Psychopharmacology of PTSD

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

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- **Ownership Equity (Partner):** WISER Systems, LLC

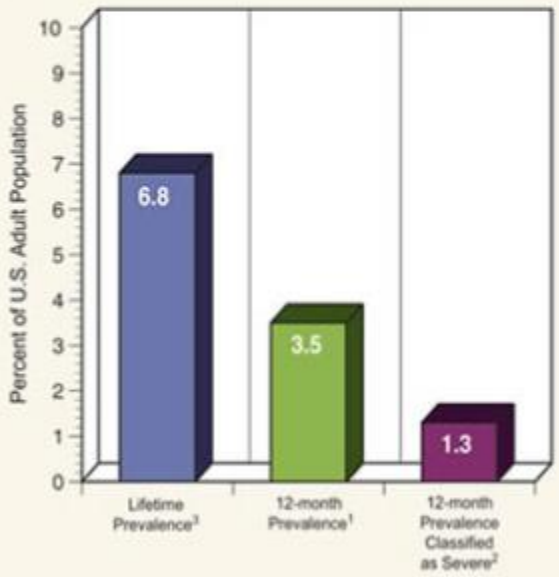
Objectives

- By the end of this brief session, you will be able to:
  - Explain the first line psychopharmacological treatments for PTSD
  - Describe psychopharmacological treatments for PTSD that have positive clinical trials
  - Identify psychopharmacological interventions for PTSD that are in development

Prevalence of Adult PTSD

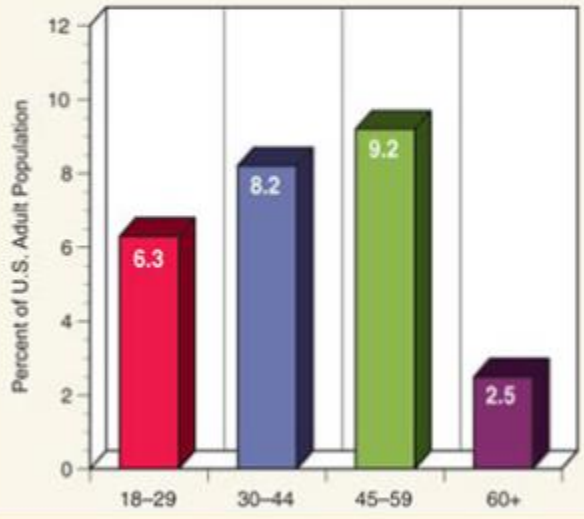
Prevalence

- **12-month Prevalence:** 3.5% of U.S. adult population[1]
- **Severe:** 36.6% of these cases (e.g., 1.3% of U.S. adult population) are classified as "severe"[2]



Demographics (for lifetime prevalence)[5]

- **Sex:** Not Reported
- **Race:** Not Reported
- **Age:**



Average Age-of-Onset: 23 years old[4]

From Kessler et al., Arch Gen Psychiatry, 2005

Comorbidity

- Other Anxiety Disorders
- Depression
- Personality Disorders
- Sleep Disorders

What Symptoms Are Being Targeted?

- **Intrusion.** For example, nightmares, unwanted thoughts of the traumatic events, flashbacks, etc.,
- **Avoidance.** For examples, avoiding places, people, conversations that might be triggers.
- **Negative alterations in cognitions and mood.** For example, negative beliefs about self or the world, persistent fear, guilt, or shame, inability to experience positive emotions.
- **Alterations in arousal and reactivity.** For example, sleep problems, exaggerated startle, hypervigilance.

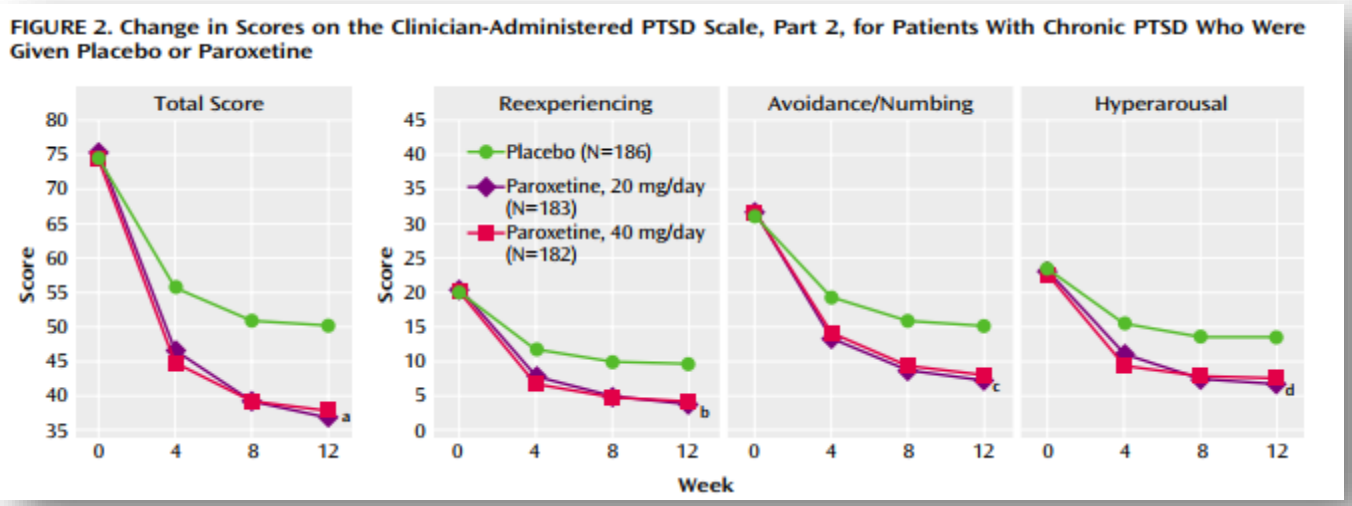
What Classes of Agents?

- SSRIs
- SNRIs
- Other novel antidepressants
- TCAs/MAOis
- Antiepileptics
- Antipsychotics
- Other agents

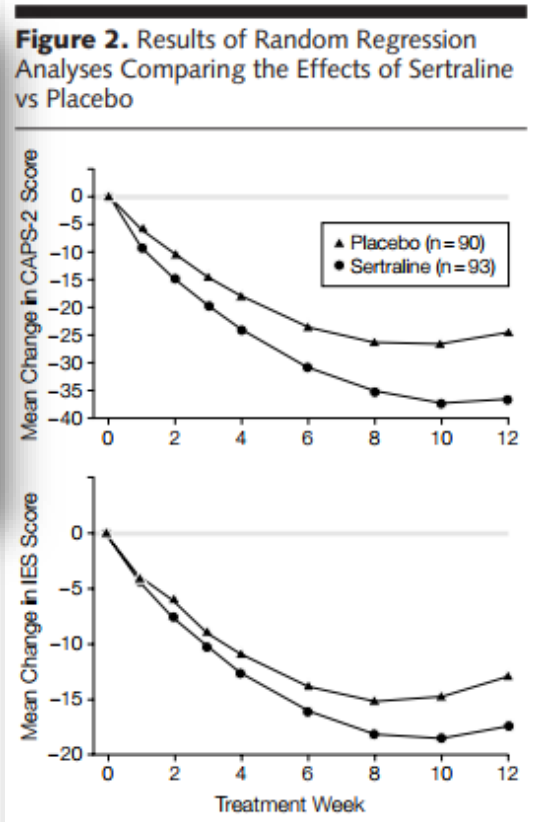
SSRIs

- Demonstrated to have the most impact on all aspects of PTSD symptoms
- Only two with FDA indications for PTSD (paroxetine and sertraline). Mostly chosen based on side effects
- Concerns are use in comorbid bipolar disorder, sleep impairments, sexual dysfunction, and other standard SSRI effects

SSRIs



Paroxetine
Marshall et al. (2001)



Sertraline
Brady et al. (2000)

SSRIs

Study or subgroup	Experimental Mean	s.d.	Total	Control Mean	s.d.	Total	Weight	SMD IV, random, 95% CI
Brady (2000)[38]	−33	28.1	94	−23.2	28.7	93	5.8%	−0.34 (−0.63, −0.05)
Brady (2005)[61]	32.56	15.69	49	32.7	28.75	45	4.1%	−0.01 (−0.41, 0.40)
Connor (1999)[40]	10.1	9.8	25	20.5	12.6	22	2.4%	−0.91 (−1.52, −0.31)
Davidson[A]	−39.4	27.12	173	−34.17	28.42	179	7.3%	−0.19 (−0.40, 0.02)
Davidson (2001)[42]	−33	23.76	100	−26.2	23.9	108	6.1%	−0.28 (−0.56, −0.01)
Eli Lilly[B]	−10.42	7.5	323	−10.59	10.21	88	6.8%	0.02 (−0.21, 0.26)
Friedman (2007)[21]	−13.1	27.5	86	−15.4	28.07	83	5.6%	0.08 (−0.22, 0.38)
Hertzberg (2000)[47]	47	8	6	42	11	6	0.8%	0.48 (−0.68, 1.64)
Marshall (2001)[50]	−38.75	27.2	375	−25.3	25.8	188	8.0%	−0.50 (−0.68, −0.32)
Marshall (2004)[64]	55.6	33.4	25	62.8	40.8	27	2.8%	−0.19 (−0.73, 0.36)
Martenyi (2002)[51]	−34.6	28.1	226	26.8	26.1	75	6.3%	−0.28 (−0.54, −0.02)
Martenyi (2007)[23]	−42.85	25.5	323	−36.6	25.7	88	6.8%	−0.24 (−0.48, −0.01)
Panahi (2011)[26]	−22.7	7.3	35	−17.5	7.5	35	3.3%	−0.69 (−1.18, −0.21)
Pfizer 588[C]	−27.4	27.12	94	−27.9	28.42	94	5.9%	0.02 (−0.27, 0.30)
Pfizer 589[D]	−13.1	27.12	84	−15.4	28.42	82	5.6%	0.08 (−0.22, 0.39)
Shaleve (2011)[27]	−31.12	29.63	23	−27.8	20.13	23	2.5%	−0.13 (−0.71, 0.45)
SKB627[E]	−36.5	26.1	109	−30.8	25.37	103	6.2%	−0.22 (−0.49, 0.05)
Tucker (2001)[53]	−35.5	24.58	151	−24.7	24.98	156	7.0%	−0.43 (−0.66, −0.21)
Tucker (2003)[68]	−41.82	29.09	23	−38.7	29.07	10	1.7%	−0.10 (−0.85, 0.64)
Van der Kolk (2007)[70]	−33.23	22.11	30	−30.95	22.6	29	3.0%	−0.10 (−0.61, 0.41)
Zohar (2002)[54]	−18.7	6.7	23	−13.5	6.6	19	2.2%	−0.77 (−1.40, −0.14)
Total (95% CI)			2377			1553	100.0%	−0.23 (−0.33, −0.12)

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 42.90$, d.f. = 20 ($P = 0.002$); $I^2 = 53\%$
Test for overall effect: $Z = 4.23$ ($P < 0.0001$)

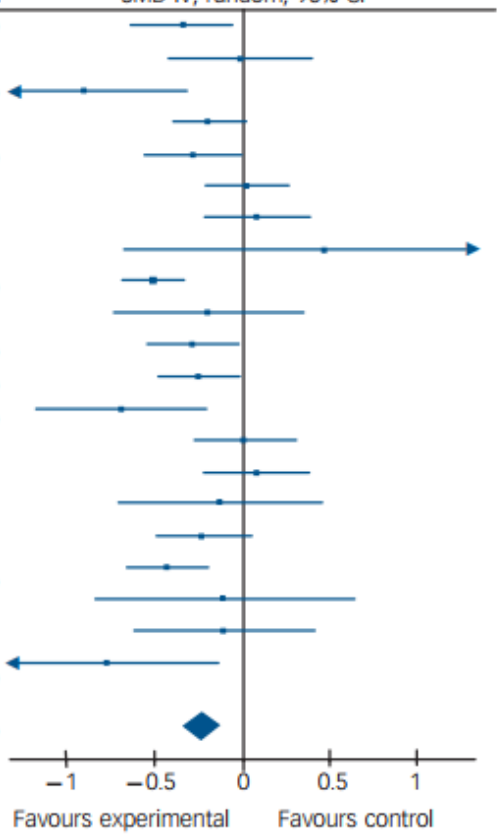


Fig. 2 Meta-analysis of selective serotonin reuptake inhibitors *v.* placebo (SMD, standardised mean difference).

Hoskins et al. (2015)

SNRIs

- No FDA indication, but positive trials for venlafaxine

Davidson et al (20016)

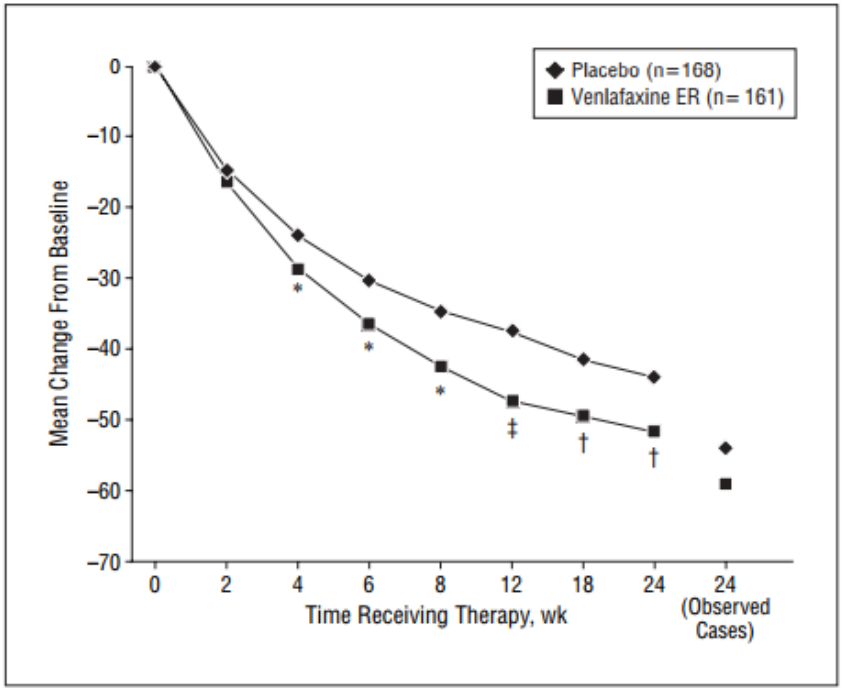


Figure 2. Change in score on the Clinician-Administered Posttraumatic Stress Disorder Scale, the abbreviated 1-Week Symptom Status Version, from the baseline score. All values represent last observation carried forward unless otherwise stated. ER indicates extended release. *P* values are based on pairwise comparisons from an analysis of covariance model with treatment as the main effect and baseline as the covariate. Asterisk indicates $P<.05$; dagger, $P<.01$; and double dagger, $P<.001$.

Other Antidepressants

- Mirtazapine – no FDA indication, but demonstrable effects and often used to promote sleep if that is an issue
- Bupropion – no FDA indication, and no evidence for efficacy on core PTSD symptoms

TCAs

- TCAs were the “original” antidepressants used for combat-related PTSD and have the most evidence for use.
- Often not used because of concerns about cardiac toxicity, especially in overdose. However, can be used – especially tertiary TCAs (imipramine*, amitriptyline*). Desipramine shown to be equivalent to paroxetine
- May have fewer sexual side effects than SSRIs and many improve sleep initiation

* No FDA indication for PTSD

MAOi

- Phenelzine* shown to be effective in the treatment of PTSD
- Dietary restrictions are not as stringent as one might think and can be managed
- Not to be used with (prescribed or illicit) stimulants, SSRIs

* No FDA indication for PTSD.

Antiepileptics

- Topirimate
  - Recent meta-analysis showed support for the use of topirimate* in PTSD (Jonah et al 2013)
  - Helpful in reducing alcohol consumption in those with an alcohol use disorder
- Two negative RCTs for divalproex* and one negative RCT for tiagabine*
- A small trial of lamotrigine* (n = 15) demonstrated possible benefit

Jeffreys (2015)

* No FDA indication for PTSD.

Antipsychotics

- Risperidone*
  - Randomized controlled trial of >240 patients with RISP added to SSRI treatment for treatment refractory PTSD showed no effect of the addition (Krystal et al 2011)
- No clear benefit to the second generation antipsychotics as monotherapy in the absence of psychotic or cycling mood symptoms

* No FDA indication for PTSD.

Other Agents

- Prazosin*
  - Dosing during the day in addition to bedtime for nightmares shows a significant reduction in daytime intrusive PTSD symptoms and nightmares (Raskind et al. 2013)
    - Mean doses were:
      - Men: 4 mg midday and 17 mg at HS
      - Women: 2 mg midday and 7 mg at HS
- D-cycloserine*
  - Still in trials. Appears to reduce some of the startle reactivity and reduces cortisol reactivity in animal models

* No FDA indication for PTSD.

Other Agents

- Methylphenidate*
  - Appears to improve cognitive symptoms in small trials
- Ketamine*
  - Some promise in early, small trials
- Cannabinoid agonists*
  - Negative effects thus far

* No FDA indication for PTSD.

Medication Options for PTSD in adults

- 1st Line
  - SSRIs (sertraline, paroxetine, fluoxetine*) – with psychotherapy
- 2nd Line
  - Other novel and traditional antidepressants*; anticonvulsant/mood stabilizers*; second generation AP medications* (if cycling mood or psychotic symptoms)
- Not recommended
  - Traditional APs*, benzodiazepines*

Friedman et al., 2000

* = no FDA indication for PTSD

Psychopharmacology for PTSD in Children

- Limited research
- “Without more and better studies documenting good effects and absence of serious side effects we urge clinicians to exercise extreme caution in using psycho-pharmacological agents for children, especially as CBT-methods are available to reduce posttraumatic symptoms and PTSD” (Dyregrov & Yule, 2006, p. 181)

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