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:

Springer	**Royalties**	**Editor**
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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**

Who will develop PTSD after a traumatic event?

- **Peritraumatic Reactions**
- Factors operating during or immediately after trauma
- Described since the Antiquity

e.g. during eruption of Vesuvius
(79 AD)

- *"You could hear the shrieks of women, the wailing of infants, and the shouting of men; some were calling their parents, others their children or their wives. People bewailed their own fate or that of their relatives, and there were some who prayed for death in their terror of dying."* (Pliny the Younger)

Birmes, Bui, et al., 2009

Peritraumatic Reactions?

- **Peritraumatic Distress**

"fear, helplessness and horror" & physical reactions = Emotional/physical response

- **Peritraumatic Dissociation**

"Alterations in the experience of time, place and persons" = Cognitive response

- Shown to predict prospectively PTSD

Brunet et al., 2001; Marmar et al., 1994; Bui et al, 2010; Vance et al, 2018

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

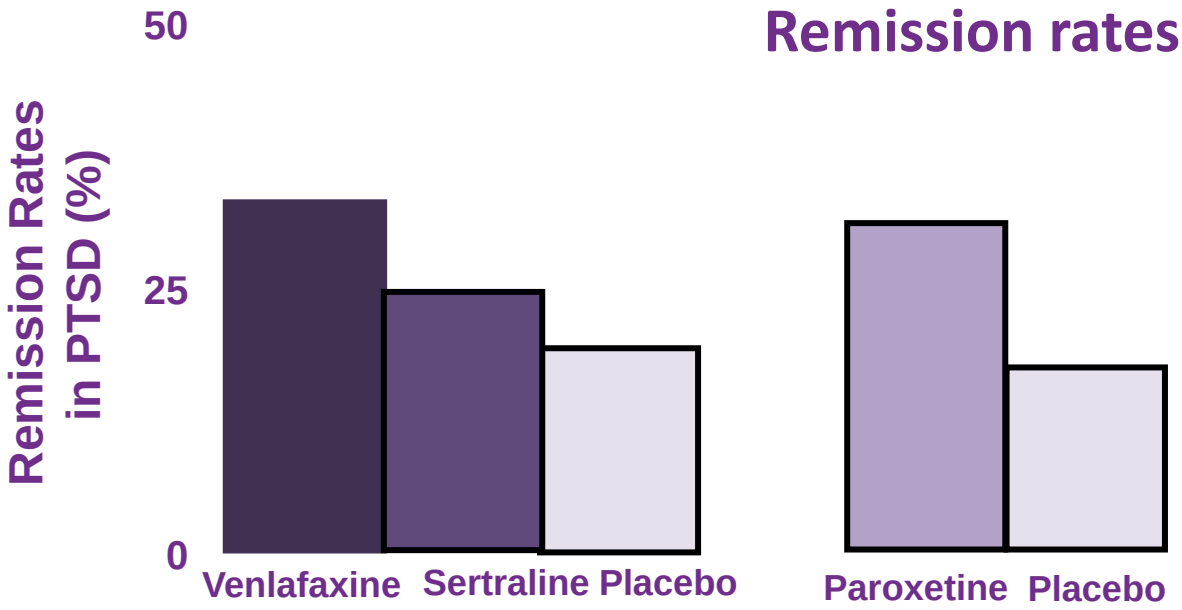
Patient

- Sam, 24 y/o non-binary 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

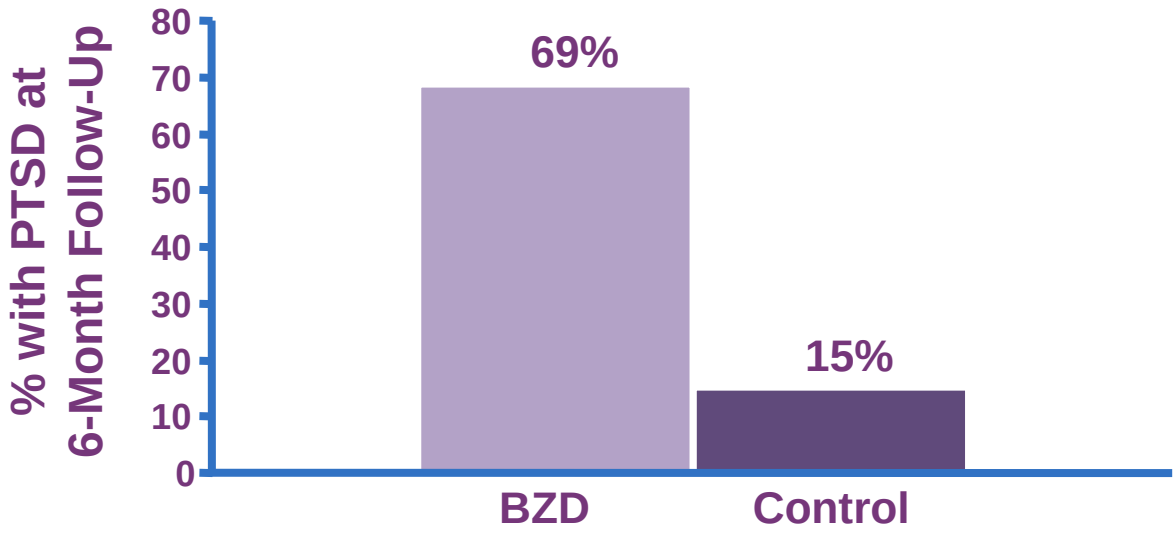
In practice: SSRI/SNRIs

- **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

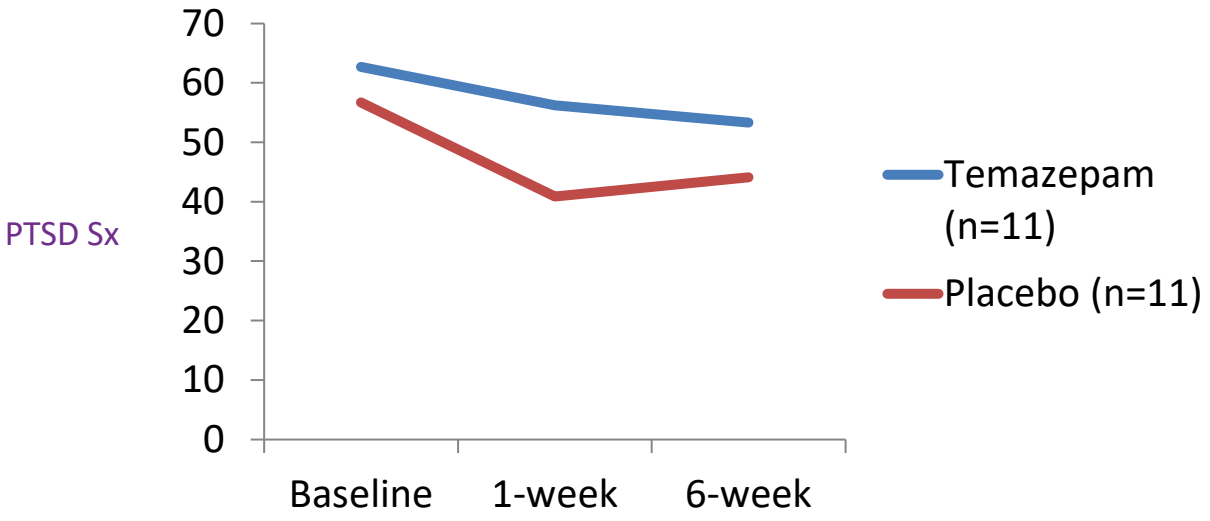


Alprazolam (N=3) or clonazepam (N=10) vs. no treatment (N=10); Gelpin et al. 1996

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)

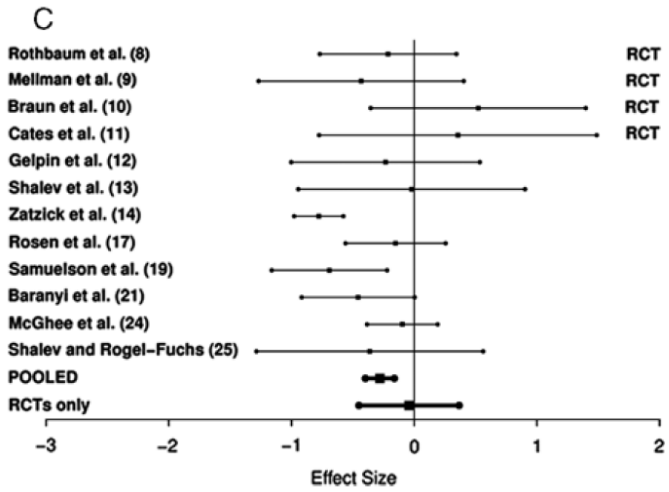


Mellman et al. 2002

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

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.



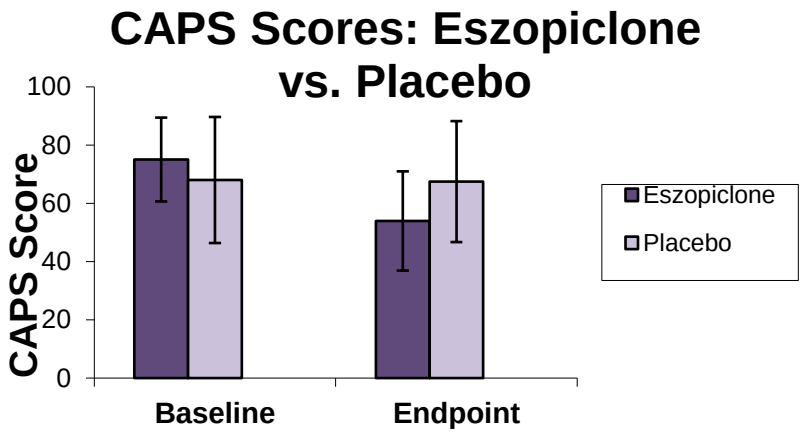
Guina et al. 2015

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



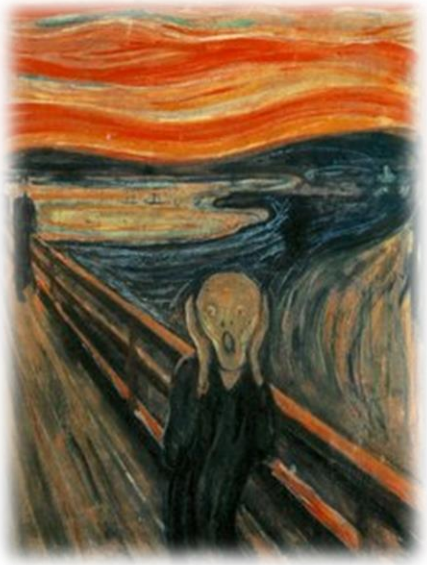
Pollack et al., 2011

- 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?

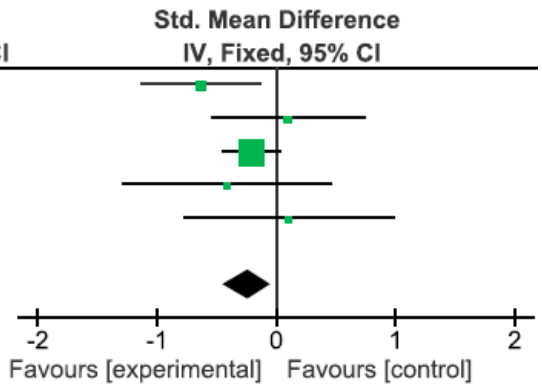
- Risperidone: 5 RCT +/-
- Olanzapine: 1 small RCT +
- Aripiprazole: 1 small RCT -
- Quetiapine: 1 small RCT +
- Small open trials + for other antipsychotics
- (two larges ongoing RCT for brexpiprazole)

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

Risperidone as adjunct

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Bartzokis 2004 (risperidone)	-14.3	16.7	33	-4.6	13.2	32	16.1%	-0.64 [-1.13, -0.14]
Hamner 2003 (risperidone)	81.3	24.3	19	79	21	18	9.6%	0.10 [-0.55, 0.74]
Krystal 2011 (risperidone)	-16.3	19.0482	123	-12.5	17.4394	124	64.0%	-0.21 [-0.46, 0.04]
Reich 2004 (risperidone)	-29.6	31.5	12	-18.6	12.3	9	5.2%	-0.42 [-1.29, 0.46]
Rothbaum 2008 (risperidone)	38.8889	24.43586	9	36.4545	21.03979	11	5.1%	0.10 [-0.78, 0.98]
Total (95% CI)			**196**			**194**	**100.0%**	**-0.24 [-0.44, -0.04]**

Heterogeneity: Chi² = 4.28, df = 4 (P = 0.37); I² = 6%
Test for overall effect: Z = 2.37 (P = 0.02)



- **Possible, especially if psychotic Sx**
- **Prefer risperidone as antipsychotic**

Hoskin et al. 2021

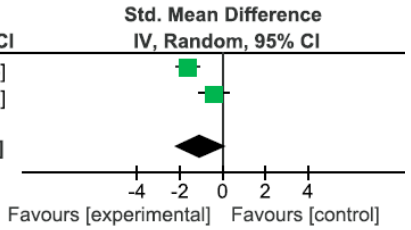
Anticonvulsant as adjunctive?

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

- **Possible, if "mixed" symptoms**

	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Akuchekian 2004 (topiramate)	32.75	8.2	34	46.62	8.8	33	51.9%	-1.61 [-2.17, -1.06]
Batki 2015 (topiramate)	42.3	16	14	49	16.5	16	48.1%	-0.40 [-1.13, 0.32]
Total (95% CI)			**48**			**49**	**100.0%**	**-1.03 [-2.22, 0.16]**

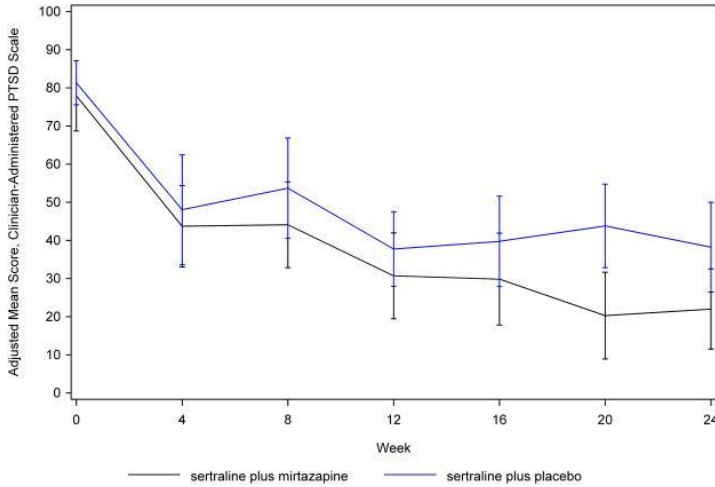
Heterogeneity: Tau² = 0.63; Chi² = 6.76, df = 1 (P = 0.009); I² = 85%
Test for overall effect: Z = 1.70 (P = 0.09)



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 / comorbid depression**

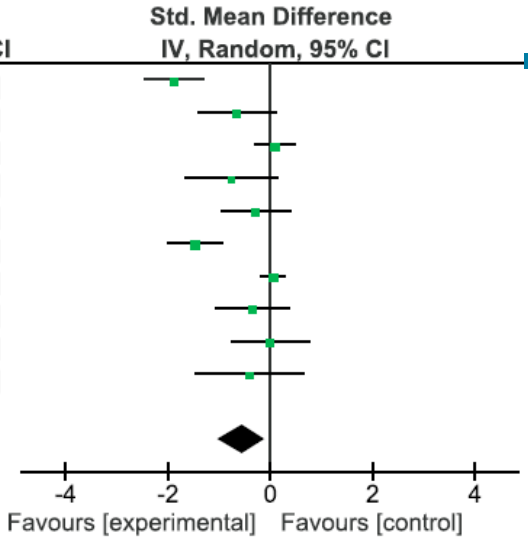
Schneier et al. 2015

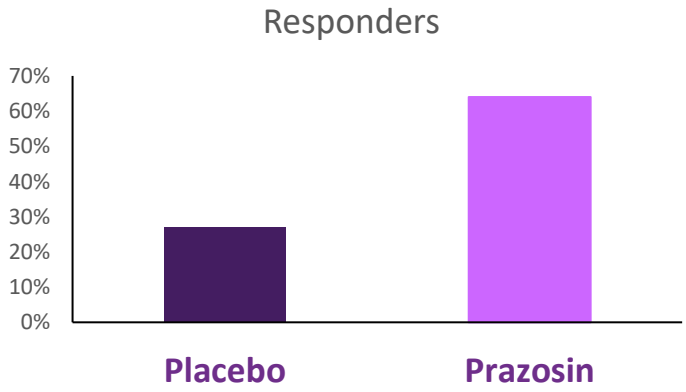
This information concerns a use that has not been approved by the US FDA.

Prazosin as adjunctive?

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ahmadpana 2013 (prazosin)	-3.64	0.78	33	-1.61	1.29	33	10.6%	-1.88 [-2.47, -1.30]
Germain 2012 (prazosin)	-10.6	16.4	15	-0.1	14.3	13	9.4%	-0.66 [-1.42, 0.11]
Petrakis 2016 (prazosin)	-33.92	37.62	50	-37.78	41.13	46	11.6%	0.10 [-0.30, 0.50]
Raskind 2003 (prazosin)	-21.8	32.3	10	2.9	30	10	8.5%	-0.76 [-1.67, 0.16]
Raskind 2007 (prazosin)	-13	20	17	-7	22	17	10.0%	-0.28 [-0.95, 0.40]
Raskind 2013 (prazosin)	52.2	23.0211	32	85.7	22.1244	35	10.8%	-1.47 [-2.01, -0.92]
Raskind 2018 (prazosin)	-11.8	19.9	135	-13.1	23.9	136	12.3%	0.06 [-0.18, 0.30]
Simpson 2015 (prazosin)	-0.6	1.2	15	-0.2	1.1	15	9.7%	-0.34 [-1.06, 0.38]
Taylor 2008 (prazosin)	-7	14	13	-7	15	13	9.4%	0.00 [-0.77, 0.77]
van Liempt 2012 (prazosin)	-13.28	18.79	7	-5.86	14.88	7	7.6%	-0.41 [-1.47, 0.65]
Total (95% CI)			**327**			**325**	**100.0%**	**-0.56 [-1.03, -0.09]**

Heterogeneity: Tau² = 0.45; Chi² = 60.74, df = 9 (P < 0.00001); I² = 85%
Test for overall effect: Z = 2.34 (P = 0.02)





- **Possible, especially if nightmares**

Raskind et al. 2013; Hoskin et al. 2021

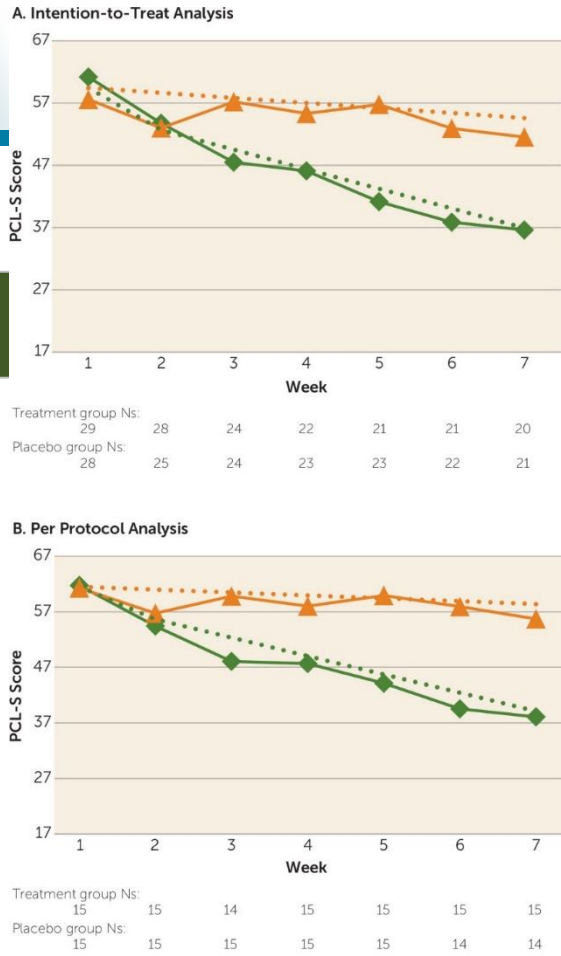
This information concerns a use that has not been approved by the US FDA.

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.

Brunet et al, 2018

Angiotensin II receptor antagonist?

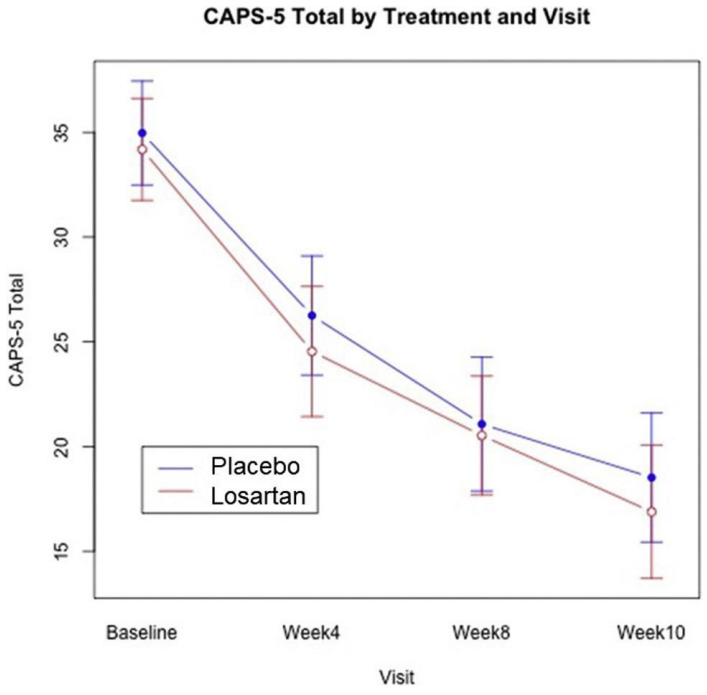
Published in final edited form as:
Biol Psychiatry. 2014 June 1; 75(11): 864–872. doi:10.1016/j.biopsych.2013.08.024.

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

- Recent RCT
- N=149
- 10 weeks losartan (25-100mg/d) vs. Placebo



Stein et al. in press

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)

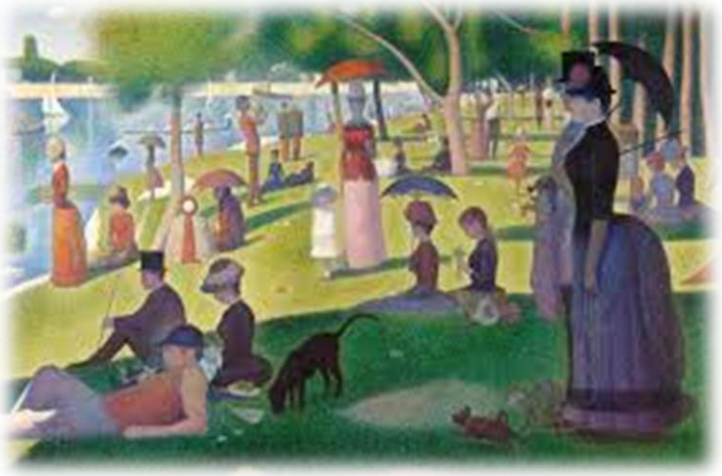
E. Angiotensin II receptor antagonist (e.g. losartan)

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

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

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

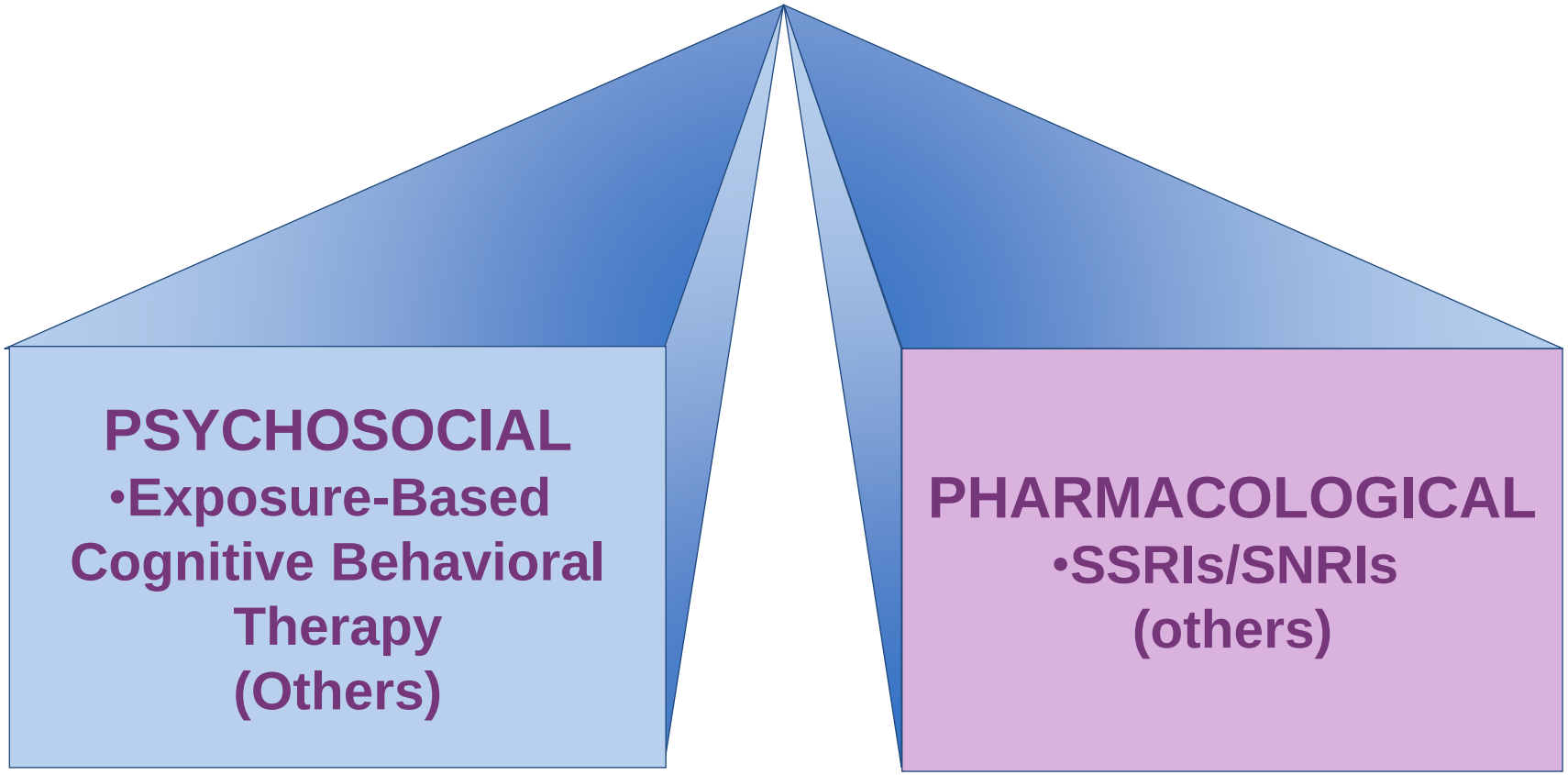


- 2 months later
  - Response : CAPS=20
  - Patient started to leave their home, call their parents, etc…

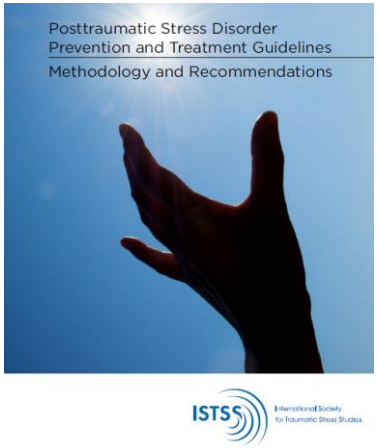
Last resort…

…or first

PTSD Treatment Options



ISTSS Guidelines 2018

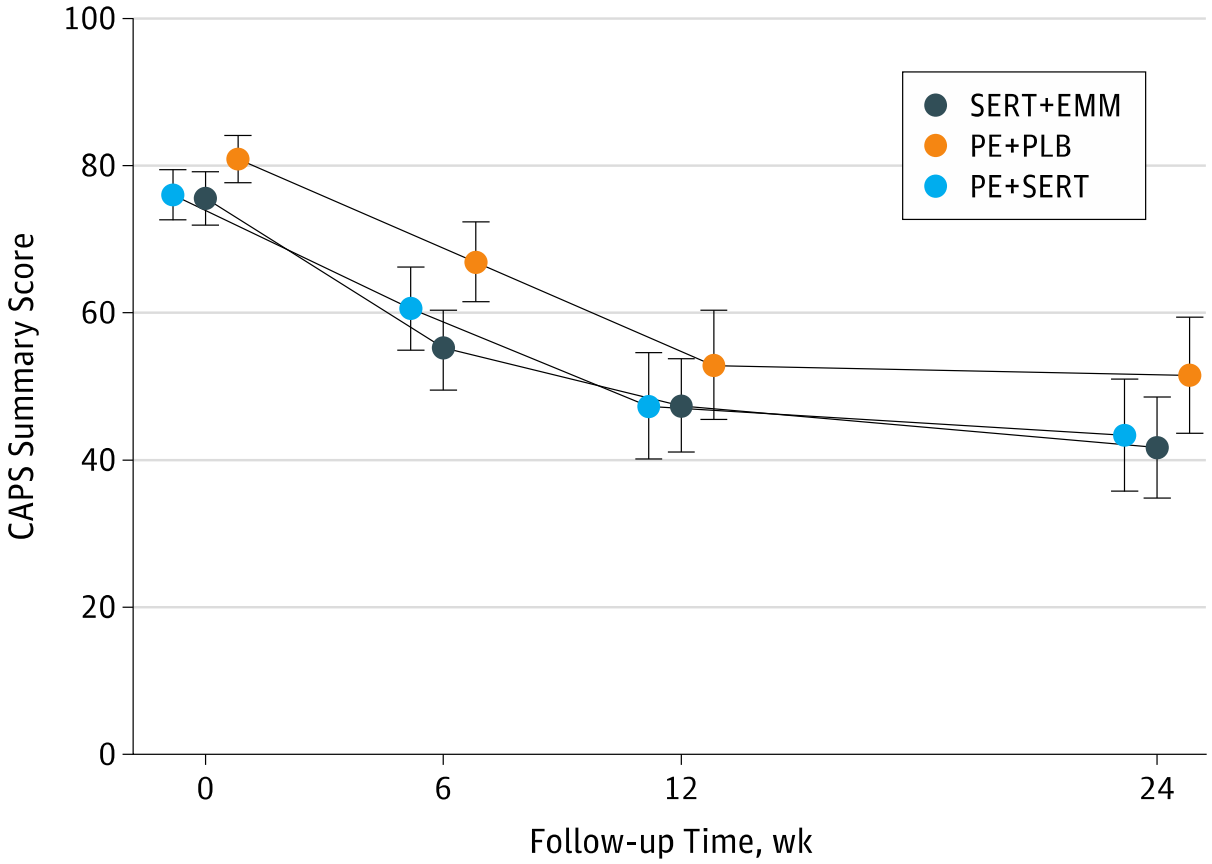


STRONG RECOMMENDATION - ***Cognitive Processing Therapy, Cognitive Therapy, EMDR, Individual CBT with a Trauma Focus (undifferentiated)***, and ***Prolonged Exposure***

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?



Rauch et al. 2019

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

Finally, Back to Sam

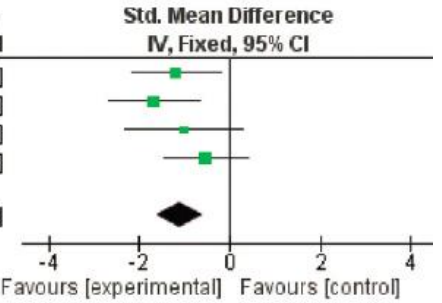
- Venlafaxine 225mg/j
- Mirtazapine 15mg/j
- Prazosin 5mg/j
- 3 months later:
  - Relapse, CAPS=35
  - Prolonged exposure
- 3 months later:
- CAPS = 10

Pharmacological-assisted Psychotherapy for PTSD?

- No efficacy of pharmacological-assisted therapy with SSRIs (4 RCTs) or D-Cycloserine (4 RCTs)
- MDMA: 4 RCTs

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Mithoefer 2010 (MDMA-AP 125mg vs PLB-AP)	-53.7	26.6736	12	-20.5	26.5872	8	27.1%	-1.19 [-2.18, -0.21]
Mithoefer 2018 (MDMA-AP 75+125mg vs MDMA-AP 30mg)	-49.4579	24.1317	19	-11.4	12.7	7	26.3%	-1.69 [-2.69, -0.69]
Oehen 2013 (MDMA-AP 125mg vs MDMA-AP 25mg)	-15.6	19.7	8	3.1	7.6	4	15.6%	-1.02 [-2.31, 0.28]
Ot'alora 2018 (MDMA-AP 100+125mg vs MDMA-AP 40mg)	-25.4857	26.7174	21	-11.5	21.2	6	31.0%	-0.53 [-1.45, 0.39]
Total (95% CI)			**60**			**25**	**100.0%**	**-1.09 [-1.60, -0.58]**

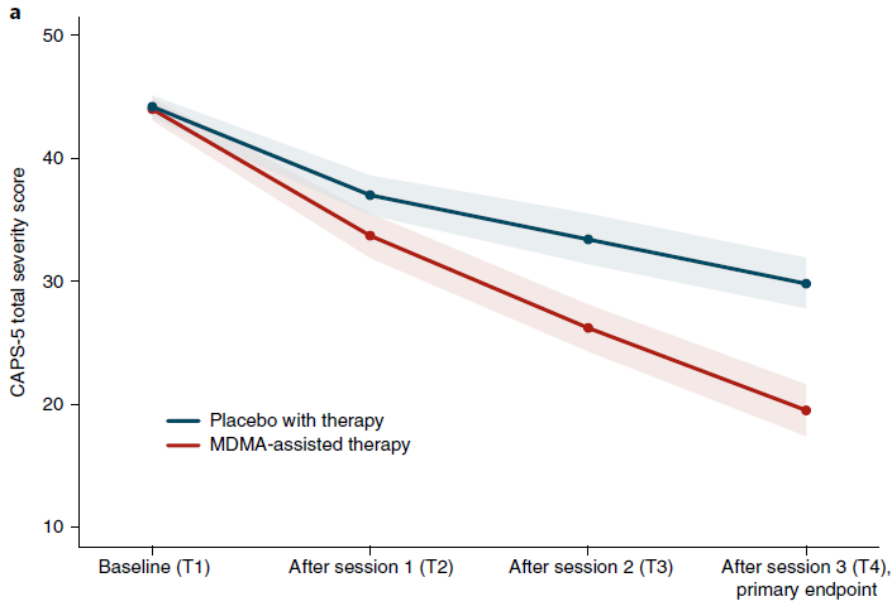
Heterogeneity: $Chi^2 = 2.86$, $df = 3$ ($P = 0.41$); $I^2 = 0\%$
Test for overall effect: $Z = 4.16$ ($P < 0.0001$)



Hoskin et al. 2021

MDMA-Assisted Therapy

- New large RCT
  - -n=90
  - -MDMA (80–180 mg)
  - -18 weeks



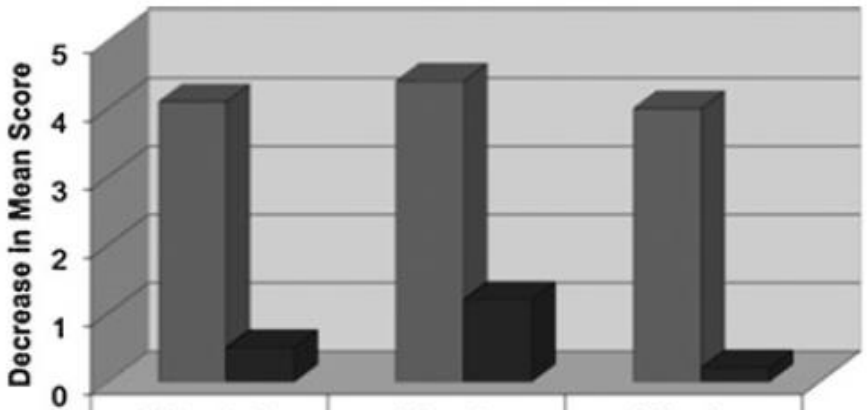
- What therapy?
  - three 90-min preparatory sessions with 2 therapists
  - three 8-h experimental sessions with MDMA vs. Placebo (4 weeks apart with 3 in between 90-min sessions)

Mitchell et al, 2021

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

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.

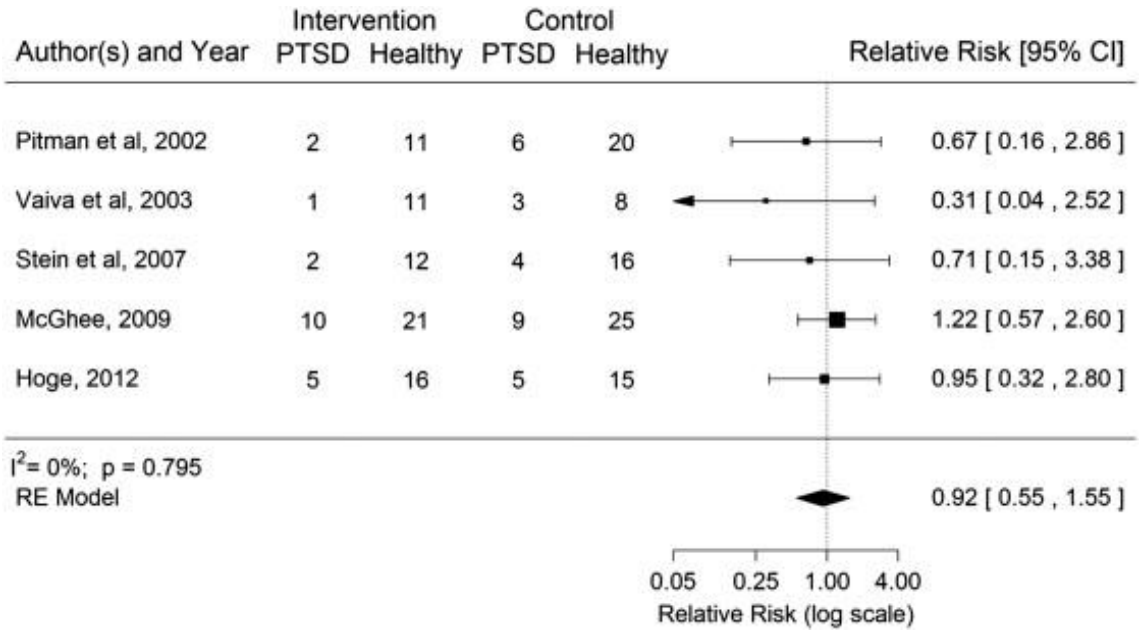
- Burned Children
- 24-week Sertraline 25-150mg (n=17) vs. PCB (n=9)
- Effect in parental ratings, not children rating
- Study escitalopram vs. psychotherapy: negative

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

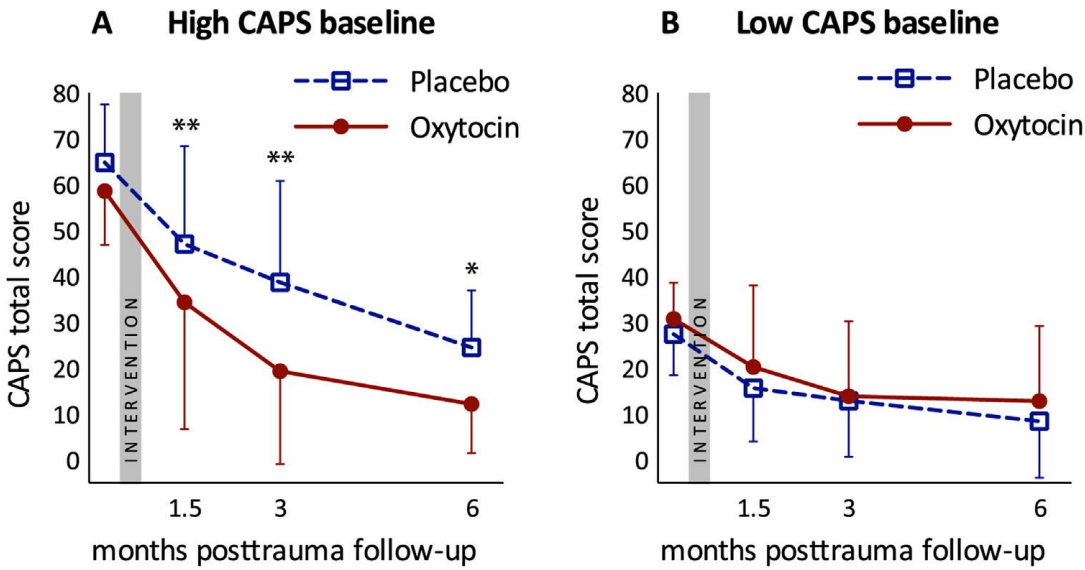
This information concerns a use that has not been approved by the US FDA.

Oxytocin?

- Intra nasal oxytocin (40IU) vs. placebo twice daily, initiated within 12 days of trauma
- No efficacy to prevent PTSD on ITT sample
- But

- CAPS moderator
- (Peritraumatic

reactions not moderators)



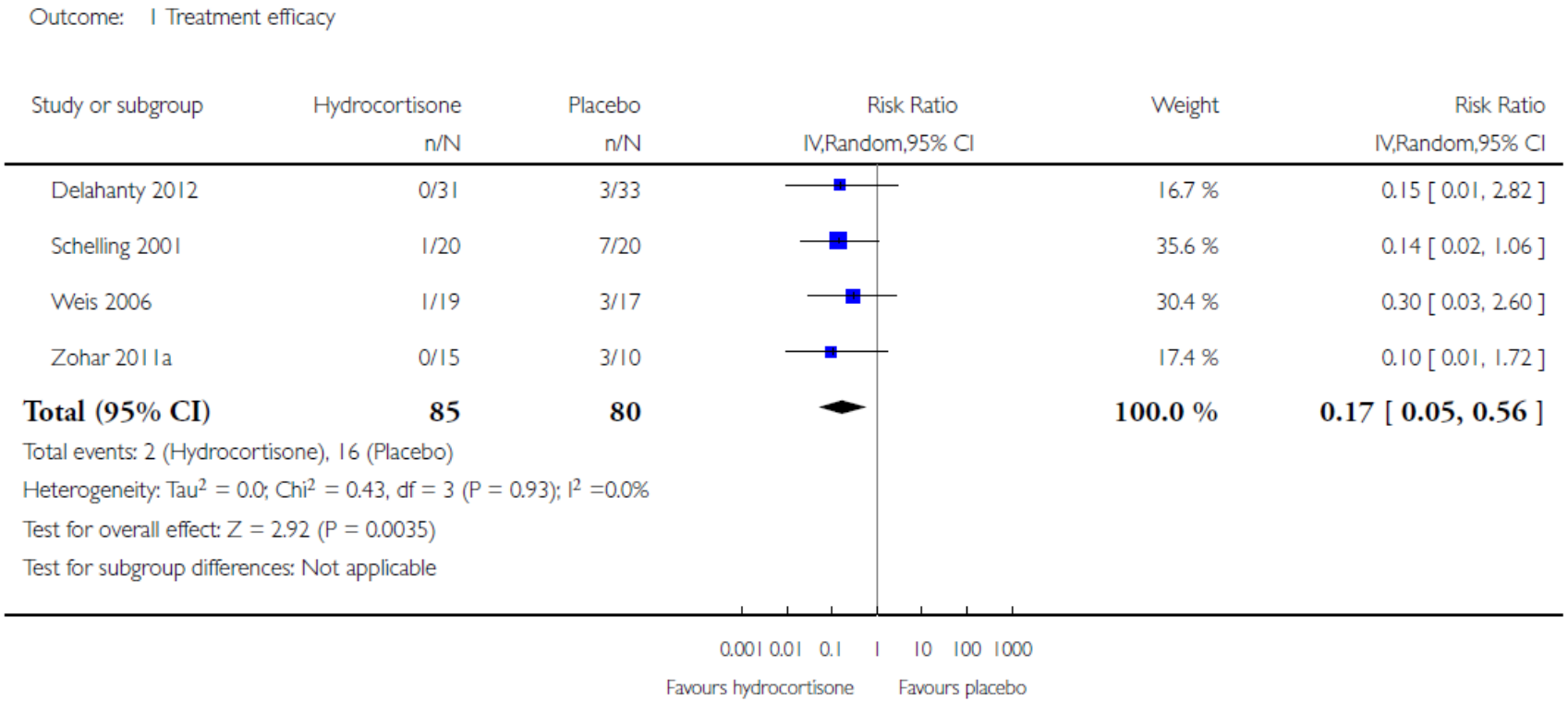
Van Zuiden et al., 2017

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



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?
  - Oxytocin?
- Avoid Benzodiazepines

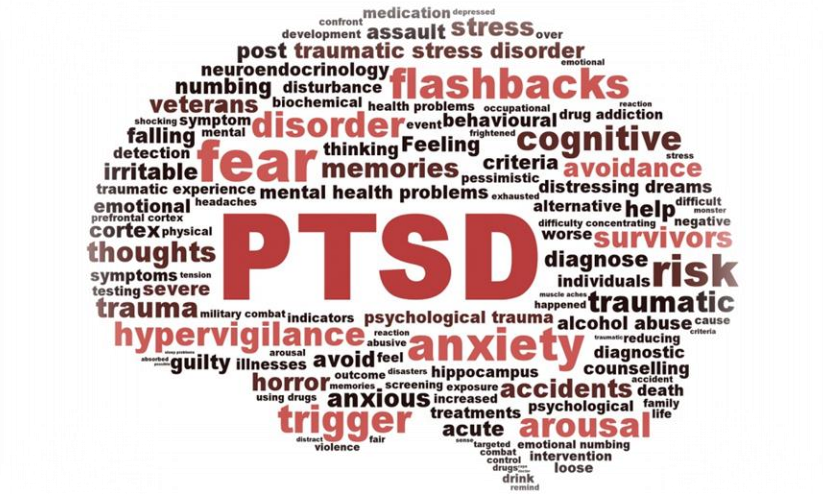
This information concerns a use that has not been approved by the US FDA.

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
    - In particular, 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
falling
mental
frightened
cognitive
detection
thinking
Feeling
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
testing
severe
individuals
risk
muscle aches
happened
trauma
military combat
indicators
psychological trauma
traumatic
alcohol abuse
cause
criteria
hypervigilance
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anxiety
reducing
arousal
diagnostic
guilty
illnesses
avoid
feel
counselling
outcome
disasters
hippocampus
horror
memories
screening
exposure
accidents
death
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using drugs
anxious
increased
psychological
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trigger
treatments
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acute
distract
fair
violence
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emotional numbing
combat
intervention
control
drugs
loose
drink
remind