85)	-0.41 (-0.88 to 0.06)	-0.38 (-1.14 to 0.38)	-1.50 (-2.22 to -0.78)
SIT	-2.75 (-4.04 to -1.46)	-1.49 (-2.53 to -0.45)		-1.26 (-2.12 to -0.40)	-0.40 (-1.33 to 0.53)	
TF-CBT	-1.37 (-1.7 to -1.03)	-2.08 (-2.53 to -1.63)	-1.94 (-2.38 to -1.50)	-0.39 (-0.70 to -0.08)	-0.83 (-1.21 to -0.45)	-0.69 (-1.07 to -0.31)
ADJUNCTIVE PHARMACOTHERAPY (USED WITH AN ANTIDEPRESSANT)						
Aripiprazole	-0.97 (-2.08 to 0.13)			-0.03 (-1.08 to 1.02)		
Divalproex	0.08 (-0.63 to 0.8)			0.38 (-0.36 to 1.12)		
Guanfacine	-0.37 (-0.78 to 0.04)			-0.11 (-0.51 to 0.29)		
Olanzapine	-0.8 (-1.71 to 0.11)			-0.8 (-1.73 to 0.14)		
Prazosin	-0.62 (-1.31 to 0.07)	-2.19 (-2.76 to -1.63)		-0.38 (-1.06 to 0.30)	-1.01 (-1.46 to -0.56)	
Risperidone	-1.16 (-1.96 to -0.36)	-1.22 (-1.46 to -0.97)		-0.19 (-0.98 to 0.6)	-0.49 (-0.71 to -0.28)	

Sub-Meta-Analyses						
	8-12 Wk Pre/Post	14-27 Wk Pre/Post	34+ Wk Pre/Post	8-12 Wk vs. Control	14-27 Wk vs. Control	34+ Wk vs. Control
SSRIs Only	-1.43 (-1.51 to -1.36)	-1.67 (-2.47 to -0.86)	-2.51 (-2.14 to -2.82)	-0.37 (-0.45 to -0.29)	0.90 (-0.67 to 0.86)	-0.30 (-0.47 to -0.12)
SSRIs + SNRIs	-1.54 (-1.61 to -1.46)	-2.36 (-2.63 to -2.09)	-2.51 (-2.14 to -2.82)	-0.50 (-0.58 to -0.43)	-0.29 (-0.50 to -0.08)	-0.30 (-0.47 to -0.12)
All Anti-Epileptics	-1.65 (-1.89 to -1.42)	-3.28 (-4.33 to -2.23)		-0.03 (-0.22 to 0.17)	0.11 (-0.82 to 1.04)	
All Anti-Psychotics	-1.36 (-1.71 to -1.01)	-1.22 (-1.46 to -0.97)		-0.49 (-0.83 to -0.15)	-0.49 (-0.71 to -0.28)	
EMDR + PE / IE + CPT	-2.74 (-2.97 to -2.50)	-4.10 (-4.45 to -3.75)	-4.54 (-4.91 to -4.16)	-1.01 (-1.20 to -0.83)	-1.03 (-1.24 to -0.82)	-0.80 (-1.03 to -0.57)
EMDR + PE / IE + CPT + SIT	-2.74 (-2.97 to -2.51)	-3.84 (-4.17 to -3.51)	-4.54 (-4.91 to -4.16)	-1.02 (-1.18 to -0.85)	-1.03 (-1.22 to -0.84)	-0.80 (-1.03 to -0.57)
All Trauma-Focused Therapies	-2.19 (-2.37 to -2.01)	-3.26 (-3.52 to -3.00)	-3.28 (-3.54 to -3.02)	-0.83 (-0.97 to -0.69)	-0.96 (-1.13 to -0.80)	-0.75 (-0.92 to -0.57)
All Non-Trauma-Focused Therapies	-1.16 (-1.60 to -0.72)	-1.43 (-1.89 to -0.98)		-0.45 (-0.89 to -0.01)	-0.29 (-0.74 to 0.17)	
All Therapies	-2.04 (-2.21 to -1.88)	-2.80 (-3.03 to -2.58)	-3.28 (-3.54 to -3.02)	-0.79 (-0.93 to -0.66)	-0.90 (-1.06 to -0.74)	-0.79 (-0.96 to -0.62)
All Medications	-1.50 (-1.56 to -1.43)	-2.36 (-2.59 to -2.13)	-2.39 (-2.60 to -2.18)	-0.43 (-0.49 to -0.36)	-0.44 (-0.58 to -0.30)	-0.32 (-0.49 to -0.15)
All Interventions	-1.54 (-1.60 t0 -1.48)	-2.17 (-2.30 to -2.03)	-2.75 (-2.91 to -2.58)	-0.50 (-0.56 to -0.44)	-0.64 (-0.75 to -0.54)	-0.55 (-0.67 to -0.43)
First Line Interventions						
APA	-1.54 (-1.61 to -1.47)	-3.11 (-3.36 to -2.86)	-2.84 (-3.01 to -2.67)	-0.48 (-0.55 to -0.41)	-0.91 (-1.08 to -0.75)	-0.52 (-0.65 to -0.40)
Australian, NICE, & WHO	-2.19 (-2.37 to -2.01)	-3.26 (-3.52 to -3.00)	-3.28 (-3.54 to -3.02)	-0.83 (-0.97 to -0.69)	-0.96 (-1.13 to -0.80)	-0.75 (-0.92 to -0.57)
ISTSS	-1.63 (-1.70 to -1.55)	-3.23 (-3.50 to -2.96)	-3.06 (-3.26 to -2.87)	-0.51 (-0.59 to -0.44)	-1.24 (-1.38 to -1.10)	-0.44 (-0.55 to -0.32)
VA/DoD	-1.65 (-1.73 to -1.58)	-2.95 (-3.16 to -2.74)	-3.48 (-3.75 to -3.22)	-0.59 (-0.66 to -0.52)	-0.70 (-0.84 to -0.56)	-0.48 (-0.62 to -0.34)
Second Line Interventions						
APA	-3.32 (-3.63 to -3.01)	-2.45 (-2.74 to -2.16)		-0.51 (-1.16 to 0.15)	-0.32 (-0.54 to -0.10)	
Australian & WHO	-1.43 (-1.51 to -1.36)	-1.67 (-2.47 to -0.86)	-2.51 (-2.14 to -2.82)	-0.37 (-0.45 to -0.29)	0.90 (-0.67 to 0.86)	-0.30 (-0.47 to -0.12)
ISTSS	-1.11 (-1.88 to -0.34)			-0.22 (-1.12 to 0.68)		
NICE	-1.35 (-1.48 to -1.22)	-1.67 (-2.47 to -0.86)		-0.37 (-0.49 to -0.24)	0.09 (-0.67 to 0.86)	-0.08 (-0.38 to 0.21)
VA/DoD	-1.12 (-1.37 to -0.88)	-2.19 (-2.76 to -1.63)	-1.53 (-2.14 to -0.92)	-0.33 (-0.57 to -0.08)	-1.03 (-1.54 to -0.52)	-0.60 (-1.20 to 0.00)

Discussion: Psychotherapy vs. Medication

- Trauma focused psychotherapy (TFP) produced comparable or larger effect sizes than medications with narrower confidence intervals despite enrolling less than a quarter participants in medication trials.

- TFP effects sizes at all time intervals (8-12 wks., 15-27 wks. and +34 wks.) and were equivalent to the top performing individual medications.

- Results suggested possible advantages for some TFP's over medication.

Discussion: Individual Therapies

- Where medications, with some notable exceptions, appeared to decrease in effect size over time, effect sizes for psychotherapies were largely stable over time.

- Some level of caution should be used in comparison of the effectiveness of TFP's against each other. Our requirement for active controls excluded a large number of otherwise well-designed psychotherapy trials with wait-list controls.

Discussion: Individual Therapies

- Stress Inoculation and EMDR were notable among psychotherapies in that their effectiveness seemed to diminish vs controls over time. Effect size for SIT was the largest among the behavioral therapies at weeks 8-12, but had diminished to a small effect size by 15-24 weeks. EMDR's effect size was large at 8-12 weeks, but non significant in 34+ weeks.

- Prolonged Exposure was the only intervention studied that demonstrated large effect sizes against controls at all time intervals.

- Cognitive Processing Therapy also performed well, demonstrating large or moderate effect sizes against controls at all three time intervals.

Discussion: Individual Medications

- Venlafaxine had the largest effect size among medications at 12 weeks, but the effects faded significantly beyond 12 weeks in both controlled and pre/post-treatment conditions.
- Conversely sertraline, fluoxetine and adjunctive prazosin demonstrated greater benefits in trials longer than 12 weeks.
- Nefazodone performed strongly under controlled and pre/post treatment conditions, but no data exists beyond 12 weeks and hepatotoxicity concerns limit its availability.

Discussion: Individual Medications

- Paroxetine, the only medication recommended under all five major guidelines, performed poorly under controlled conditions. It had a small effect at 8-12 weeks and failed to achieve significant effects beyond 12 weeks.

- Given the chronic nature of PTSD with greater than 50% of patients having symptoms lasting >3 months we would favor medications with effects increasing or sustaining (Sertraline, Prazosin) over time as first line over those with diminishing effects (Venlafaxine).

Translation to Clinical Practice

Translation to Clinical Practice

- The results suggest only a handful of medications (Sertraline, Prazosin, Venlafaxine, possibly Nefazodone) with best evidence for the treatment of PTSD.

- Some of these medications require long trials (34+ weeks) to demonstrate maximum efficacy.

- Often critical review of a patient's previous medication history with close eye on length and dosage in previous trials is needed.

Translation to Clinical Practice

- Psychotherapy, with an established TFP, is probably an indispensable component of effective PTSD treatment.
- Prolonged exposure, followed by cognitive processing therapy seem to be the best choice if multiple options are available.
- In cases where providers are difficult to locate, many approved treatments can be performed in an intensive treatment program and benefits seen to persist following completion of treatment.

References

CRS Report RL32492, American War and Military Operations Casualties: Lists and Statistics, by Nese F. DeBruyne and Anne Leland.

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