MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Management of Posttraumatic Stress Disorder

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Disclosures

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

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Taylor & Francis	**Contribution to editorial expenses**	**Editor-in-Chief**

When Does an Event Become Traumatic?

PER **DSM-5** DEFINITION:

- Objective Event: Life-threatening/ injuring event
  - Direct victim
  - Witness
  - Learning of someone close
  - **Repeated and extreme exposure to aversive details of trauma (e.g. first responders, etc…) – no media unless work-related**

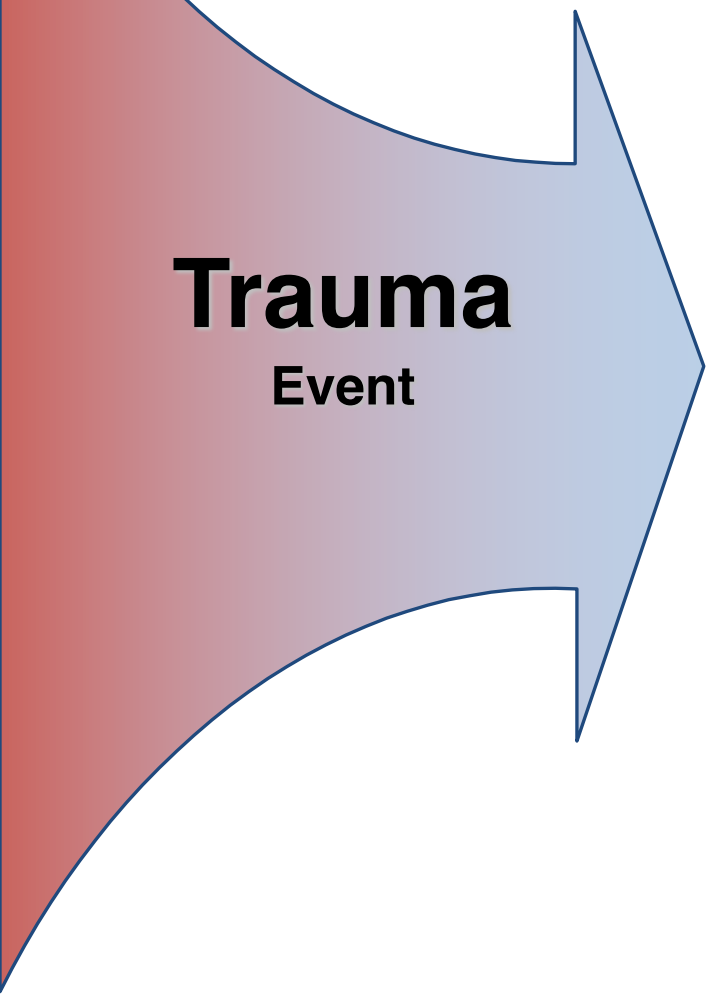
When Does It Become Pathological?

PER DSM-5 DEFINITION:

Timeframe

- **< 3 days** = not classified as “pathological”
- **3 days to 1 month** = ACUTE STRESS DISORDER
- **> 1 Month** = POSTTRAUMATIC STRESS DISORDER (no more Acute vs. Chronic)

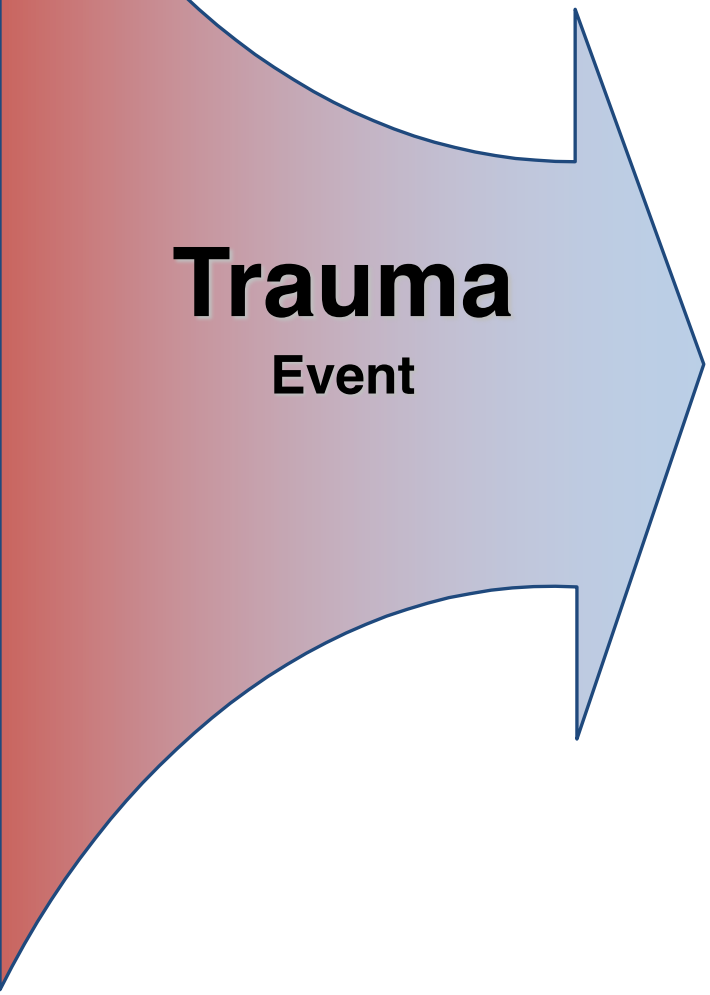
Acute Stress Disorder



- **9 out of 14 criteria:**
- Dissociative/numbing symptoms
  - eg: derealization, “being in a daze”…
- Persistent reexperiencing and intrusive symptoms
  - eg: flashbacks, intrusive thoughts...
- Avoidance of stimuli
  - eg: thoughts/feelings & places/people…
- Anxiety or hyperarousal symptoms
  - eg: sleep disturbances, startle…
- **3 days => *1 month***

APA, 2013

PTSD



- Persistent reexperiencing and intrusive symptoms (≥**1**)
  - E.g.: flashbacks, intrusive thoughts…
- Avoidance (≥**1**)
  - E.g.: thoughts/feelings & places/people…
- Alterations in cognitions and mood (≥***2***)
  - E.g.: distorted cognitions about cause consquences of trauma
- Anxiety or hyperarousal symptoms (≥***2***)
  - E.g.: sleep disturbances, startle…
- ***≥1 month***

APA, 2013

Epidemiology of PTSD

- Lifetime PTSD in North America: **7% to 9%**
- 12-month prevalence rates in North America: **3.5% to 5%**
- Lifetime prevalence rates in Europe somewhat lower (**2%**)

Alonso et al., 2004; Breslau, et al., 1991; Kessler et al., 2005; Kessler, et al., 1995; Kessler et al., 2005; Kilpatrick et al., 2003; Norris, 1992; Resnick, et al., 1993

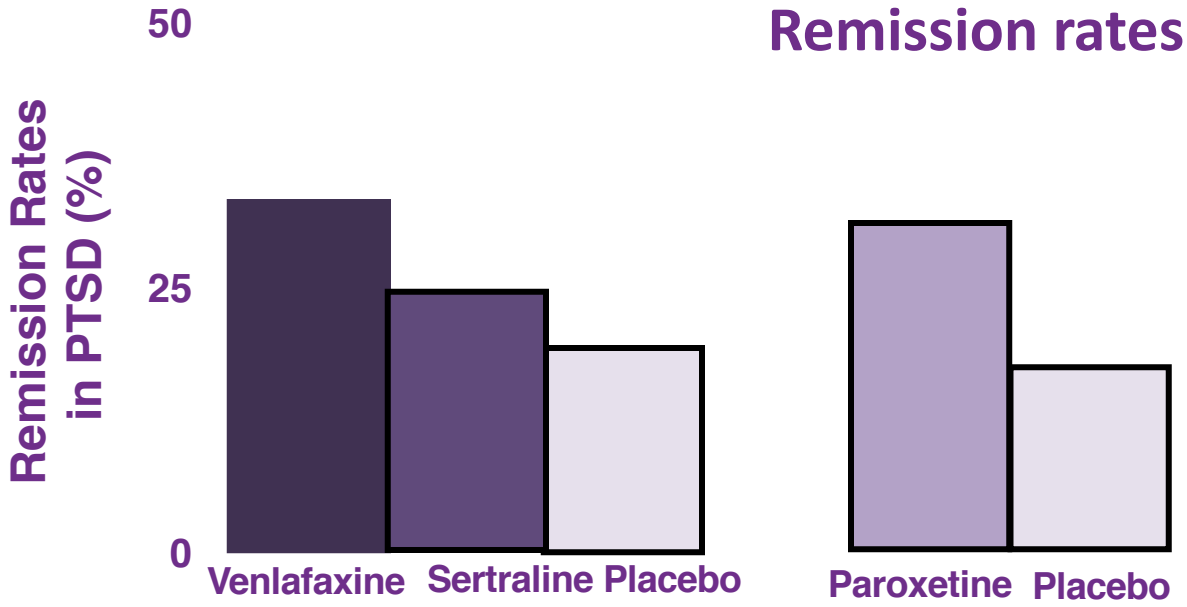
Patient

- Sam, 24 y/o non-binaire presenting for Sx evolving since a rape one year ago
- PTSD, comorbid MDE
- ETOH x2/wk, MJ x1/wk
- Main complaints are:
  - Trouble sleeping, nightmares
  - “scared of everything”
  - Lack of interest
- CAPS-5 score = 45

First line pharmacotherapy?

- ☐ Paroxetine
- ☐ Fluoxetine
- ☐ Sertraline
- ☐ Citalopram
- ☐ Escitalopram
- ☐ Fluvoxamine
- ☐ Venlafaxine
- ☐ Duloxetine

SSRI/SNRI?



Venlafaxine study: CAPS-SX ≤20; Davidson et al. 2006

Paroxetine study: CAPS-2 <20; Tucker et al. 2001

This information concerns a use that has not been approved by the US FDA.

First line pharmacotherapy?

- ✓ **Paroxetine**: FDA-approved
- ✓ **Fluoxetine**: efficacy ≥2 RCTs
- ✓ **Sertraline**: FDA-approved
- ☐ Citalopram
- ☐ Escitalopram
- ☐ Fluvoxamine
- ✓ **Venlafaxine**: efficacy ≥2 RCTs
- ☐ Duloxetine

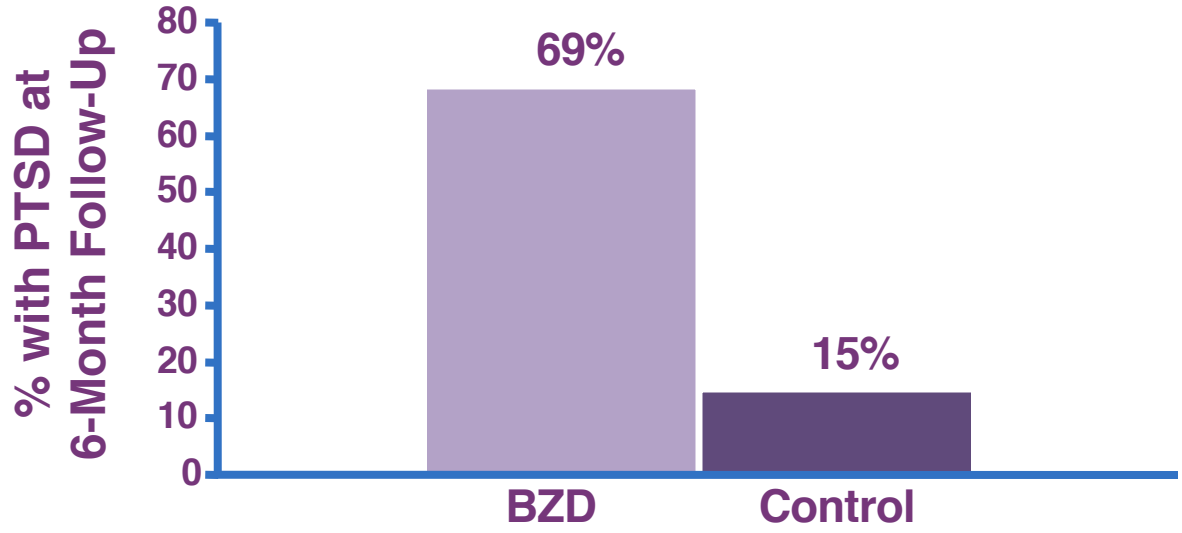
In practice: SSRI/SNRIs

- **FDA approved:**
  - sertraline
  - paroxetine
- **Non FDA-approved, but like effective:**
  - venlafaxine
  - fluoxetine

- **SSRIs and SNRIs: "Start low, go slow, but go"**
  - Typically higher dosages than MDD
  - Typically slower increase in dosage

What about Benzodiazepines?

Impact of Early Benzodiazepine on Recovery in PTSD

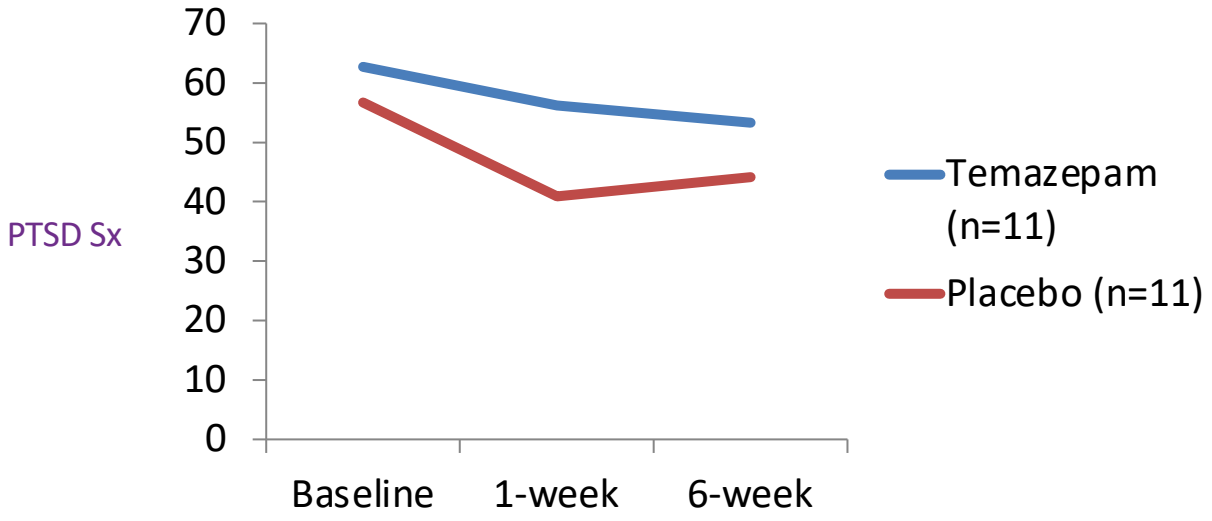


Alprazolam (N=3) or clonazepam (N=10) vs. no treatment (N=10); Gelpin et al. 1996

This information concerns a use that has not been approved by the US FDA.

Impact of Early Benzodiazepine on Recovery in PTSD

- Trauma victims
- 7 days of temazepam vs. PCB (14-d post trauma)



Mellman et al. 2002

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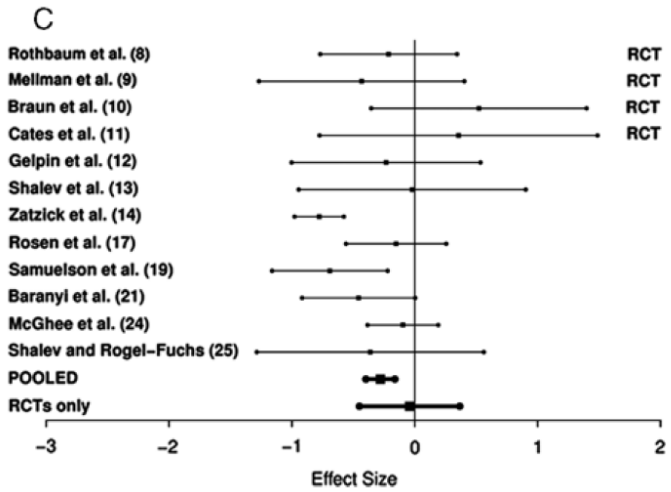
What about Benzodiazepines?

- **APA 2004 Guidelines**; Benzodiazepines cannot be recommended as monotherapy for PTSD
- **IOM report 2009**: evidence is inadequate to determine the efficacy of benzodiazepines in the treatment of PTSD
- Risk substance abuse and interference with extinction learning.



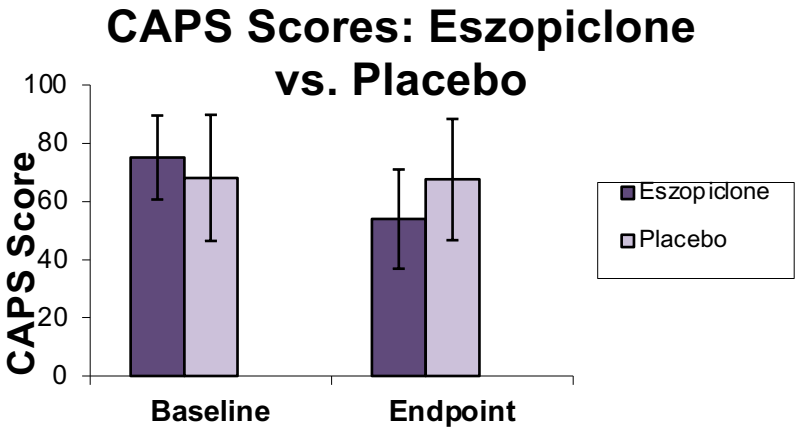
Guina et al. 2015

PTSD Is a Fear-Based Disorder

- Not a problem with forgetting the trauma
- But problem with learning extinction
- BZD may block new memory formation

And a Z-drug?

- Crossover RCT (n=24) 3 weeks of eszopiclone 3mg



Pollack et al., 2011

- Not replicated in RCT (12-wk, n=25) (not even on sleep)

Valdespino-Hayden et al., ISTSS, 2017

This information concerns a use that has not been approved by the US FDA.

Back to Sam

- paroxetine "Start low, go slow, but go"
- Eszopiclone 3mg
- 4 weeks later:
  - Could not go above 20mg
  - Slight improvement in sleep
  - CAPS-5 score = 40

Second line

- Switch to venlafaxine "Start low, go slow, but go"
- 6 weeks later:
  - Venlafaxine 225mg
  - Patient improved
  - CAPS-5 score = 33

This information concerns a use that has not been approved by the US FDA.

What adjunctive?

A. NaSSA (e.g. mirtazapine)

B. Antipsychotic (e.g. risperidone)

C. Anticonvulsant (e.g. pregabalin)

D. Alpha-1 adrenergic receptor antagonist (e.g. prazosin)

E. Angiotensin II receptor antagonist (e.g. losartan)

F. Beta-blocker (e.g. propranolol)

This information concerns a use that has not been approved by the US FDA.

Antipsychotic as adjunctive?

- Risperidone: 2 small RCT +, 1 large RCT -
- Olanzapine: 1 small RCT +
- Aripiprazole: 1 small RCT -
- Quetiapine: 1 small RCT +
- Small open trials + for other antipsychotics
- (two larges ongoing RCT for brexpiprazole)

- **Possible, especially if psychotic Sx**

This information concerns a use that has not been approved by the US FDA.

Anticonvulsant as adjunctive?

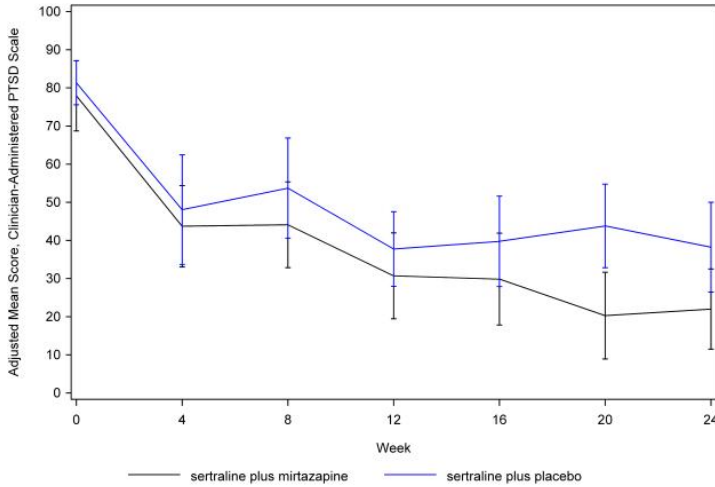
- Pregabaline: 1 small RCT +
- Topiramate: 1 small RCT + , 1 small RCT -
- Divalproate: 1 small RCT +

- **Possible, if “mixed” symptoms**

This information concerns a use that has not been approved by the US FDA.

Mirtazapine as adjunct?

- Small RCT, N=36, 24 weeks
- Sert+mirtazapine vs. sert+placebo
- Difference at wk20 but no differences at Wk24



- **Possible, especially if insomnia**

Schneier et al. 2015

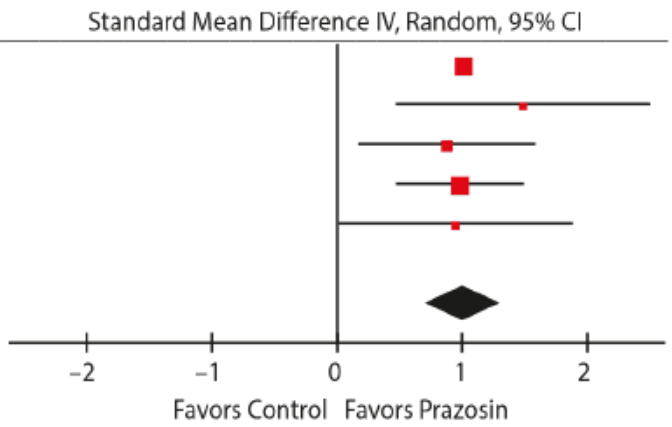
This information concerns a use that has not been approved by the US FDA.

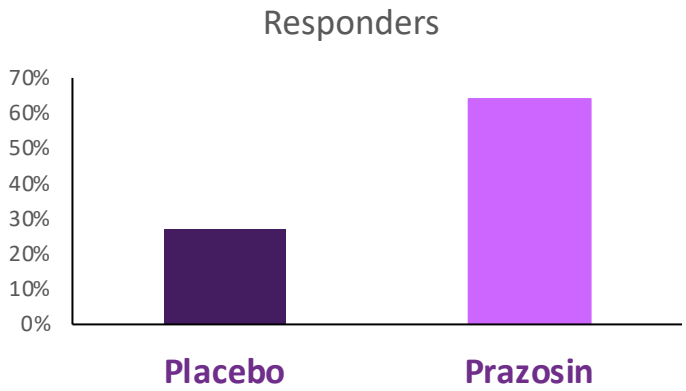
Prazosin as adjunctive?

Figure 2B. Nightmares

Study or Subgroup	Standard Mean Difference	Standard Error	Weight, %	Standard Mean Difference IV, Random, 95% CI
Ahmadpanah et al[20]	1.0097	0.2623	32.2	1.01 (0.50–1.52)
Raskind et al[22]	1.4863	0.5184	8.2	1.49 (0.47–2.50)
Raskind et al[7]	0.8765	0.3611	17.0	0.88 (0.17–1.58)
Raskind et al[8]	0.9815	0.2597	32.8	0.98 (0.47–1.49)
Taylor et al[9] (civilian)	0.9482	0.4775	9.7	0.95 (0.01–1.88)
Total (95% CI)			100.0	1.01 (0.72–1.30)

Heterogeneity: $Tau^2 = 0.00$; $\chi^2_4 = 1.01$, $P = .91$; $I^2 = 0\%$.
Test for overall effect: $Z = 6.79$, $P < .00001$.





- **Possible, especially if nightmares**

Raskind et al. 2013; Singh et al. 2016

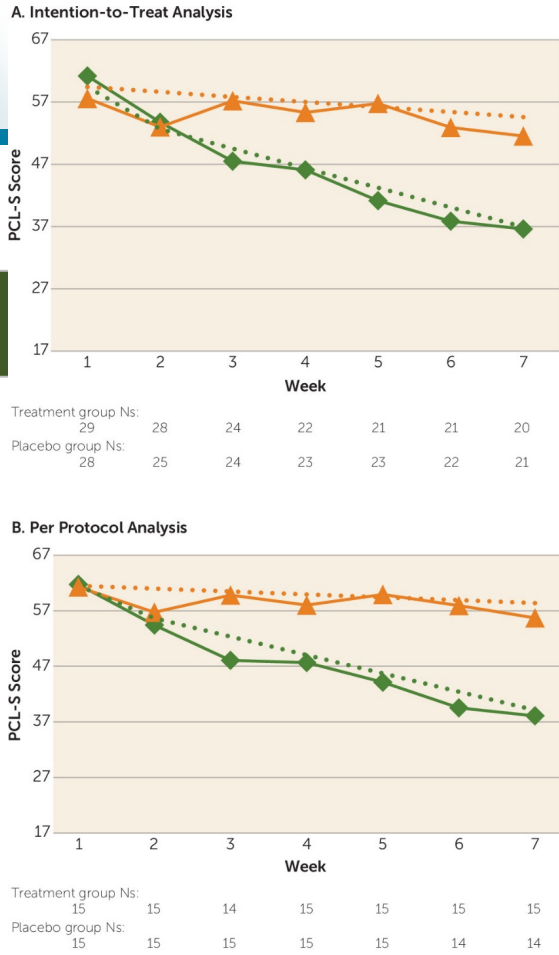
This information concerns a use that has not been approved by the US FDA.

Betablocker as adjunctive?

- No data
- But…

From: Reduction of PTSD Symptoms With Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial

The American Journal of Psychiatry

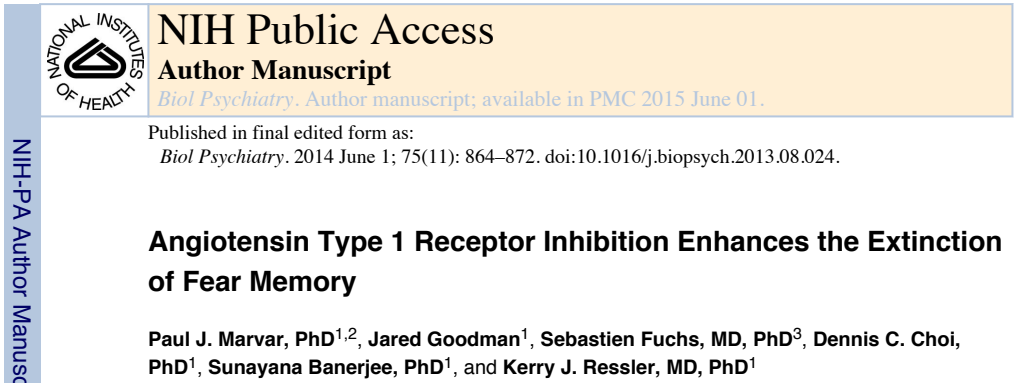


a PCL-S=PTSD Checklist–Specific. The raw average and model average PCL-S values (range, 17–85) are derived from the mixed linear model following each of six treatment sessions (weeks 2 to 7), controlling for the PCL-S score obtained at the first treatment session (week 1). The time-by-group estimated difference score at week 7 was 14.58 ($p<0.001$) for the intention-to-treat analysis and 16.74 ($p<0.001$) for the per protocol analysis.

This information concerns a use that has not been approved by the US FDA.

Angiotensin II receptor antagonist?

- No data
- but…



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Published in final edited form as:
Biol Psychiatry. 2014 June 1; 75(11): 864–872. doi:10.1016/j.biopsych.2013.08.024.

Angiotensin Type 1 Receptor Inhibition Enhances the Extinction of Fear Memory

Paul J. Marvar, PhD[1,2], **Jared Goodman**[1], **Sebastien Fuchs, MD, PhD**[3], **Dennis C. Choi, PhD**[1], **Sunayana Banerjee, PhD**[1], and **Kerry J. Ressler, MD, PhD**[1]

Marvar et al. 2014

- RCT recently completed

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B. Antipsychotic (e.g. risperidone)

C. Anticonvulsant (e.g. pregabalin)

D. Alpha-1 adrenergic receptor antagonist (e.g. prazosin)

E. Angiotensin II receptor antagonist (e.g. losartan)

F. Beta-blocker (e.g. propranolol)

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Back to Sam

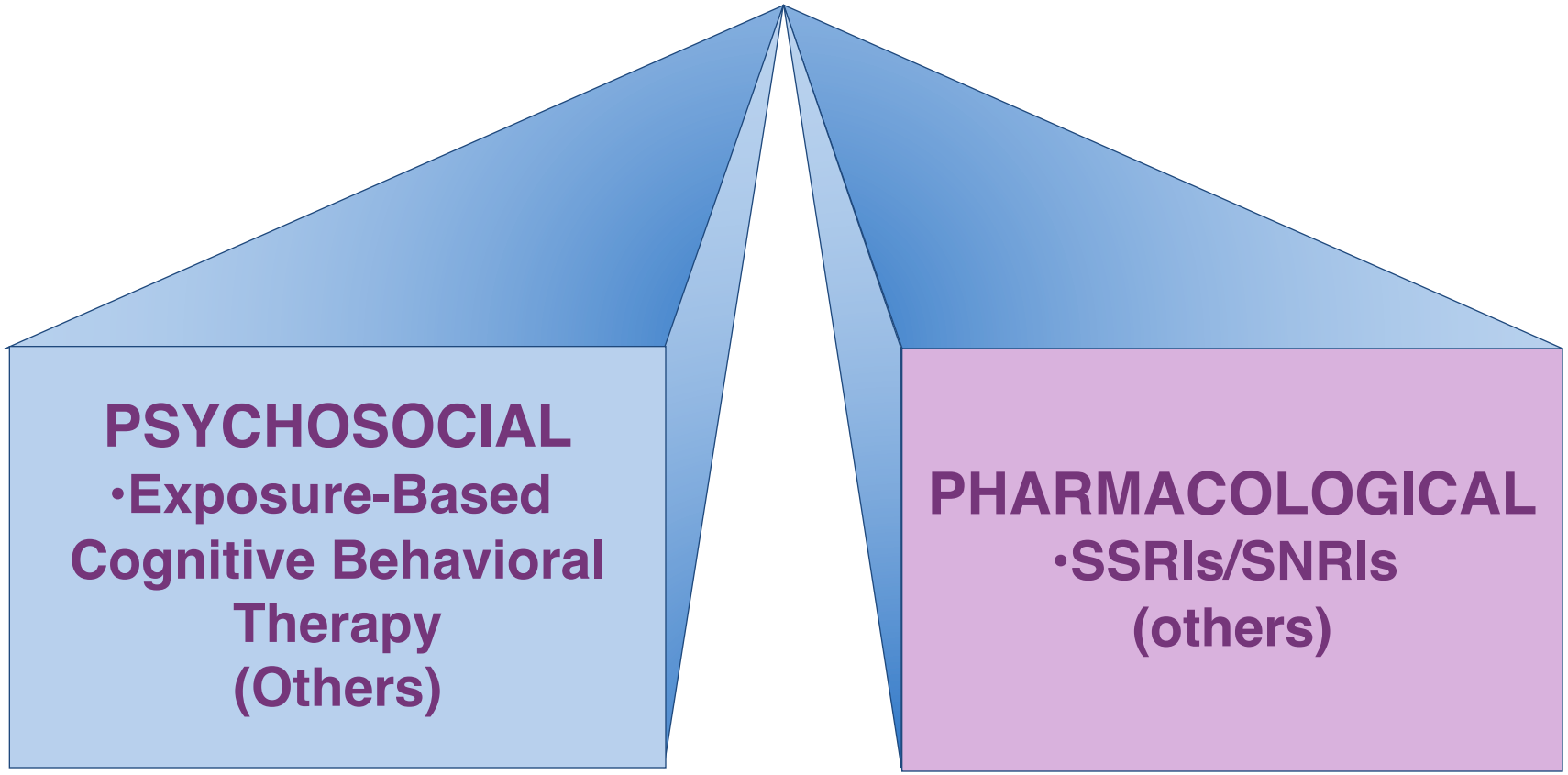
- venlafaxine 225mg/j
- Stop Zopiclone 7.5mg/j
- Mirtazapine 15mg
- 1 month later:
  - Improved sleep
  - Response : CAPS=26
  - Prazosin ramped up to 5mg

- 2 months later
  - Response : CAPS=20
  - Patient started to go out of their home, called their parents, etc…

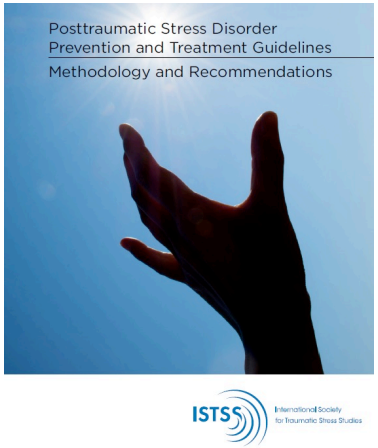
Last resort…

…or first

PTSD Treatment Options



ISTSS Guidelines 2018

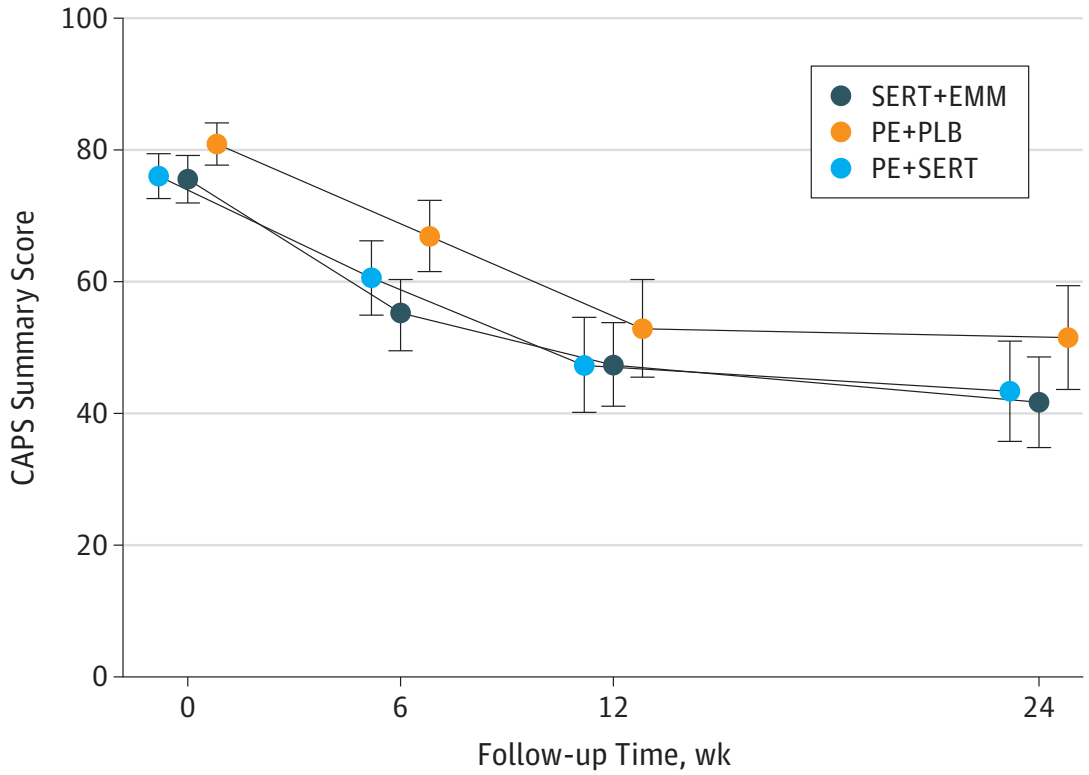


STRONG RECOMMENDATION - Cognitive Processing Therapy, Cognitive Therapy, EMDR, Individual CBT with a Trauma Focus (undifferentiated), and *Prolonged Exposure*

STANDARD RECOMMENDATION - CBT without a Trauma Focus, Group CBT with a Trauma Focus, Guided Internet-based CBT with a Trauma Focus, Narrative Exposure Therapy, and *Present Centred Therapy*

INTERVENTIONS WITH LOW EFFECT - Fluoxetine, Paroxetine, Sertraline and *Venlafaxine*

How do they compare?



PE indicates prolonged exposure therapy; PLB, placebo; PTSD, posttraumatic stress disorder; and SERT, sertraline hydrochloride. Error bars represent 95% CIs.

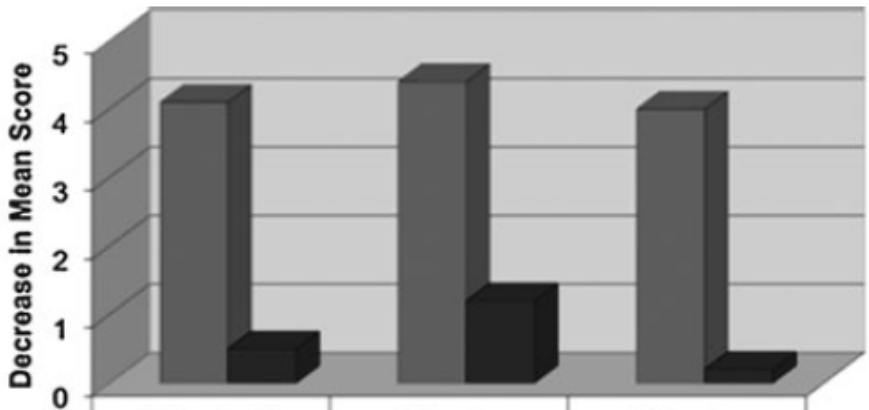
Rauch et al. 2019

Finally, Back to Sam

- Venlafaxine 225mg/j
- Mirtazapine 15mg/j
- Prazosin 5mg/j
- 3 months later:
  - Relapse, CAPS=35
  - Prolonged exposure
- 3 months later:
- CAPS = 10

Is there a “morning after” pill for PTSD?

SSRI?



	Week 8	Week 12	Week 24
Sertraline	4.1	4.4	4.0
Placebo	0.5	1.2	0.2

FIG. 1. Mean parent-reported posttraumatic stress disorder (PTSD) score change from Baseline over 24 weeks: Sertraline versus placebo.

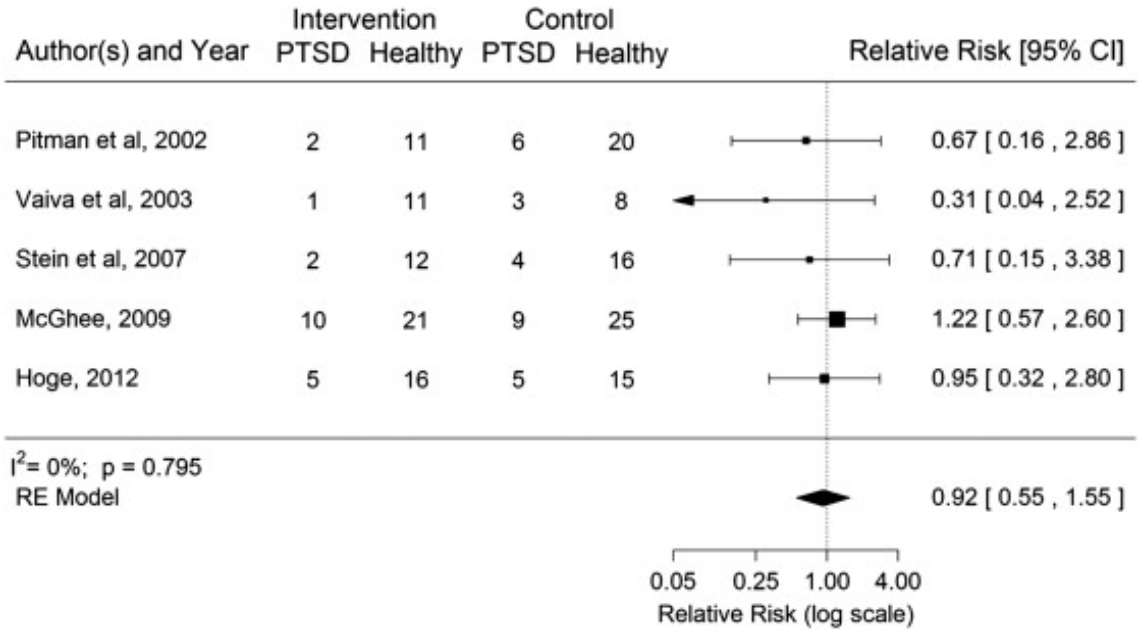
- Burned Children
- 24-week Sertraline 25-150mg (n=17) vs. PCB (n=9)
- Effect in parental ratings, not children rating
- Study escitalopram vs. psychotherapy: negative

Stoddard et al. 2011; Shalev et al. 2012

This information concerns a use that has not been approved by the US FDA.

Propranolol?

- Recent Meta-analysis including:
  - N=214 pooled
  - Across 5 studies
  - No effect!



- Another meta-analysis
  - On 3 studies
  - No effect

Amos et al. 2014; Argolo et al. 2015

This information concerns a use that has not been approved by the US FDA.

Opioids?

- A few retrospective/naturalistic studies
- Early use of opiate post-trauma to manage pain associated with decreased risk for PTSD
- No RCT

Holbrook et al. 2010; Mouthaan et al. 2015; Sheridan et al. 2014

This information concerns a use that has not been approved by the US FDA.

Hydrocortisone?

- Cochrane review
- 4 RCTs hydrocortisone *vs.* placebo
- Moderate evidence of effect

Amos et al. 2014

Outcome: 1 Treatment efficacy

Study or subgroup	Hydrocortisone n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Delahanty 2012	0/31	3/33		16.7 %	0.15 [0.01, 2.82]
Schelling 2001	1/20	7/20		35.6 %	0.14 [0.02, 1.06]
Weis 2006	1/19	3/17		30.4 %	0.30 [0.03, 2.60]
Zohar 2011a	0/15	3/10		17.4 %	0.10 [0.01, 1.72]
Total (95% CI)	**85**	**80**		**100.0 %**	**0.17 [0.05, 0.56]**

Total events: 2 (Hydrocortisone), 16 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.43$, df = 3 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 2.92 (P = 0.0035)

Test for subgroup differences: Not applicable

0.001 0.01 0.1 1 10 100 1000

Favours hydrocortisone Favours placebo

This information concerns a use that has not been approved by the US FDA

Pharmacotherapy After Acute Trauma

- Possibly helpful?
  - Antidepressants?
  - Beta blockers?
  - Opiates?
  - Glucocorticoids?
- Avoid Benzodiazepines

This information concerns a use that has not been approved by the US FDA.

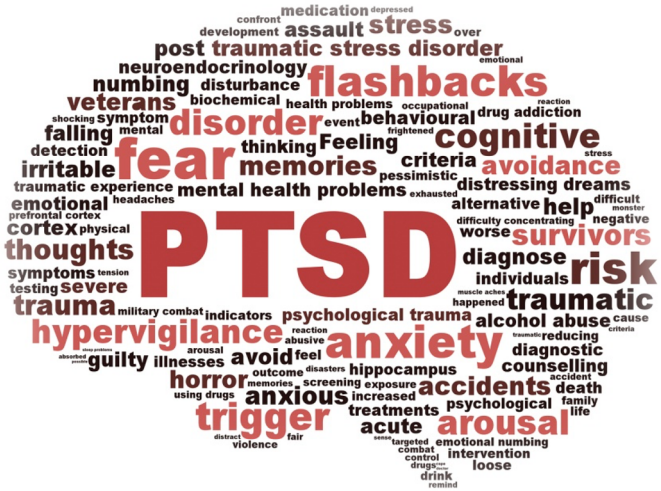
Conclusions

- **There is a "Crisis in the Pharmacotherapy of PTSD"**
  - Only two FDA-approved medications
  - Only one class
  - Efficacy is quite relative

- **Novel approaches**
  - New pathways : ketamine, Fatty Acid Amide Hydrolase (FAAH) inhibitor, oxytocin
  - Pharmacologically-assisted psychotherapy
    - propranolol / angiotensine II recept antagonist? / D-cycloserine
    - MDMA-Assisted Therapy

Krystal et al. 2017, Bui et al. 2019

Thank you!


medication
depressed
confront
development
assault
stress
over
post traumatic stress disorder
emotional
neuroendocrinology
numbing
disturbance
flashbacks
veterans
biochemical
health problems
occupational
reaction
drug addiction
shocking
symptom
disorder
event
behavioural
frightened
falling
mental
Feeling
cognitive
detection
thinking
stress
irritable
fear
memories
criteria
avoidance
traumatic experience
mental health problems
pessimistic
exhausted
distressing dreams
emotional
headaches
alternative
help
difficult
monster
prefrontal cortex
difficulty concentrating
negative
cortex
physical
PTSD
worse
survivors
thoughts
diagnose
symptoms
tension
individuals
risk
testing
severe
muscle aches
happened
traumatic
trauma
military combat
indicators
psychological trauma
alcohol abuse
cause
criteria
hypervigilance
reaction
abusive
anxiety
traumatic
reducing
arousal
guilty
illnesses
avoid
feel
diagnostic
counselling
outcome
disasters
hippocampus
horror
memories
screening
exposure
accidents
death
accident
using drugs
anxious
increased
psychological
family
life
trigger
treatments
arousal
acute
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emotional numbing
combat
intervention
control
drugs
loose
drink
remind