U.S. Department of Veterans Affairs

Medication in the Treatment of PTSD

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Research Advisory Committee on Gulf War Veterans Illness
July 7, 2020March 2020

National Center for PTSD
POSTTRAUMATIC STRESS DISORDER

Overview

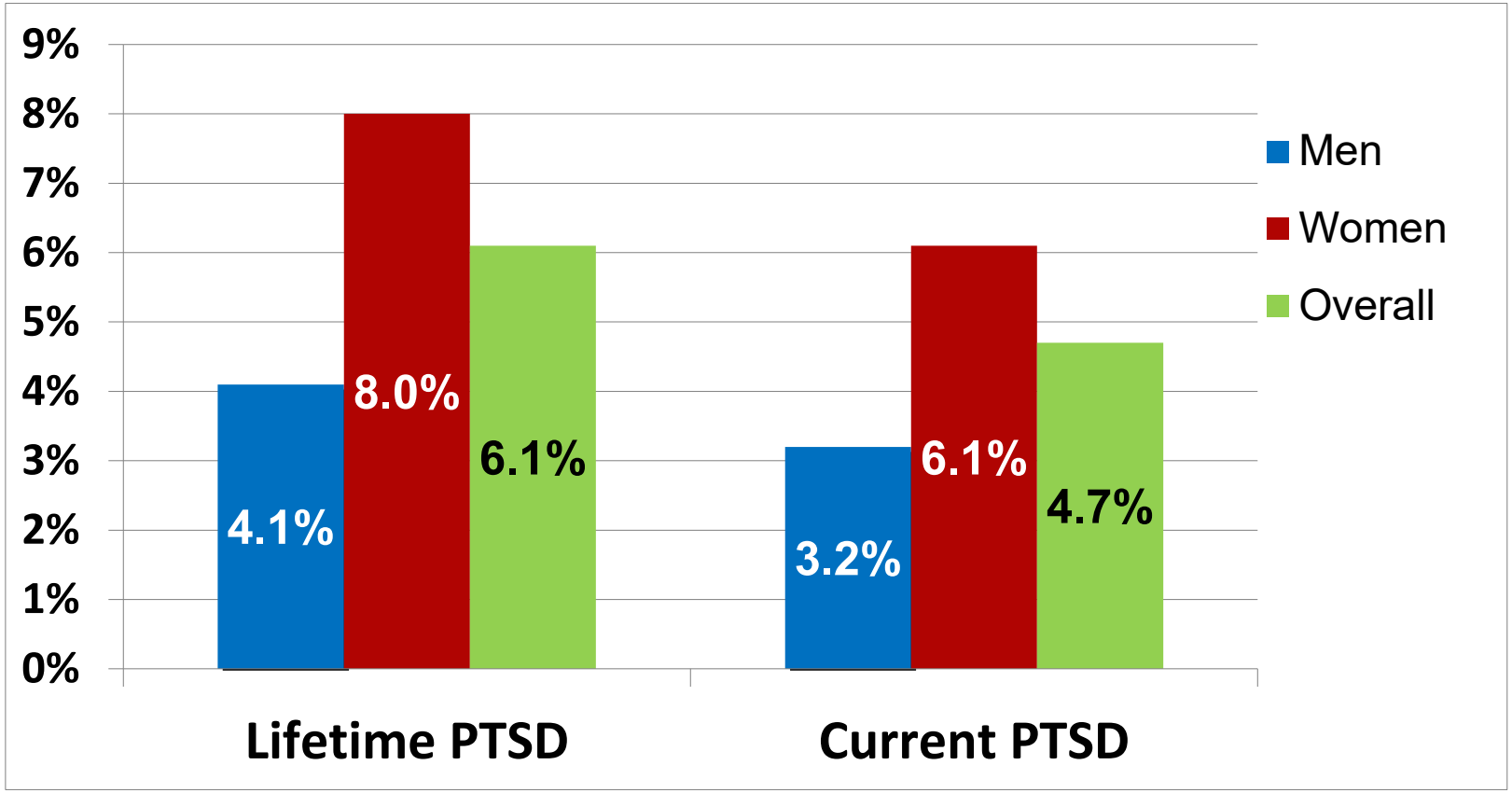
- Background on PTSD
- Meta-analytic findings on PTSD treatment
- VA/DoD Practice Guideline for PTSD
- Ongoing research

DSM-5 PTSD Diagnostic Criteria

- Exposure to a traumatic event in which the person:
  - Experienced, witnessed, or was confronted by death or serious injury to self or others
  - Includes occupational exposure, e.g., first responders
- Symptoms
  - 20 symptoms in 4 clusters: *intrusion, avoidance, changes in cognition and mood (e.g., numbing, guilt), hyperarousal*
  - Last > 1 month
  - Cause clinically significant distress or impaired functioning

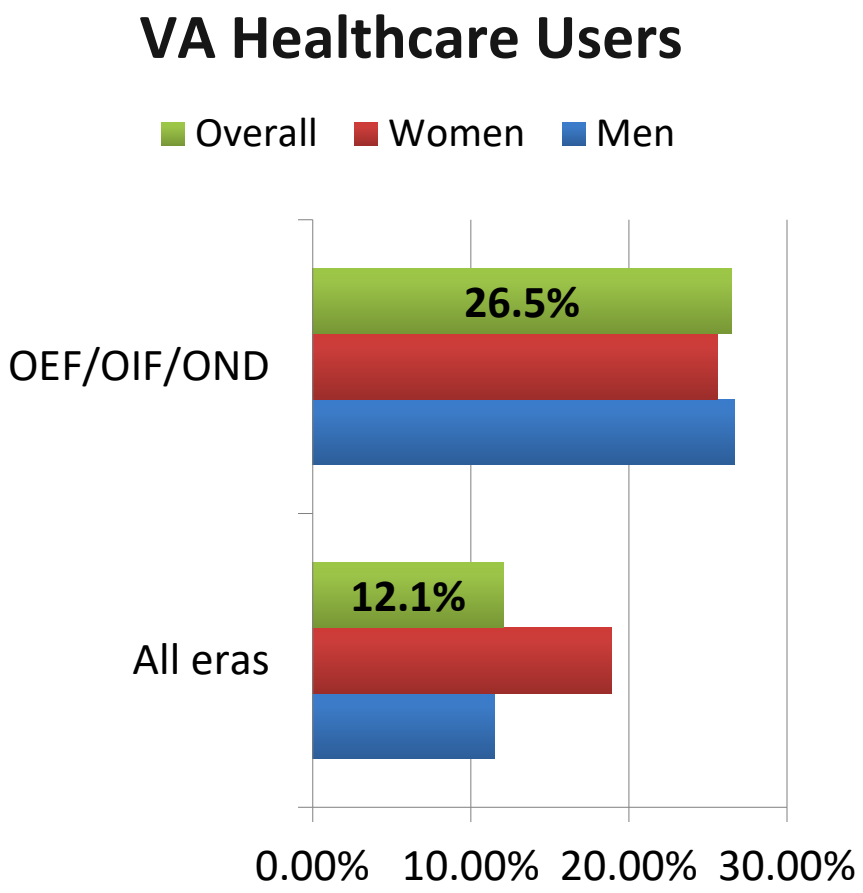
– American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 2014

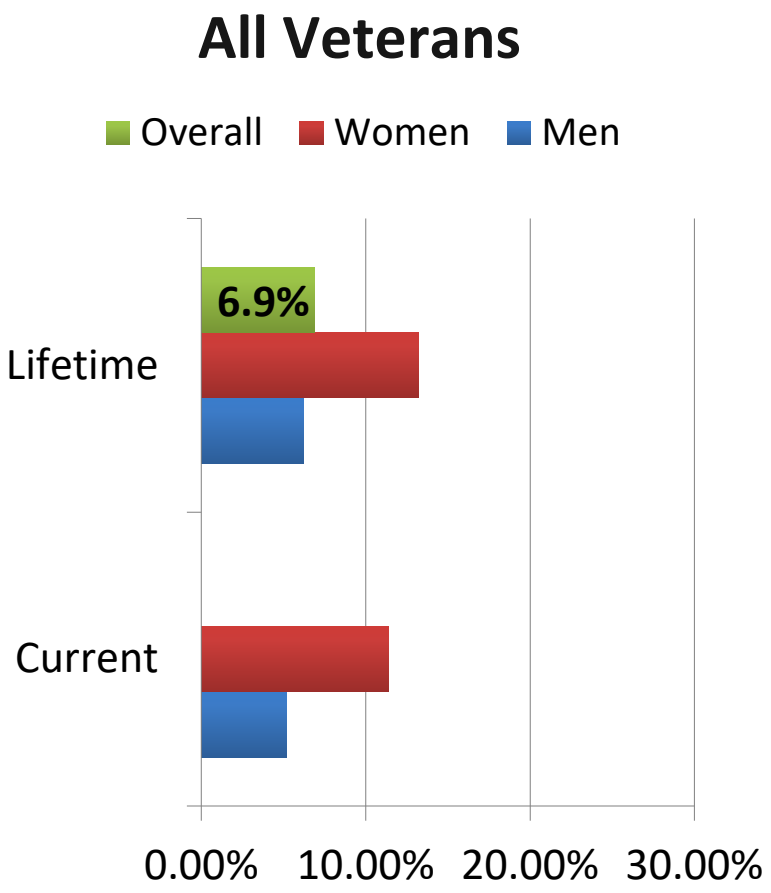
DSM-5 PTSD Prevalence in the United States



US General population estimates from NESARC-III; Goldstein et al., 2016

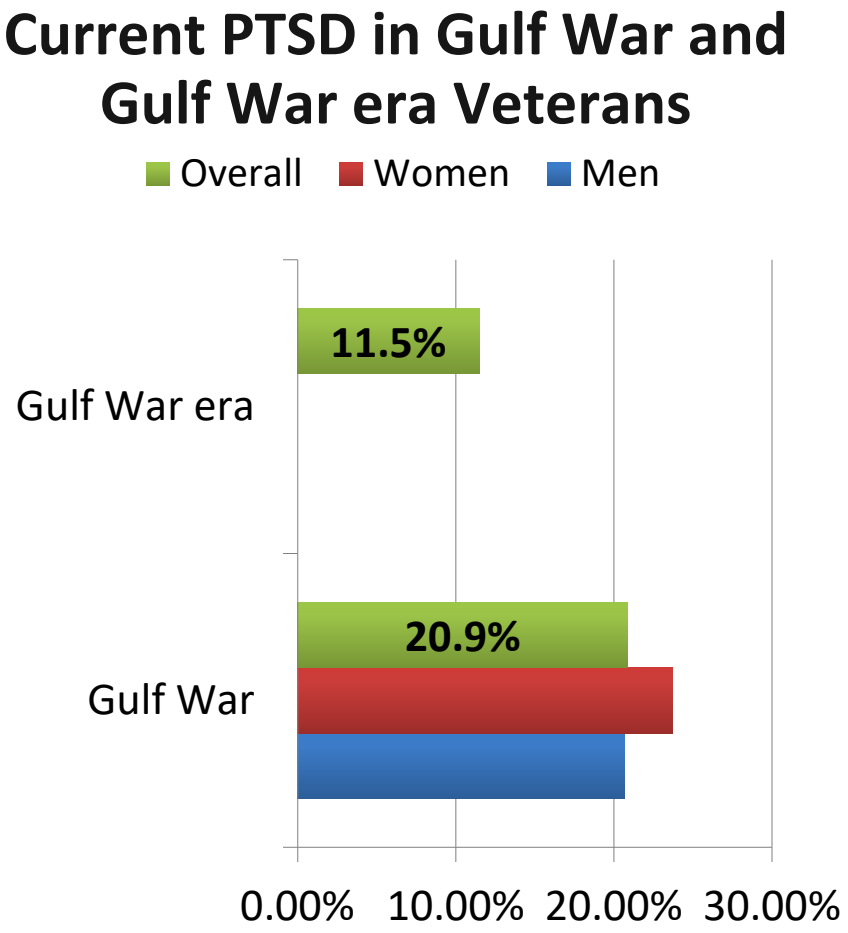
DSM-5 PTSD Prevalence in Veterans

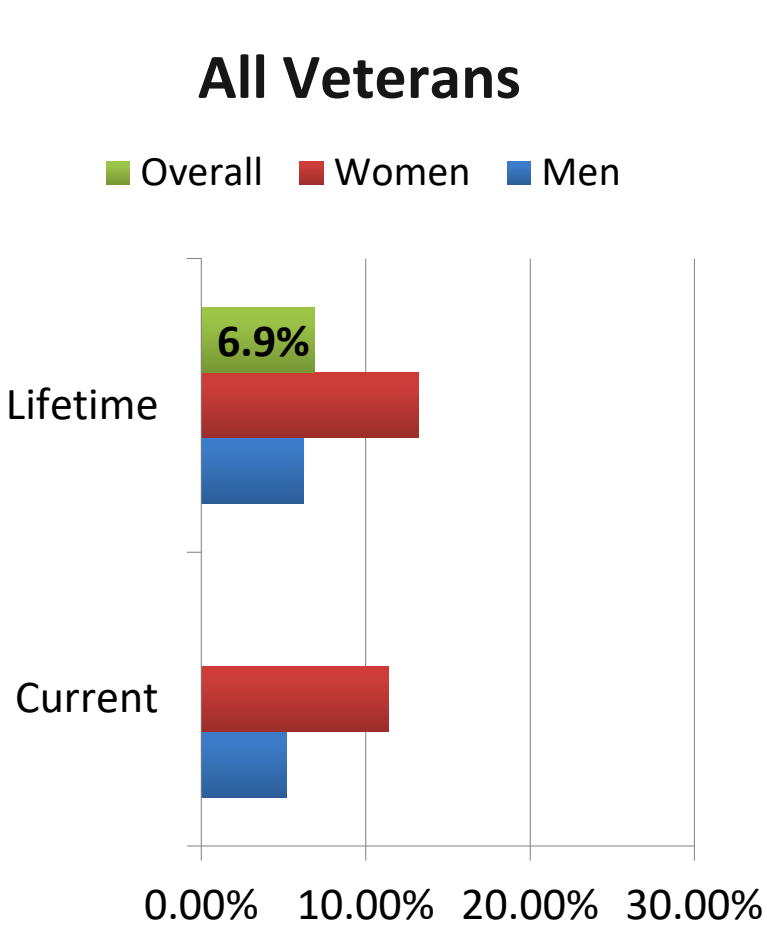




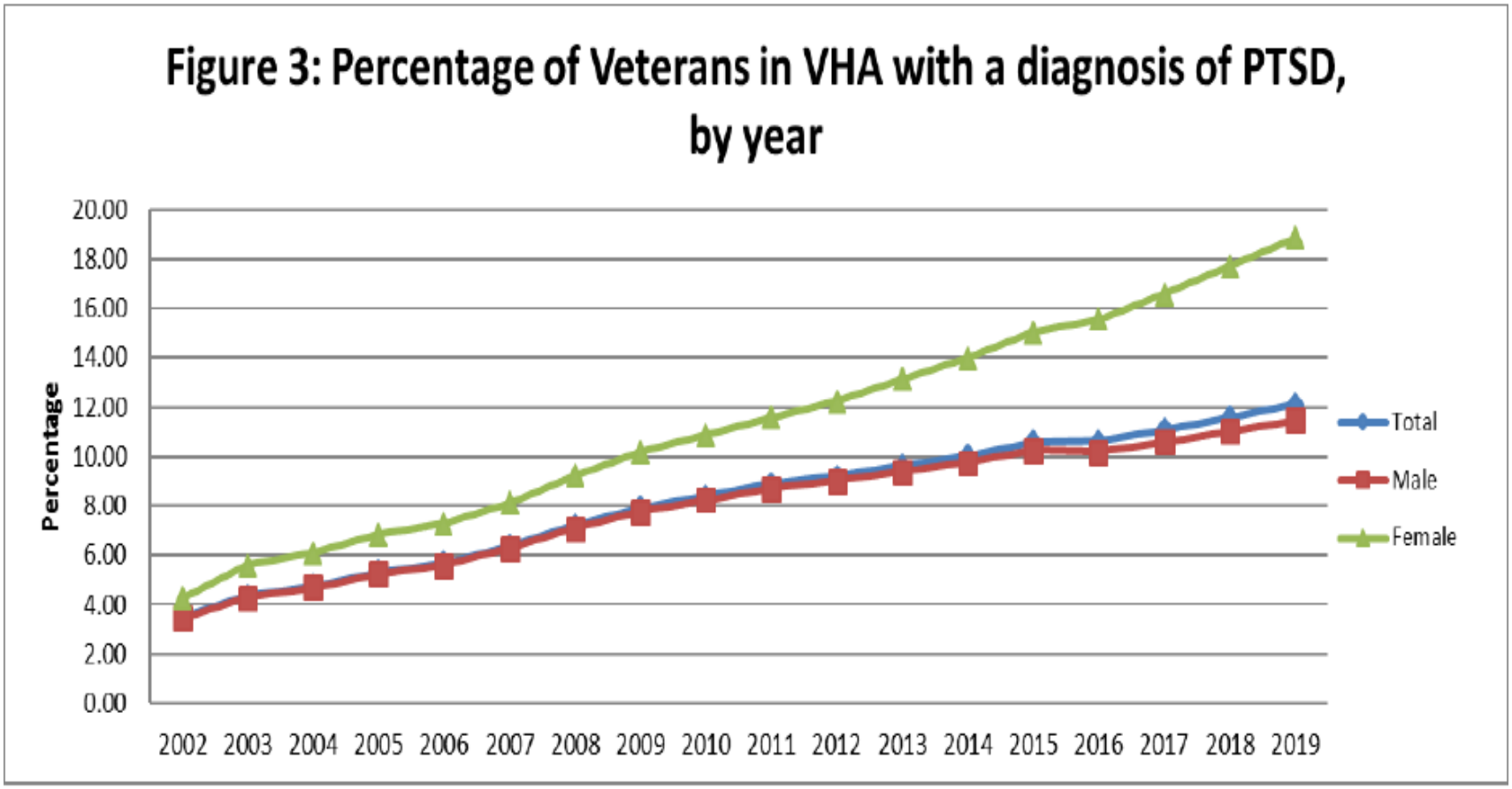
VA estimates from Harpaz-Rotem, I. & Hoff, R. (2020). FY2020 Overview of PTSD Patient Population Data Sheet. VA Office of Mental Health and Suicide Prevention (10NC5). West Haven, CT: Northeast Program Evaluation Center. All Veterans estimates from NESARC-III: Lehavot et al., 2018; Smith et al., 2016

DSM-5 PTSD Prevalence in Veterans



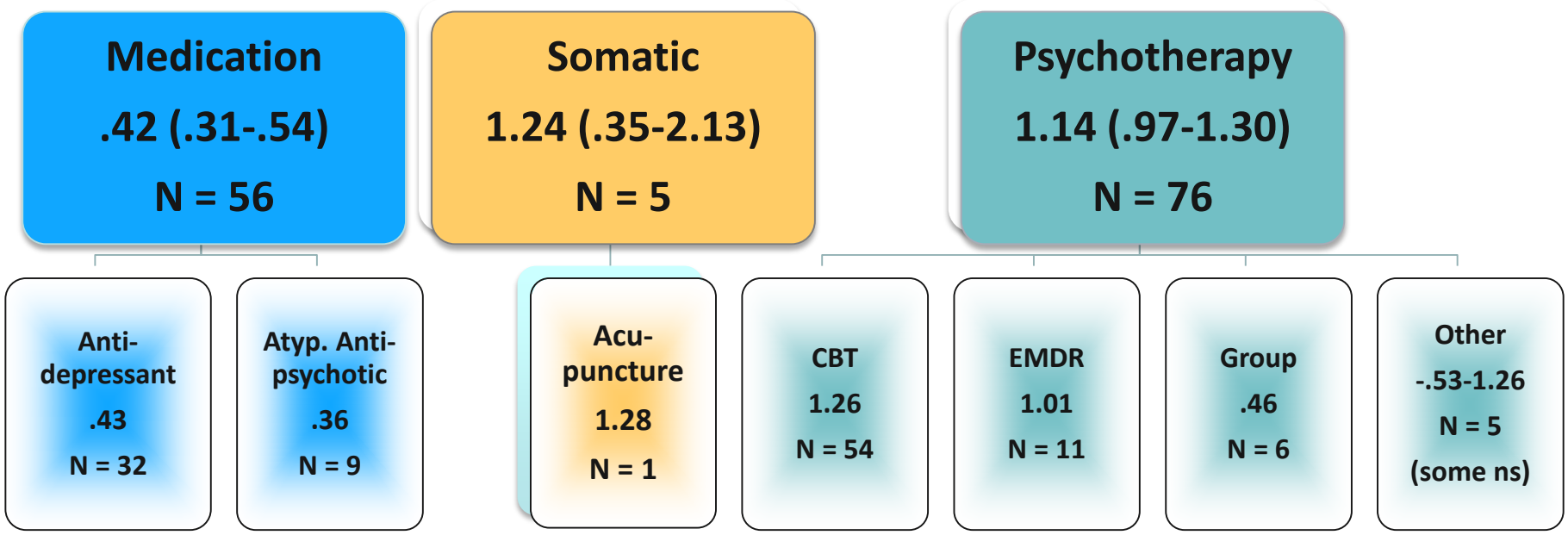


Gulf War estimates from Follow-up Study of a National Cohort of Gulf War and Gulf Era Veterans: Dursa et al., 2016, 2019. All Veterans estimates from NESARC-III: Lehavot et al., 2018; Smith et al., 2016



Harpaz-Rotem, I. & Hoff, R. (2020). FY2020 Overview of PTSD Patient Population Data Sheet. VA Office of Mental Health and Suicide Prevention (10NC5). West Haven, CT: Northeast Program Evaluation Center.

(Some types of) Medication, Psychotherapy, and Somatic Treatments are Effective for PTSD

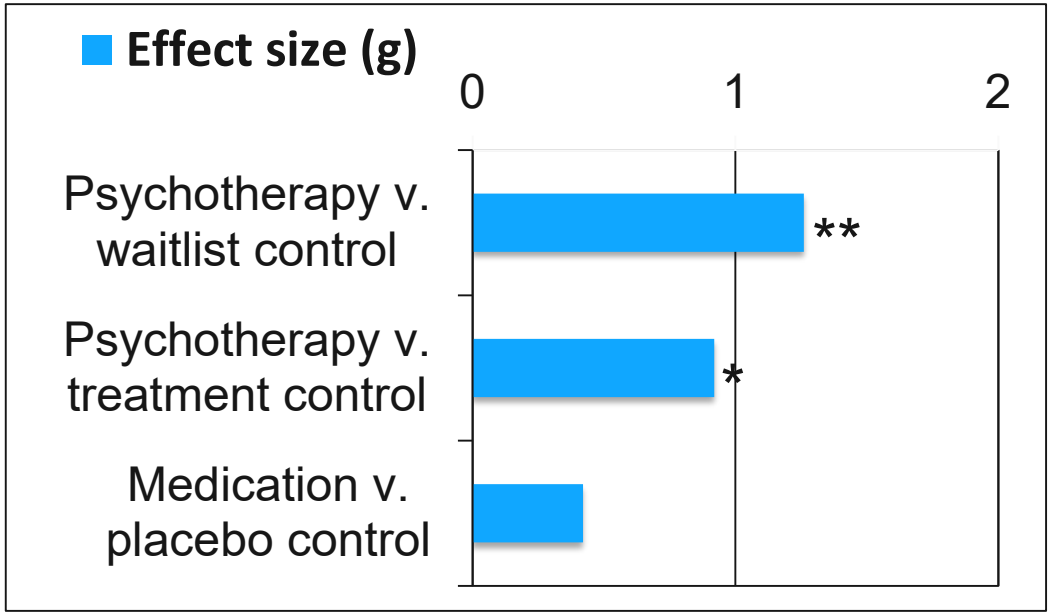


– Watts, Schnurr et al. (2013). Effect sizes are represented as a modified Hedges *g*, indicating benefit relative to a control group. N = number of comparisons. 1st and 2nd level significant effects are shown.

Psychotherapy is More Effective Than Medication

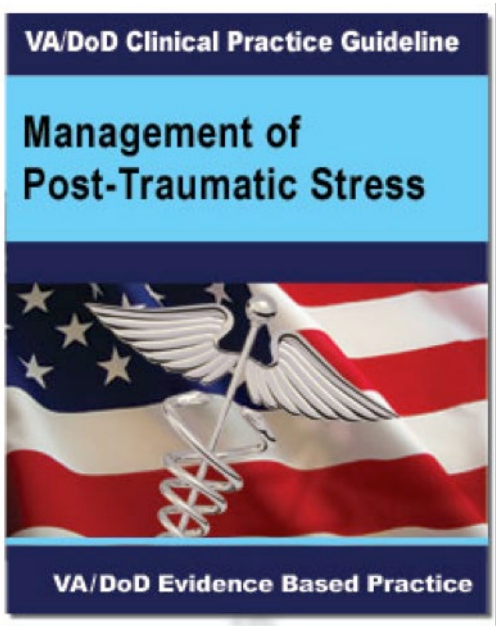
** Psychotherapy waitlist control v. medication, $p<.01$

* Psychotherapy treatment control v. medication, $p<.05$



– Watts, Schnurr et al. (2013). Effect sizes are represented as a modified Hedges *g*, indicating benefit relative to a control group.

VA/DoD PTSD Guideline (2017)



- Guidelines are designed to provide information and assist decision making
- Guidelines are not intended to define a standard of care

www.healthquality.va.gov/guidelines/MH/ptsd/

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Criteria

- **Strong For** (or "*We recommend offering this option …")*
- **Weak For** (or "*We suggest offering this option …")*
- **Weak Against** (or "*We suggest not offering this option …")*
- **Strong Against** (or "*We recommend against offering this option …")*

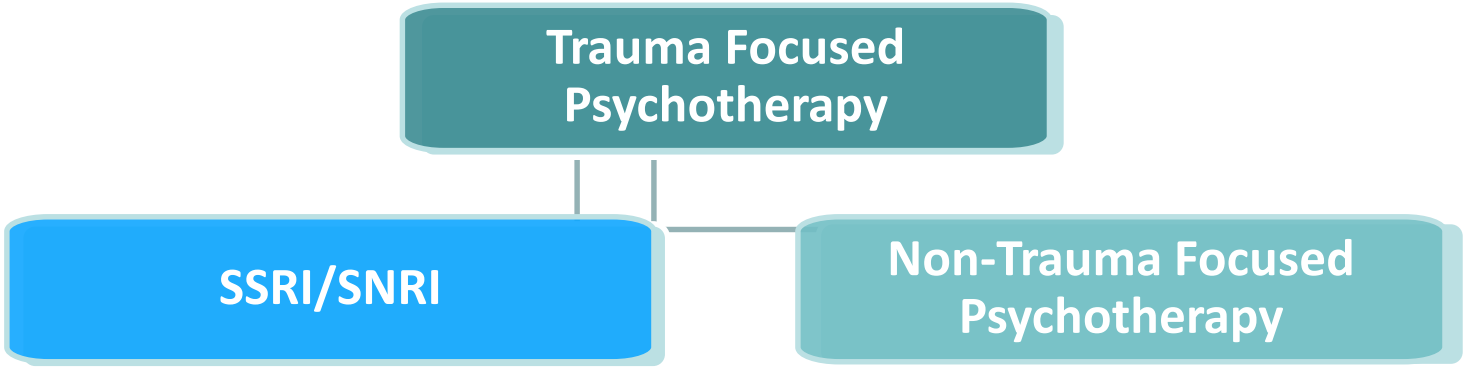
Insufficient is used when there was a lack of evidence or the evidence did not permit a definitive conclusion

Source: GRADE Guidelines: 15. Going from evidence to recommendation determinants of a recommendation's direction and strength. Journal of Clinical Epidemiology, 66, (2013), 726-735.

Treatment Selection: TF Therapy over Medication

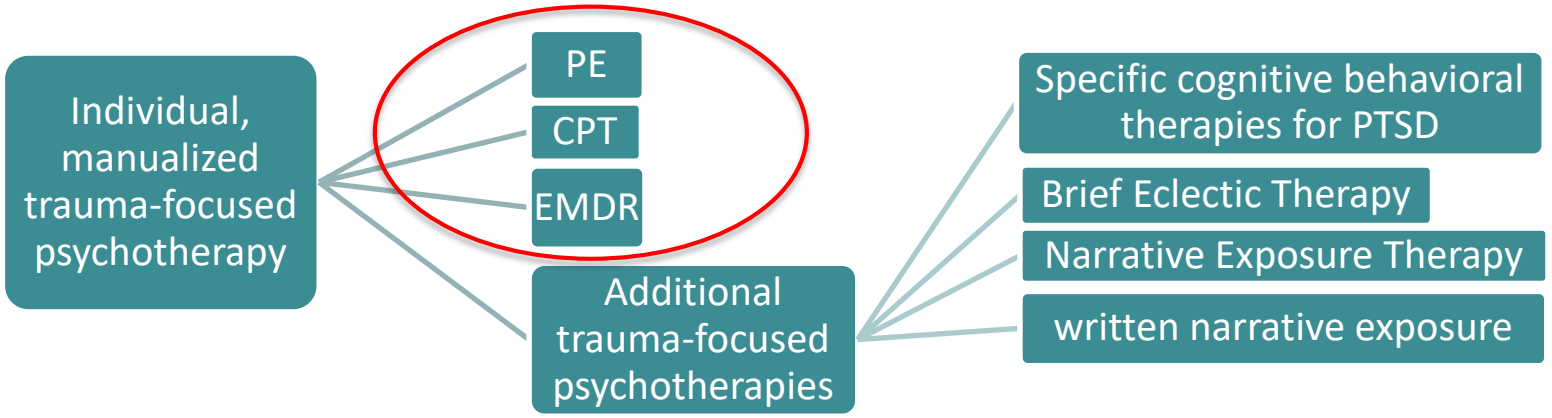
***We <u>recommend</u>* individual, manualized trauma focused psychotherapy over other pharmacologic and non-pharmacologic interventions for the primary treatment of PTSD.**

When individual trauma focused psychotherapy is not readily available or not preferred, *we <u>recommend</u>* pharmacotherapy or individual non-trauma-focused psychotherapy. There is *insufficient* evidence to recommend one over the other.

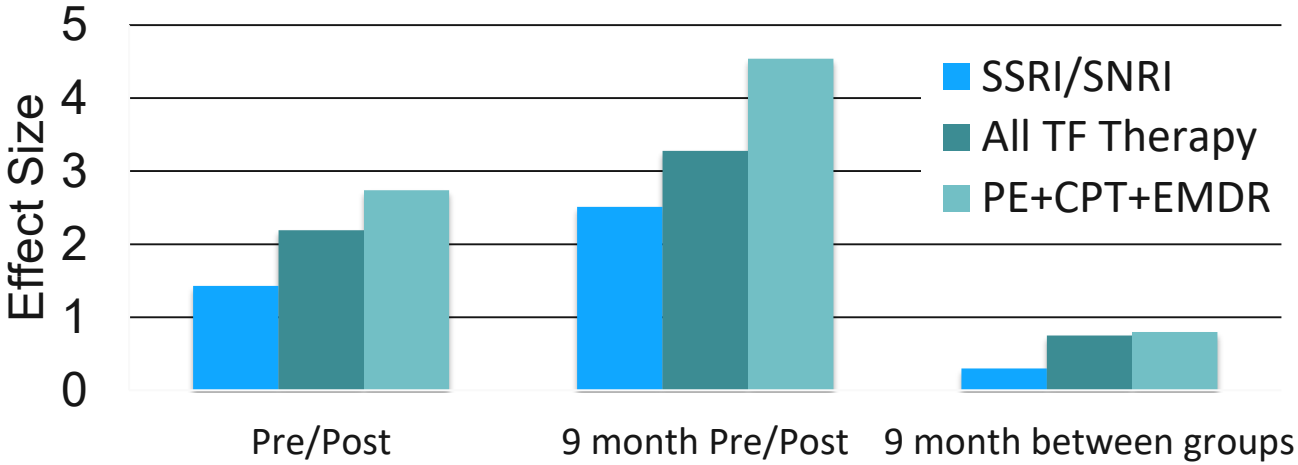


Recommended Trauma-Focused Psychotherapy

We recommend individual, manualized trauma-focused psychotherapies that have a primary component of exposure and/or cognitive restructuring to include Prolonged Exposure (PE), Cognitive Processing Therapy (CPT), Eye Movement Desensitization and Reprocessing (EMDR), specific cognitive behavioral therapies for PTSD, Brief Eclectic Therapy (BEP), Narrative Exposure Therapy (NET), and written narrative exposure.



Evidence-Based Psychotherapy is More Effective than Evidence-Based Medication



Included only studies with active controls and clinician-rated outcomes

	8-12 wk pre/post	9 month pre/post	9m. Between Group
SSRI/SNRI	1.43 (1.36 to 1.51)	2.51 (2.14-2.82)	**.30** (.12-.47)
All TF Therapy	2.19 (2.01-2.37)	3.28 (3.02-3.54)	**.75** (.57-.92)
PE+CPT+EMDR	2.74 (2.50-2.97)	4.54 (4.16-4.91)	**.80** (.57-1.03)

– Lee et al., 2016

VA/DoD 2017 PTSD Guideline Monotherapy Recommendations

Quality of Evidence	Recommend For	Suggest For	Suggest Against	Recommend Against
Moderate	Sertraline Paroxetine Fluoxetine Venlafaxine		Prazosin (exc. Tx of PTSD-assoc. nightmares)	
Low		Nefazodone	Quetiapine Olanzapine Citalopram Amitriptyline	Divalproex Tiagabine Guanfacine
Very Low		Imipramine Phenelzine	Lamotrigine Topiramate	Risperidone Benzodiazepines D-cycloserine Hydrocortisone Ketamine

Table 1. Medications Filled as Prescriptions in the Year Following Initial PTSD Diagnosis, 2004–2013

	Fiscal Year				
	2004	2007	2010	2013	Overall
New PTSD Episodes	51,750	69,604	84,850	82,546	731,520
Mean Number of Psychotropics	3.5 ± 2.5	3.5 ± 2.6	3.6 ± 2.7	3.5 ± 2.7	3.5 ± 2.7
All Antidepressants	85.1 (44,026)	82.7 (57,544)	80.1 (68,001)	78.0 (64,394)	81.0 (592,505)
Amitriptyline	5.7 (2948)	4.6 (3195)	3.8 (3221)	3.7 (3074)	4.2 (31,019)
Mirtazapine	12.4 (6392)	12.3 (8578)	12.9 (10,973)	13.0 (10,722)	12.6 (92,460)
Nefazodone	1.2 (638)	0.3 (237)	0.1 (116)	0.1 (50)	0.3 (2097)
Phenelzine	0.0 (20)	0.0 (10)	0.0 (8)	0.0 (8)	0.0 (92)
Trazodone	33.4 (17,296)	32.3 (22,484)	30.5 (25,847)	29.7 (24,489)	31.0 (226,812)
Any SSRI or SNRI	70.1 (36,290)	67.6 (47,064)	65.7 (55,740)	63.1 (52,112)	66.3 (485,194)
Fluoxetine	13.9 (7212)	11.8 (8246)	9.5 (8022)	11.5 (9481)	11.3 (82,346)
Paroxetine	10.3 (5331)	7.0 (4842)	5.0 (4266)	6.0 (4951)	6.6 (48,215)
Sertraline	26.0 (13,449)	16.3 (11,367)	21.4 (18,145)	31.2 (25,771)	22.9 (167,613)
Venlafaxine	9.2 (4770)	8.5 (5882)	8.4 (7121)	11.7 (9680)	9.1 (66,747)
All Anticonvulsants	21.8 (11,267)	22.8 (15,871)	26.0 (22,080)	29.1 (24,005)	24.9 (182,077)
Gabapentin	11.1 (5739)	12.1 (8399)	15.2 (12,851)	18.2 (15,001)	14.1 (102,791)
Topiramate	2.1 (1072)	2.6 (1832)	3.3 (2764)	4.3 (3517)	3.1 (22,803)
Valproic acid	7.3 (3794)	6.8 (4723)	6.8 (5732)	6.2 (5152)	6.7 (49,197)
Prazosin	6.1 (3171)	9.6 (6690)	17.3 (14,641)	25.8 (21,291)	15.0 (110,048)
All Atypical Antipsychotics	29.7 (15,390)	23.8 (16,562)	20.3 (17,185)	16.9 (13,944)	21.8 (159,757)
Olanzapine	4.5 (2347)	1.9 (1342)	1.7 (1444)	1.6 (1298)	2.0 (14,691)
Quetiapine	18.9 (9758)	15.8 (10,970)	11.5 (9728)	9.0 (7426)	13.3 (97,542)
Risperidone	9.9 (5126)	6.1 (4248)	5.1 (4323)	4.7 (3917)	5.8 (42,311)
All Typical Antipsychotics	1.8 (946)	1.8 (1275)	1.8 (1526)	1.8 (1485)	1.8 (13,304)
All Addiction Medicines[a]	7.8 (4027)	12.4 (8665)	12.9 (10,984)	12.9 (10,637)	11.9 (87,361)
All Sedative Hypnotics	38.2 (19,776)	37.9 (26,353)	41.3 (35,085)	35.4 (29,262)	38.9 (284,877)
Zolpidem	4.6 (2404)	7.9 (5532)	18.2 (15,472)	14.3 (11,837)	13.0 (95,086)
Any benzodiazepine	34.9 (18,066)	32.9 (22,907)	29.4 (24,979)	25.1 (20,756)	30.3 (221,309)
All Opioids[b]	35.4 (18,325)	37.8 (26,301)	38.3 (32,473)	34.6 (28,564)	36.9 (270,103)
All Stimulants	1.1 (592)	1.5 (1060)	2.3 (1991)	3.3 (2702)	2.1 (15,690)
Lithium	1.8 (942)	1.4 (951)	1.4 (1162)	1.5 (1254)	1.4 (10,580)
Buspirone	5.1 (2665)	4.7 (3241)	4.9 (4168)	6.4 (5269)	5.1 (37,614)

- Krystal et al., 2017; data from B. Shiner

Anticonvulsant Medication Use in Veterans with PTSD in VA

- N = 732,520 VA users entering treatment for PTSD, 2004-2013
  - 24.9% received an anti-convulsant
  - **94.6% had an indication for anticonvulsant use**
  - 51.2% initiated anticonvulsant use before PTSD treatment
- Gabapentin was most frequently prescribed and increased most over time

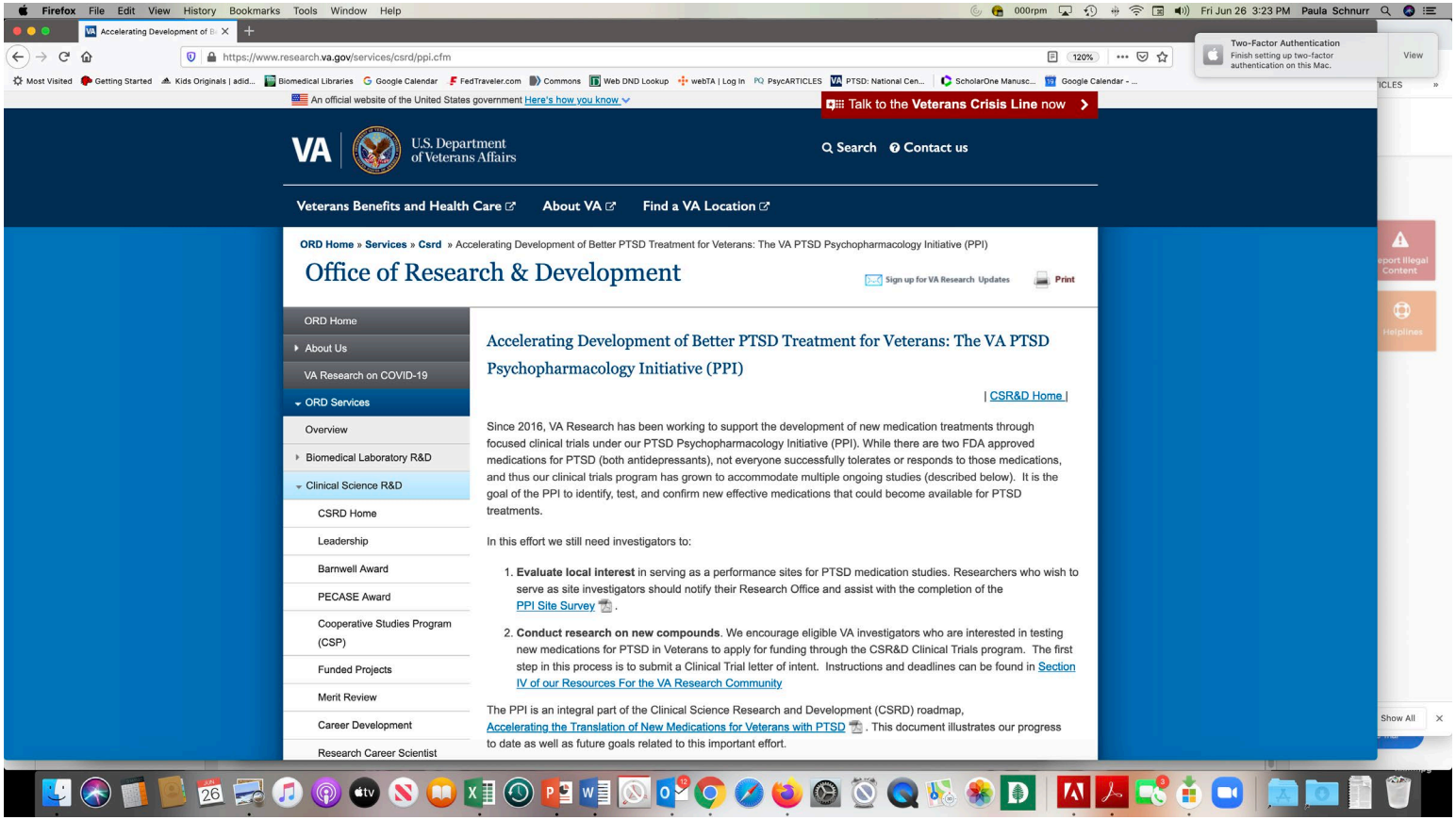
- Shiner et al., 2017

Recommendations from "*It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group*"

- The urgent need to find effective pharmacologic treatments for PTSD should be considered a national mental health priority.
- There is a need to increase the number of early phase clinical trials through novel collaborations among government, industry, and academia.
- There is a need to develop new trial designs and/or methodologies specifically in the area of PTSD psychopharmacology trials.
- Foundational studies are required to inform the optimal prescription of commonly prescribed medications for the treatment of PTSD.
- The development of a psychopharmacology clinical trials workforce and infrastructure for PTSD would advance the goal of increasing clinical trials in this area.
- Studies exploring the pathophysiology of PTSD will be critical to inform the rational development of novel pharmacologic interventions.
- There is a need to continue to invest in initiatives in translational neuroscience to enhance the expansion of the pipeline of new PTSD pharmacotherapeutics.

- Krystal et al., 2017

VA Office of Research and Development: PTSD Psychopharmacology Initiative



CSP #2016: The National Adaptive Trial for PTSD-Related Insomnia (NAP)

- Four arms, 12-weeks, of oral medication at bedtime (placebo, trazodone 200 mg, gabapentin 2000 mg, eszopiclone 3 mg)
- 1224 patients from 34 VA Medical Centers; veterans with treatment-resistant PTSD-related insomnia
- Primary outcome: Insomnia Severity Index (self-rated)
- Secondary outcome: CAPS (rated centrally)
  - Additional clinical outcomes (CGI, QOL, etc.)
- Exploratory outcomes: actigraphy, molecular biomarkers
- Adaptive: interim analysis will inform discontinuation of futile arms
  - discontinuation will not reduce target recruitment, increasing power of remaining comparisons
- PI: J. Krystal
- VACSCC: Palo Alto

Ketamine for Treatment-Resistant Symptoms of Military-Related PTSD

- Funding: Consortium to Alleviate PTSD and NCPTSD (DOD, VA)
- Ongoing trial: 167 randomized patients from three sites (Veterans: VA Connecticut, VA Minneapolis, Active Duty: BAMC)
- 3 arms: placebo, ketamine 0.2 mg/kg, ketamine 0.5 mg/kg
- Design:
  - Primary: twice weekly infusions for 4 weeks
  - Secondary: 4-week follow-up for duration of benefit
- Outcome measure:
  - Primary: PCL-5 (self-rated)
  - Secondary: CAPS, mood, anxiety, CGI, QOL
- Exploratory outcomes: biochemical biomarkers
- PI: J. Krystal

A Promising Direction: Medication-Enhanced Psychotherapy

- **Efforts underway to use medication to boost evidence-based psychotherapy with, e.g., ketamine, cannabidiol, oxytocin**
  - **e.g., VA is currently sponsoring a placebo-controlled randomized clinical trial of cannabidiol with Prolonged Exposure Therapy**
- **Also research on MDMA with other psychotherapy**
- **Blinding is a challenge for studying some of these medications**

Current State of the Evidence on Medication for PTSD

- Several medications are effective, but the best medications are less effective than the best psychotherapies
- Medication-assisted psychotherapy is promising, but at a preliminary state; placebo control is challenging
- Research is needed, especially to develop novel medications