A Review of Pharmacotherapy for PTSD

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Epidemiology of PTSD and Health Burden

- US lifetime prevalence 6-8%
- 9% current prevalence in primary care clinic in one report
- Contributor to disability, suicide, violence
- Often chronic or lifelong
- Comorbidity
  - psychiatric (suicide, depression, alcohol, drug, dementia)
  - medical (pain, TBI, CVD, metabolic, inflammatory, autoimmune)

The Earliest Observations on Pharmacotherapy for PTSD

- **“…..we have found that patients of the kind we used to abreact, have done well by other means……the MAOI and tricyclic antidepressants are more valuable”**
- **“With phenelzine, the patients felt calmer and stopped having nightmares and flashbacks…..startle reactions and violent outbursts ceased”**
- **Thompson’s 1977 trial of amitriptyline-perphenazine vs counselling in accident neurosis**

Sargant and Slater. 1972; Hogben and Cornfield, 1981; Thompson, 1977

Standard of Care Pharmacotherapy for PTSD

- Nearly all guidelines recommend SSRI/SNRI at Grade A level of evidence
- ISTSS Practice Guidelines 2009 - “The best evidence supports the use of SSRIs and SNRIs as first-line drugs…”
- VA/DoD Guidelines 2010 - “Strongly recommend SSRI or SNRI.”
- ISTSS for TCA, mirtazapine and MAOI level A. VA/DoD for TCA, MAOI level B.

ISTSS Guidelines 2009; VA/DoD 2010

General Goals of Pharmacotherapy in PTSD

- Reduce core symptoms (Clusters B,C,D,E)
- Improve function and quality of life
- Treat accompanying disorders or problems (e.g. alcohol problems, depression, smoking)
- Increase resilience
- Prevent relapse

Outline

- Monotherapies with supportive data
- Monotherapies with negative or equivocal data
- Drugs under investigation
- Combining drug and psychotherapy
- Combining drugs
- Relapse prevention

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Treatment of Posttraumatic Stress Disorder With Amitriptyline and Placebo

Jonathan Davidson, MD; Harold Kudler, MD; Rebecca Smith, RN; Steven L. Mahorney, MD;
Steven Lipper, MD, PhD; Elliott Hammett, MD; William B. Saunders, MPH; Jesse O. Cavenar, Jr, MD

• **Amitriptyline hydrochloride was compared with placebo in 46 veterans with chronic posttraumatic stress disorder. Treatment continued up to 8 weeks, and efficacy was measured by five observer and two self-rated scales. Percent recovery rates were higher for amitriptyline than placebo on two measures. In patients who completed 4 weeks (n = 40), better outcome with amitriptyline was noted on the Hamilton depression scale only. In the group completing 8 weeks of treatment (n = 33), the drug was superior to placebo on Hamilton depression, Hamilton anxiety, Clinical Global Impression severity, and Impact of Event scales. There was no evidence for drug effects on the structured interview for posttraumatic stress disorder. Drug-placebo differences were greater in the presence of comorbidity in general, although recovery rates were uniformly low in the presence of major depression, panic disorder, and alcoholism. At the end of treatment, 64% of the amitriptyline and 72% of the placebo samples still met diagnostic criteria for posttraumatic stress disorder.**

(*Arch Gen Psychiatry*. 1990;47:259-266)

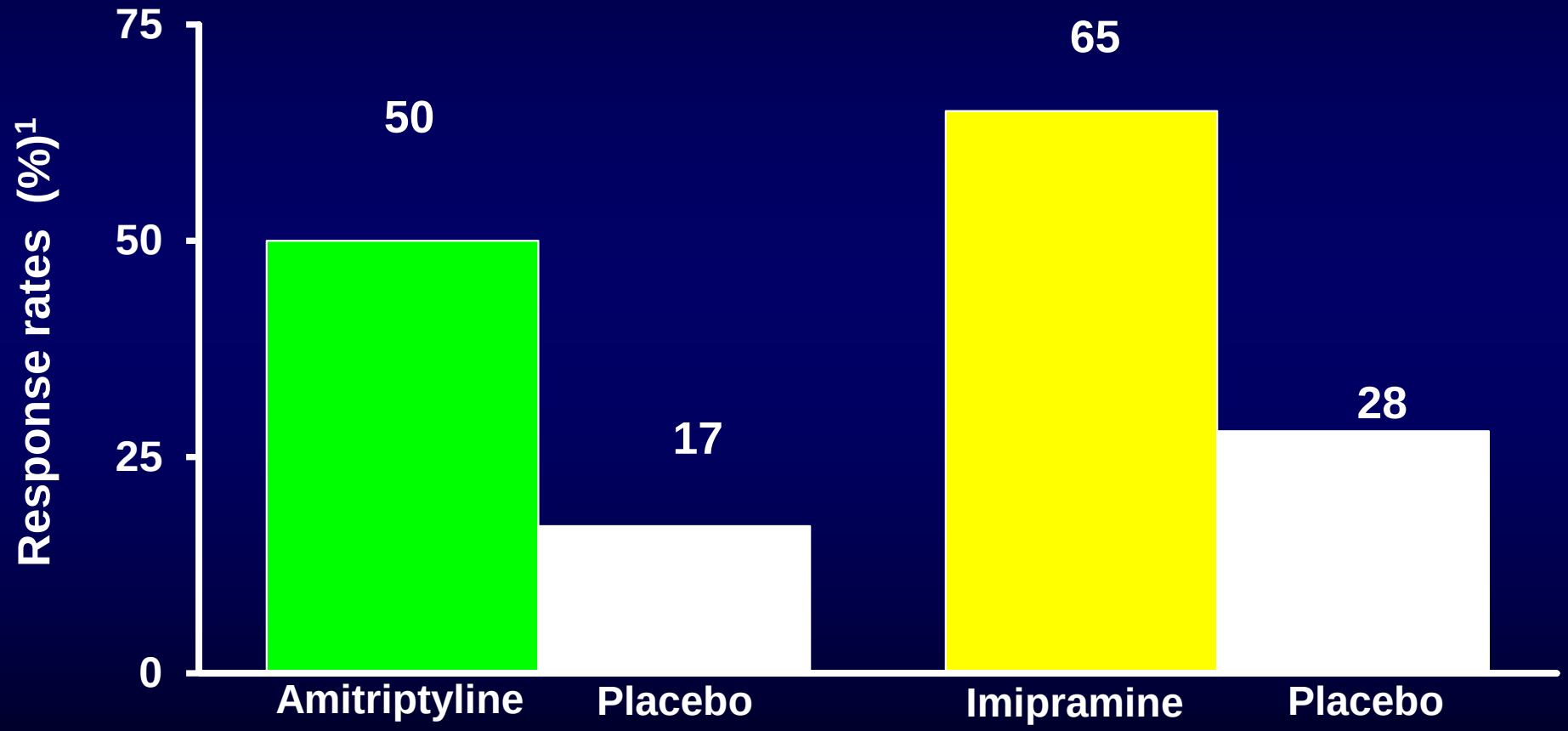
Pharmacotherapy for Posttraumatic Stress Disorder Using Phenelzine or Imipramine

THOMAS R. KOSTEN, M.D., JULIA B. FRANK, M.D., ELISHEVA DAN, P.A., CHRISTOPHER J. McDOUGLE, M.D., AND EARL L. GILLER, JR., M.D., PH.D.[1]

Sixty male veterans with posttraumatic stress disorder (PTSD) participated in an 8-week, randomized trial comparing phenelzine ($N = 19$), imipramine ($N = 23$), and placebo ($N = 18$). Mean treatment retention was better on phenelzine (7.4 weeks) than on imipramine (5.6 weeks) or placebo (5.5 weeks). By week 5, both medications significantly reduced PTSD symptoms, as assessed by the Impact of Events Scale (IES), but the 44% improvement on phenelzine was greater than the 25% improvement on imipramine. The intrusion, but not the avoidance, subscale of the IES showed significant improvement, and the initial mild to moderate depressive symptoms did not significantly improve.

—*J Nerv Ment Dis* 179:366–370, 1991

Response Rates to AT and IMIP in PTSD in VA Studies



Davidson et al, 1990; Kosten et al 1991

[1] CGI-I

Use of Low Dose TCA in Chronic PTSD

- 18 Bataan POWs seen 37 years later
- Ages 57-67
- Marked and often incapacitating PTSD
- Doxepin 25-100 mg
- Response to treatment “very dramatic”
- First restful sleep in 35 years
- Other symptoms subsided or abated completely

White NS Hosp Comm Psych 1983

It’s More Than Just the Drug

- **“It is imperative that all physicians treating these former POWs make a major attempt to establish a trusting relationship that allows the veteran to describe his symptoms……”**

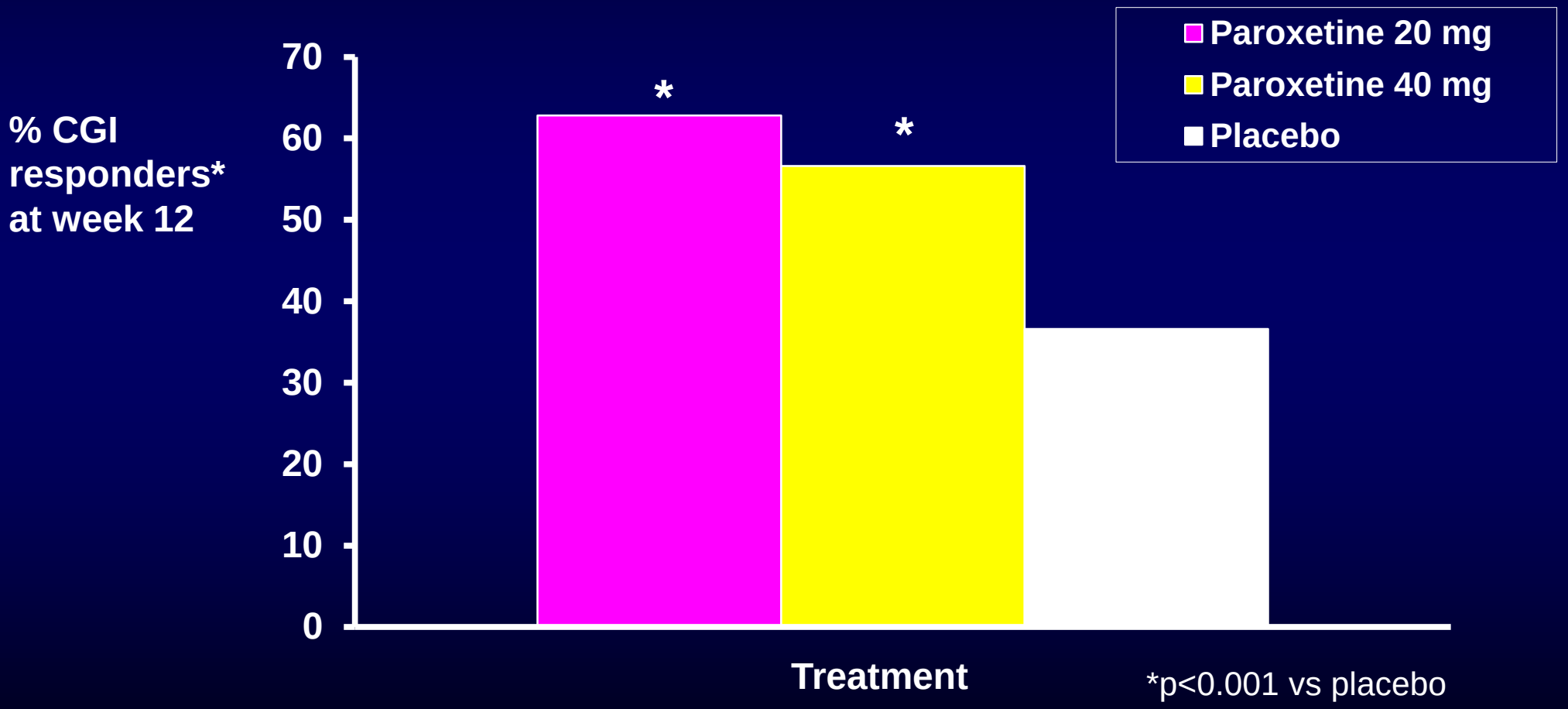
White NS Hosp Comm Psych 1983

Most Extensively Studied Drugs in PTSD

- Sertraline *
- Paroxetine *
- Venlafaxine XR
- Fluoxetine

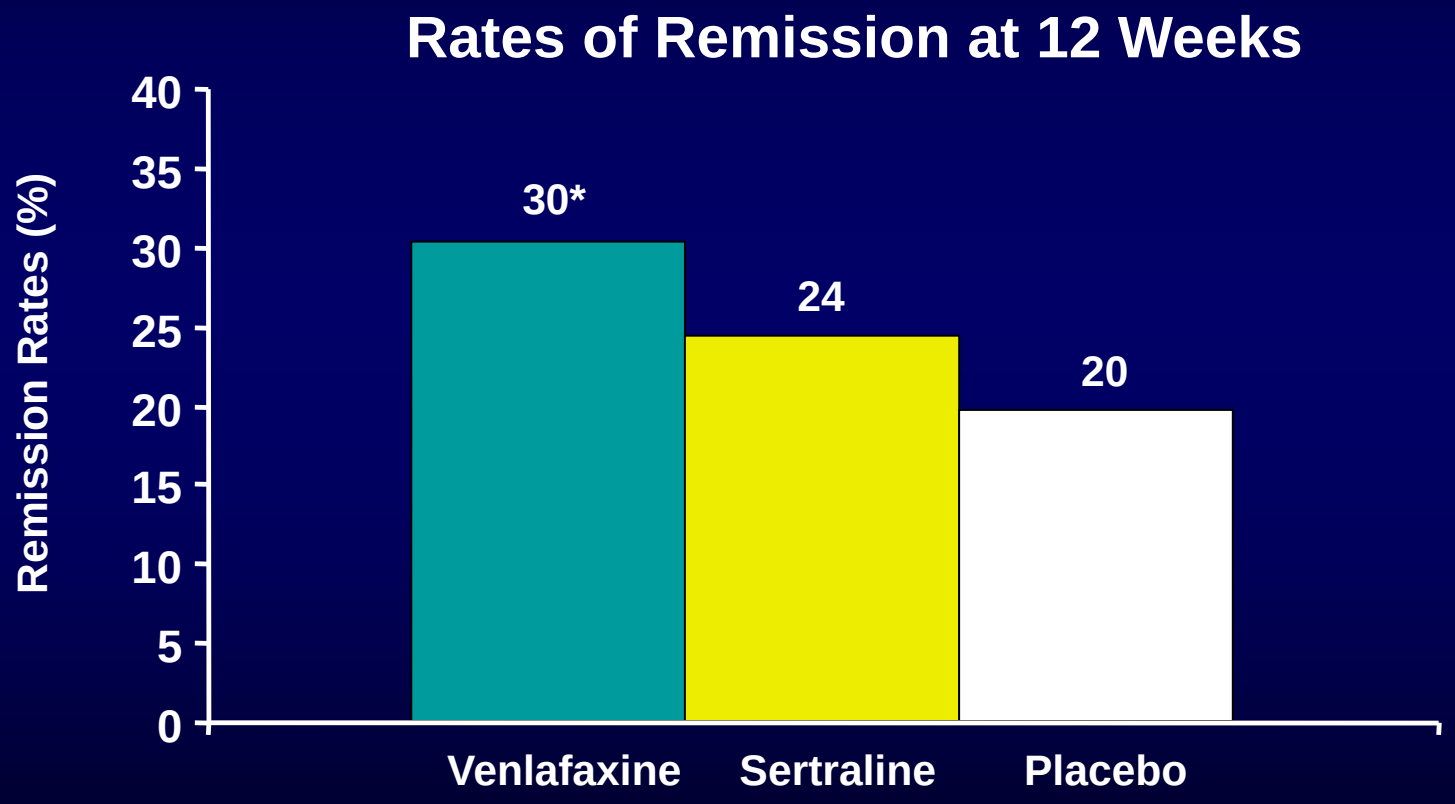
* Approved by FDA for use in PTSD (USA). ALL OTHER TREATMENTS DESCRIBED IN THIS TALK ARE NOT APPROVED FOR TREATING PTSD.

Response Rates to Paroxetine in PTSD



Marshall et al 2001

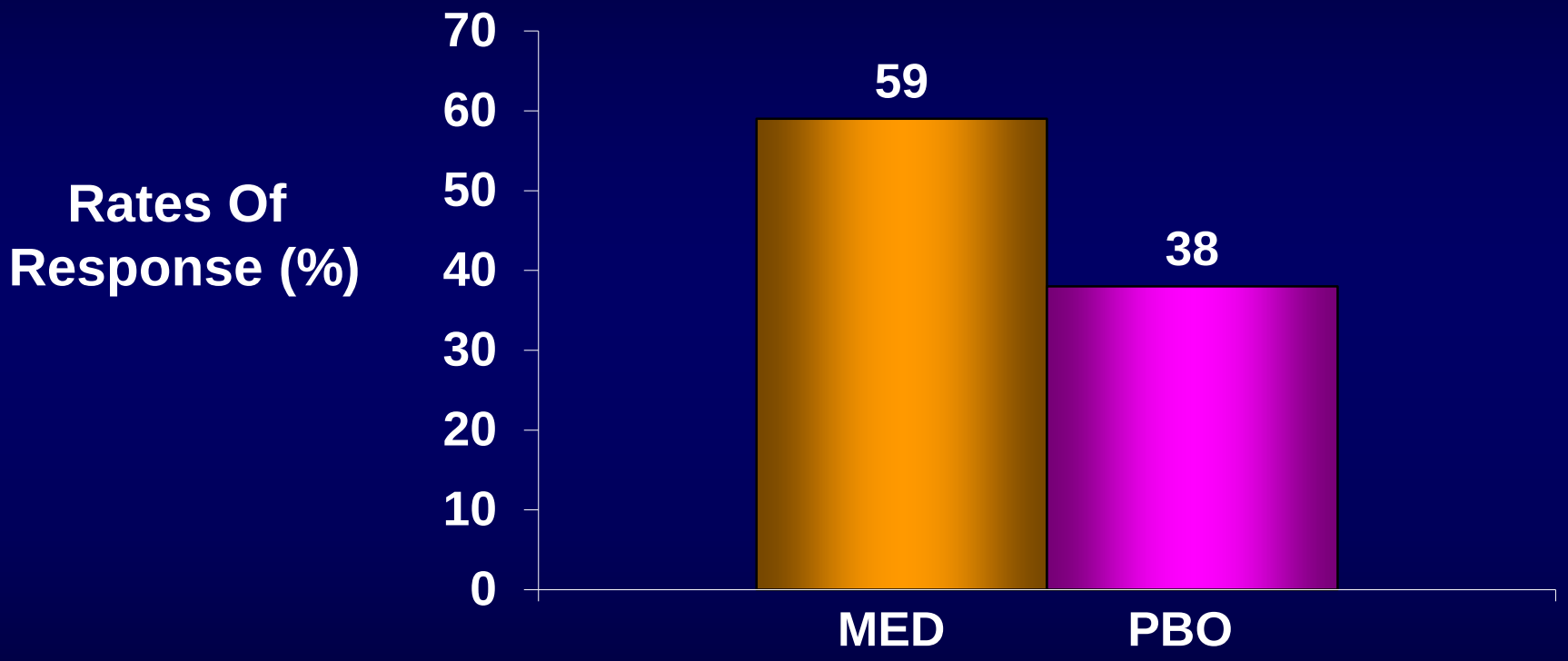
Low Remission Rates with Antidepressants in PTSD



*P=.05, Venlafaxine>Placebo

Davidson JR, et al. Arch Gen Psychiatry 2006.

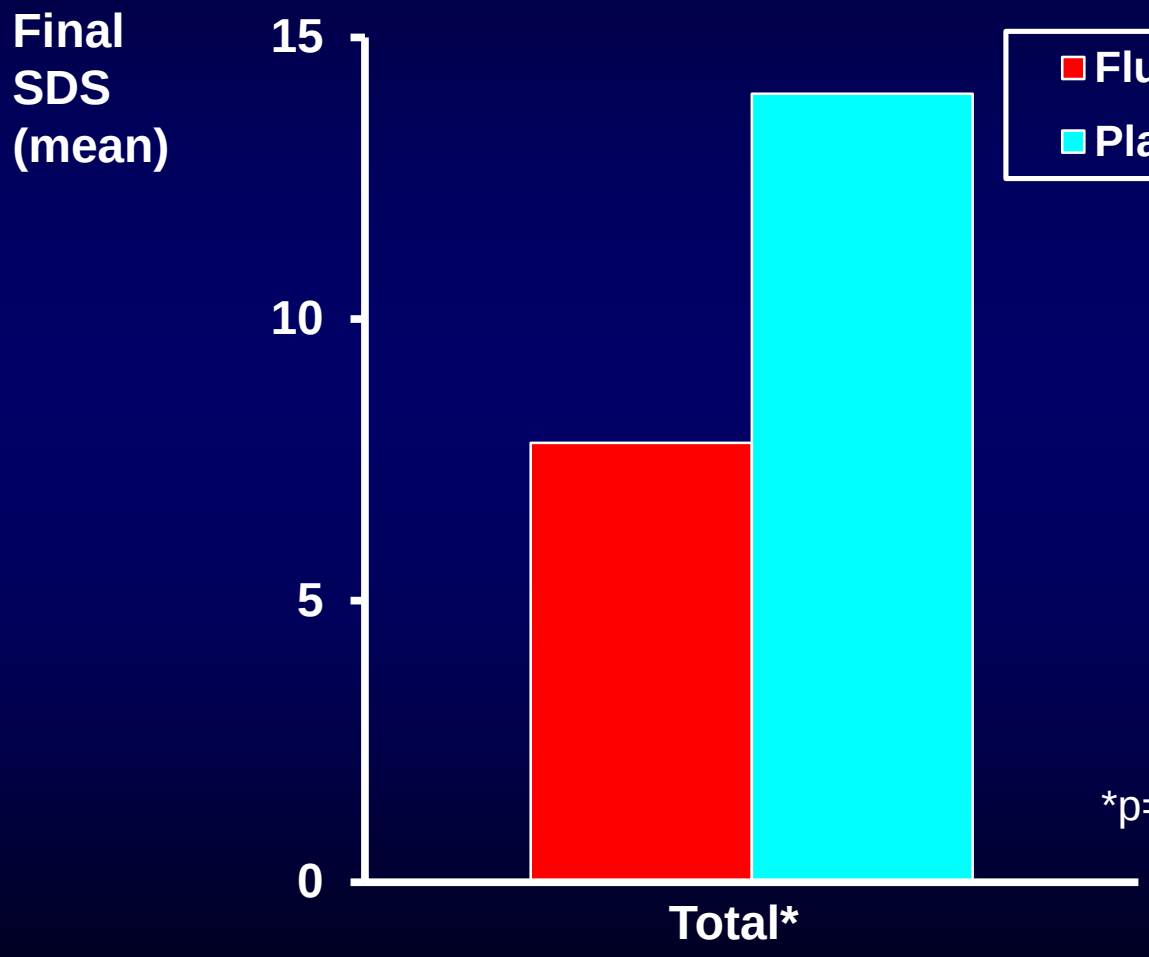
Cochrane Collaboration Review on Pharmacotherapy for PTSD



NNT = 4.85, based on 13 trials

Stein DJ et al. 2006.

Fluoxetine Efficacy in PTSD: Improvement in Disability



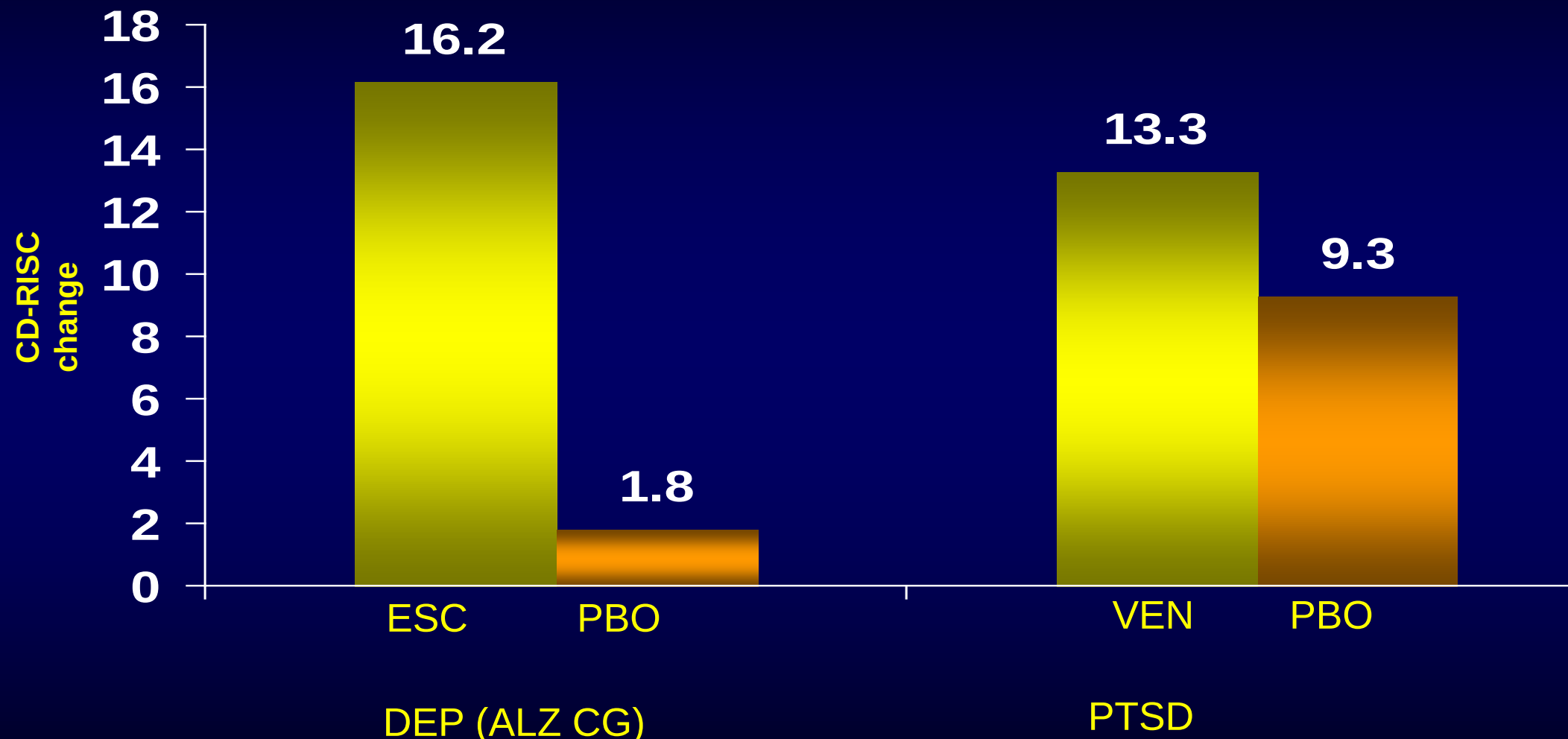
Subscales

- **work (p=0.02)**
- **family (p=0.02)**
- **social/leisure (p=0.02)**

*p=0.02; SDS, Sheehan Disability Scale

Connor et al 1999

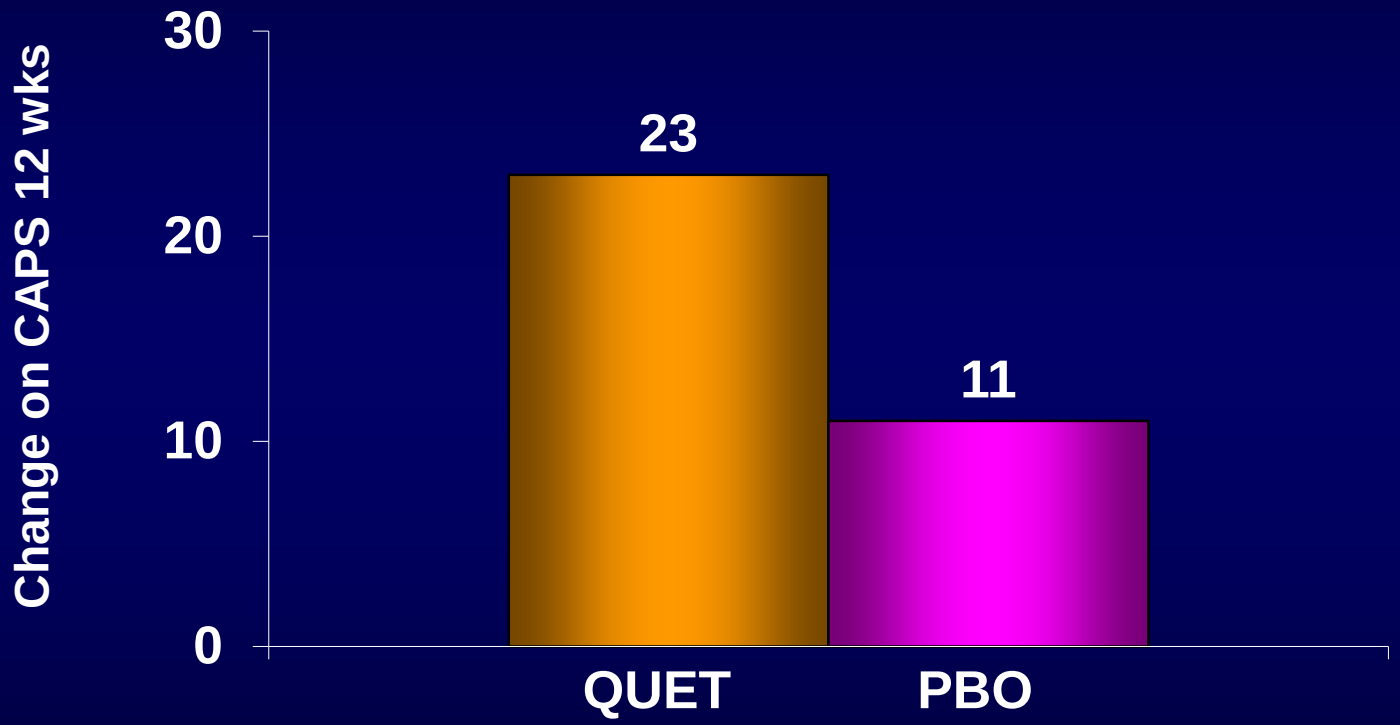
Antidepressants improve resilience in populations under stress *



*** p<0.05 both studies. ES = 0.47 and 0.35**

(Lavretsky et al 2010; Davidson et al 2008)

Quetiapine vs Placebo Monotherapy in Veterans with PTSD



n=80. QUET dose 400-800 mg. AEs = dry mouth 15%; sleepiness 13%; sedation 7%

Villareal et al. Am J Psychiatry 2016

Outline

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Mood Stabilizers/Anticonvulsants: Disappointment As Monotherapy *

- Lamotrigine (weak signal in small sample)
- Tiagabine
- Divalproex sodium
- Topiramate (mixed results)

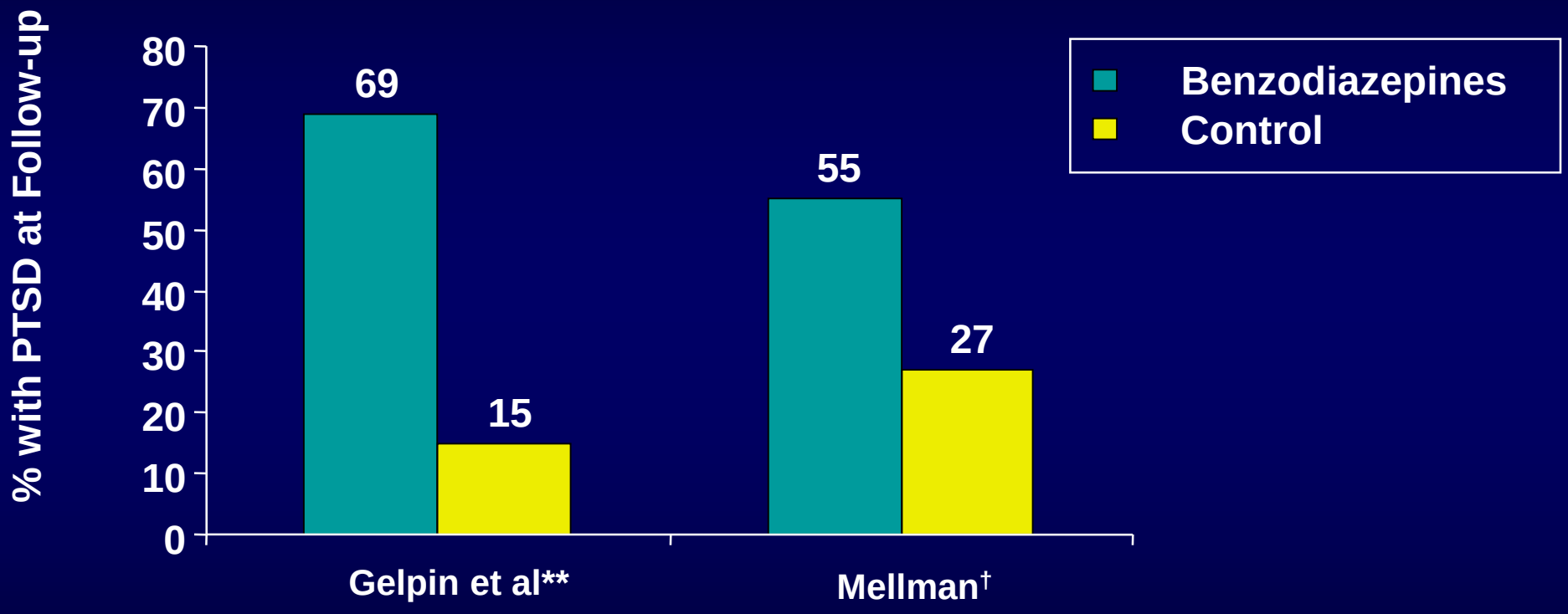
*** All were placebo-controlled – adequate samples except lamotrigine**

Other Ineffective or Equivocal Drugs for PTSD *

- Bupropion **
- Alprazolam
- Guanfacine
- Nefazodone (single positive study)
- Olanzapine

*** All were placebo-controlled – almost all in VA or military samples**
**** May have role for smoking cessation and for AD-induced sexual AEs**

Anti-Therapeutic Effects of Benzodiazepines in ASD



6 months and 6 weeks, respectively. All cases of depression occurred in benzodiazepine group*

**Gelpin E, et al. J Clin Psych 1996. Alprazolam (n = 3) or clonazepam (n = 10) vs no treatment (n = 10)
†Mellman TA, et al. J Clin Psych 2002. Temazepam (n = 11) vs placebo (n = 10).

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Other Drugs Investigated for PTSD

- **Neurosteroids**

  -ganaxolone

- **Glutamatergics**

  -ketamine, tianeptine

- **Monoaminergic**

  -prazosin, carvedilol, nepicastat

- **Tricyclic**

  -cyclobenzaprine

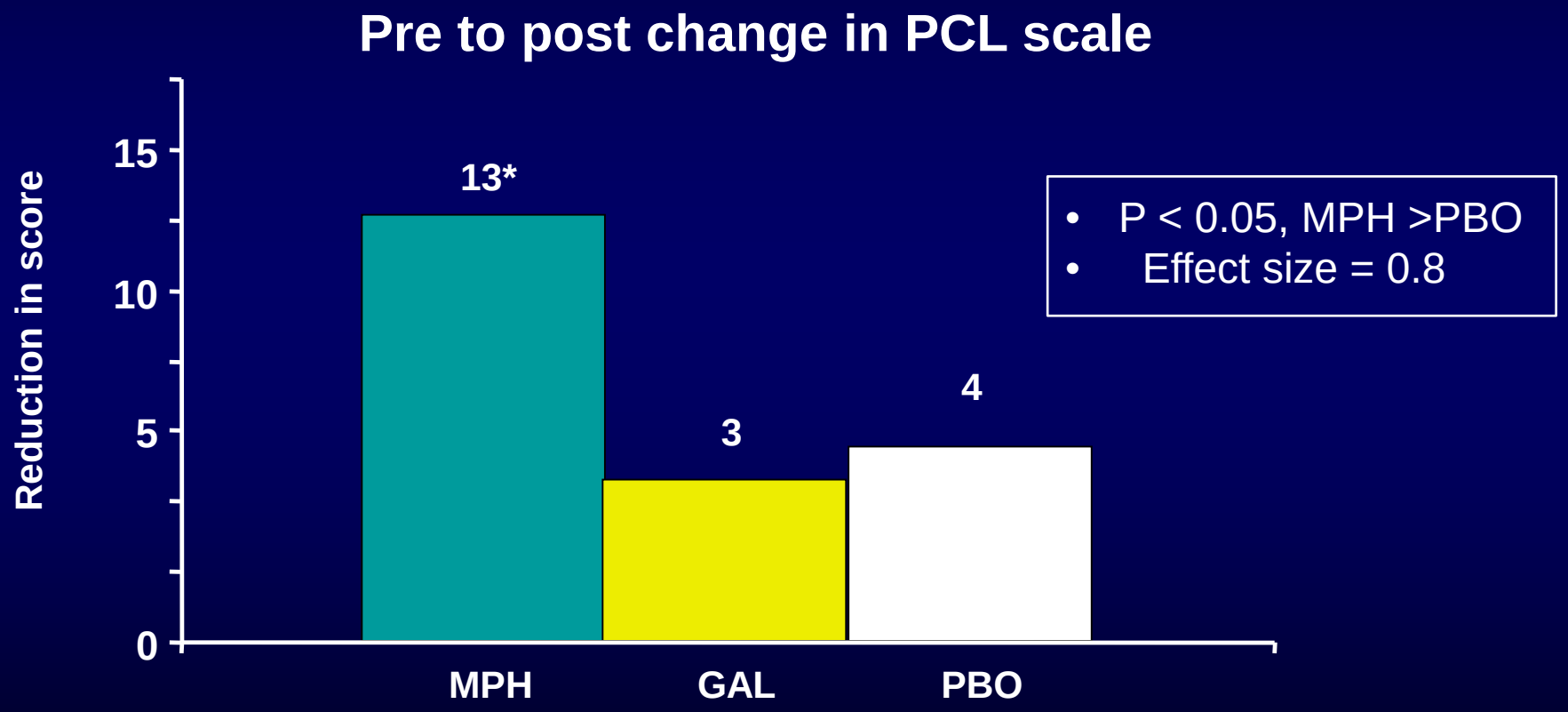
- **HPA modulators**

  -GSK561679, hydrocortisone

- **NK1 antagonists**

  -aprepitant, orvepitant, GR205171

Methylphenidate in PTSD/mTBI



McAllister et al NPP 2015.

Perspectives

Vintage treatments for PTSD: A reconsideration of tricyclic drugs

Jonathan Davidson

Psychopharm

Journal of Psychopharmacology
1–6

DOI: 10.1177/0269881114565143
jop.sagepub.com
SAGE

Abstract

Serotonin (SSRI) and serotonin-norepinephrine (SNRI) reuptake inhibitors (SSRI) are the first-line recommended drug treatments for post-traumatic stress disorder (PTSD); but despite their benefits, much residual pathology remains and no new drugs have yet emerged with a clearly demonstrated benefit for treating the disorder. A case is made that tricyclic drugs deserve a closer look, based on their ability to affect several of the main neurotransmitters that are relevant to PTSD. Their promising efficacy, which was shown 30 years ago, had not been followed up, until a recent trial of desipramine found advantages over a SSRI in PTSD with comorbid alcohol dependence. Opportunities exist for studying newer and purportedly safer tricyclic formulations, as well as further the work with older, established compounds. A reappraisal of their risk:benefit ratio seems in order, when treating PTSD.

Underutilized TCAs Deserve a Second Look in PTSD

Trimipramine – weak uptake inhibitor; favorable CV profile; 5HT2, H1, DA2 antag

Loxapine – low dose 5HT2 – favorable weight profile

Amoxapine – low dose powerful 5HT2 effects

Nortriptyline – weak AC effects and little weight gain – blood levels

Cyclobenzaprine – sublingual formulation – 5HT2a, H1, alpha-1 antag

Doxepin and amitriptyline – low dose AH effects

Tianeptine – 5HT uptake enhancer and glutamate modulator

Stahl 2008; Davidson 2015; Lee 2016

Neuropsychopharmacology (2012) 37, 996–1004

www.neuropsychopharmacology.org

Noradrenergic *vs* Serotonergic Antidepressant with or without Naltrexone for Veterans with PTSD and Comorbid Alcohol Dependence

Ismene L Petrakis*[,1], Elizabeth Ralevski[1], Nitigna Desai[2], Louis Trevisan[1], Ralitza Gueorguieva[1], Bruce Rounsaville[1,3] and John H Krystal[1]

[1]VA Connecticut Healthcare System, Yale University School of Medicine, West Haven, CT, USA; [2]Bedford VA Medical Center, Boston University School of Medicine, Boston, MA, USA

Superiority of DMI over PAROX in Veterans with PTSD and Alcohol Dependence

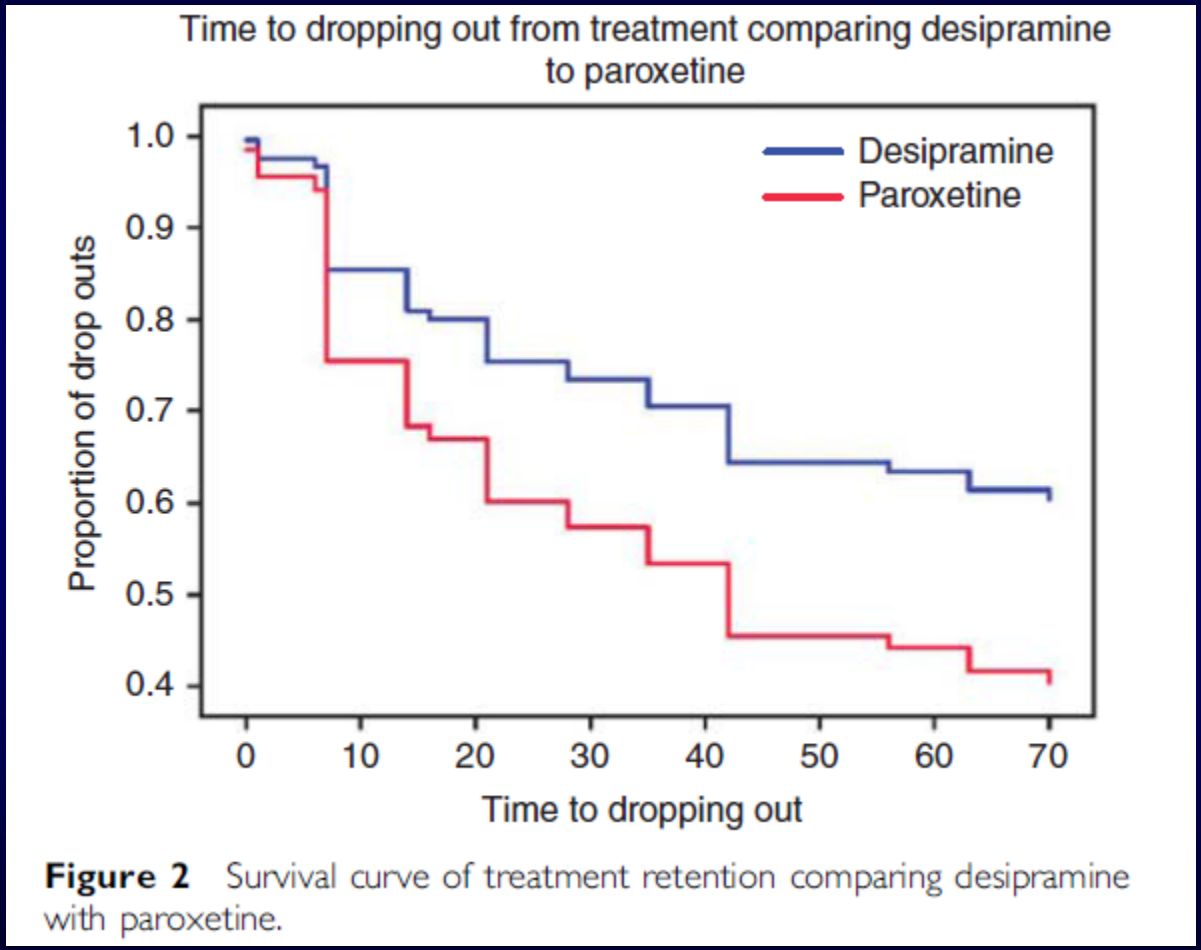


Figure 2 Survival curve of treatment retention comparing desipramine with paroxetine.

Petrakis et al. NPP 2012

Superiority of DMI over PAROX in Veterans with PTSD and Alcohol Dependence

- Study retention
- Percent of heavy drinking days
- Drinks per drinking days
- Number of drinks per week
- Similar CAPS reductions (Δ = 36 and 33 DMI & PAR)
- “NE uptake inhibitors may present advantages when treating male veterans with PTSD and AD”

Petrakis et al 2012

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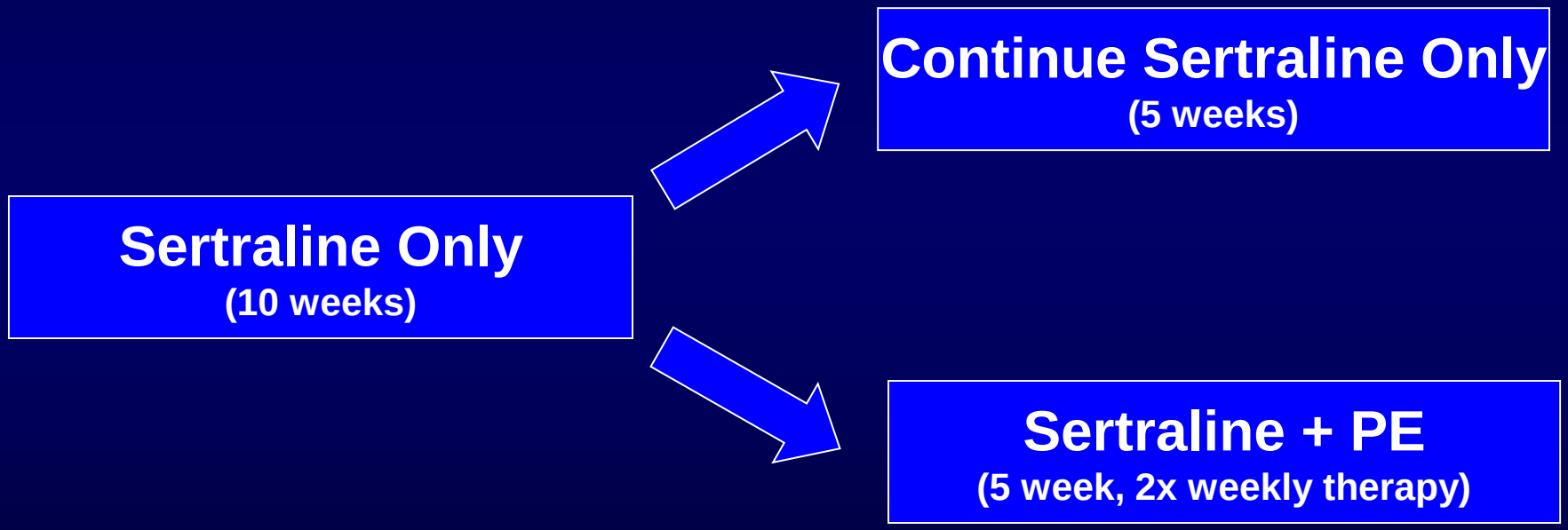
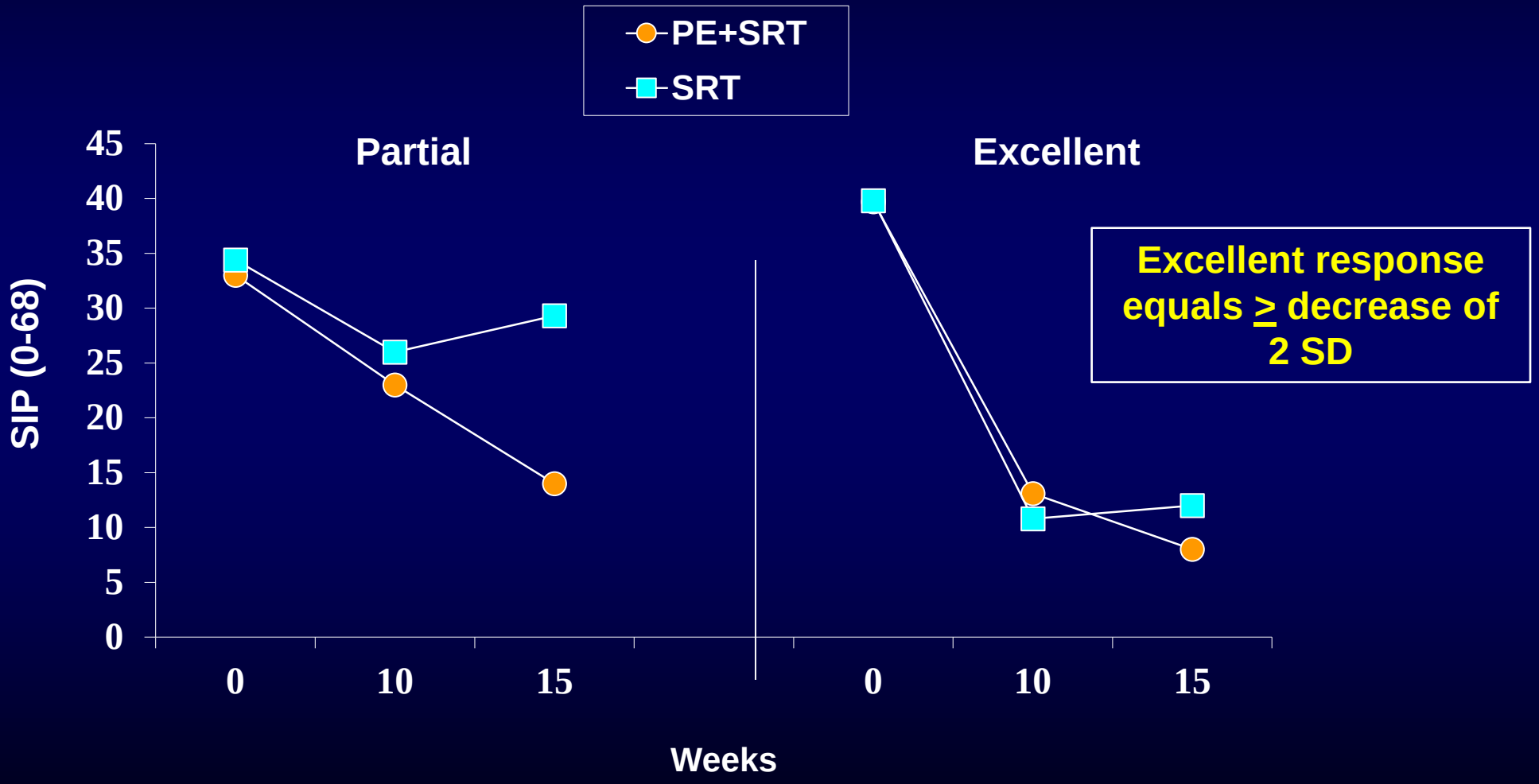
CBT augmentation of sertraline in PTSD



PTSD: PE Following Partial or Excellent SRT Response

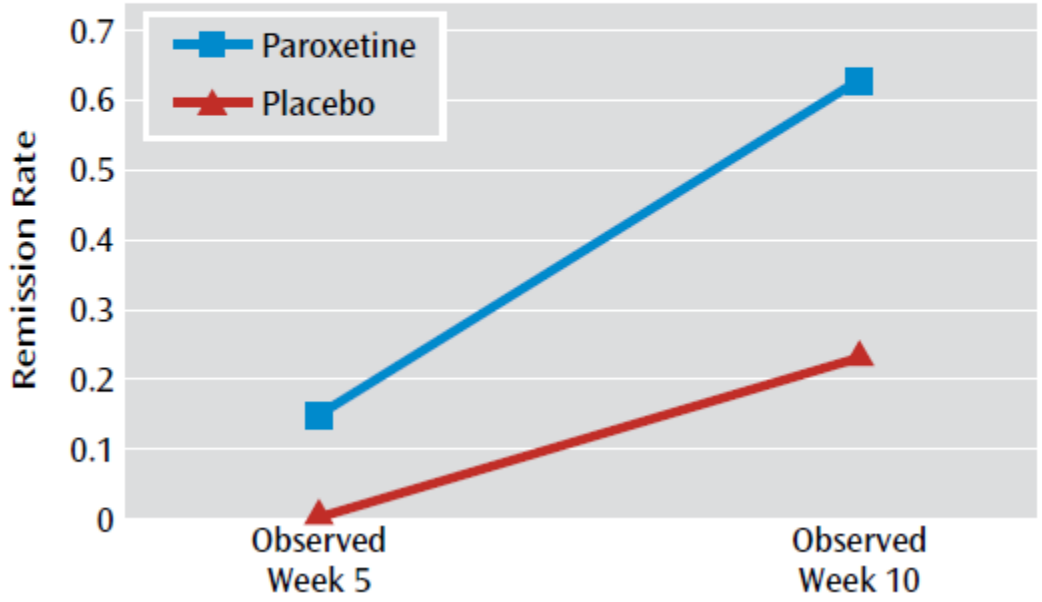
Completer Sample (n=42)



Rothbaum et al J Tr Stress

Combined Prolonged Exposure Therapy and Paroxetine for PTSD Related to the World Trade Center Attack: A Randomized Controlled Trial

FIGURE 3. Remission Rates During Acute Treatment With Prolonged Exposure Therapy Plus Paroxetine or Prolonged Exposure Therapy Plus Placebo Among Patients With PTSD Related to the World Trade Center Attack



Schneier et al AJP 2011

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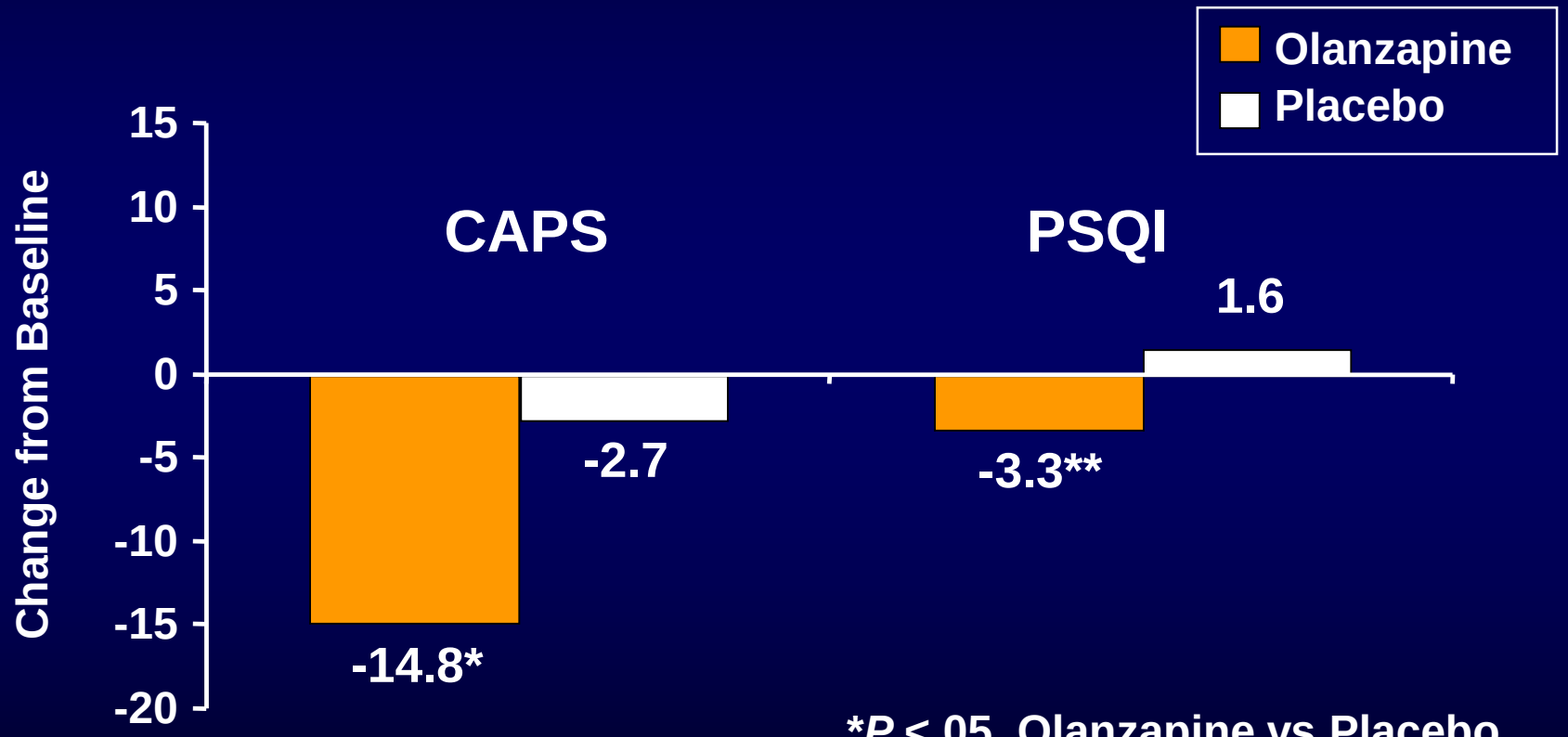
Are Two Drugs Better Than One?:

Use in Combination or Augmentation

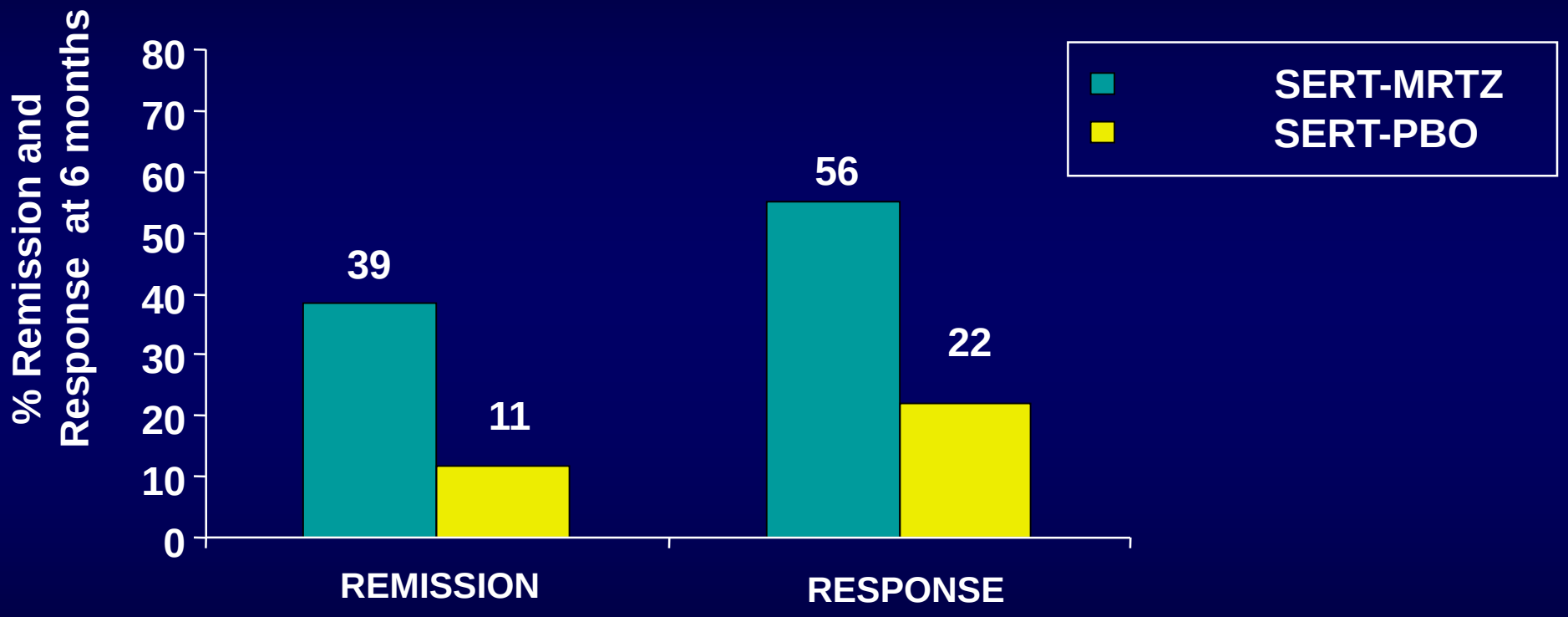
Adjunctive Olanzapine for SSRI-Resistant Combat-Related PTSD



*P <.05, Olanzapine vs Placebo
**P=.01, Olanzapine vs Placebo

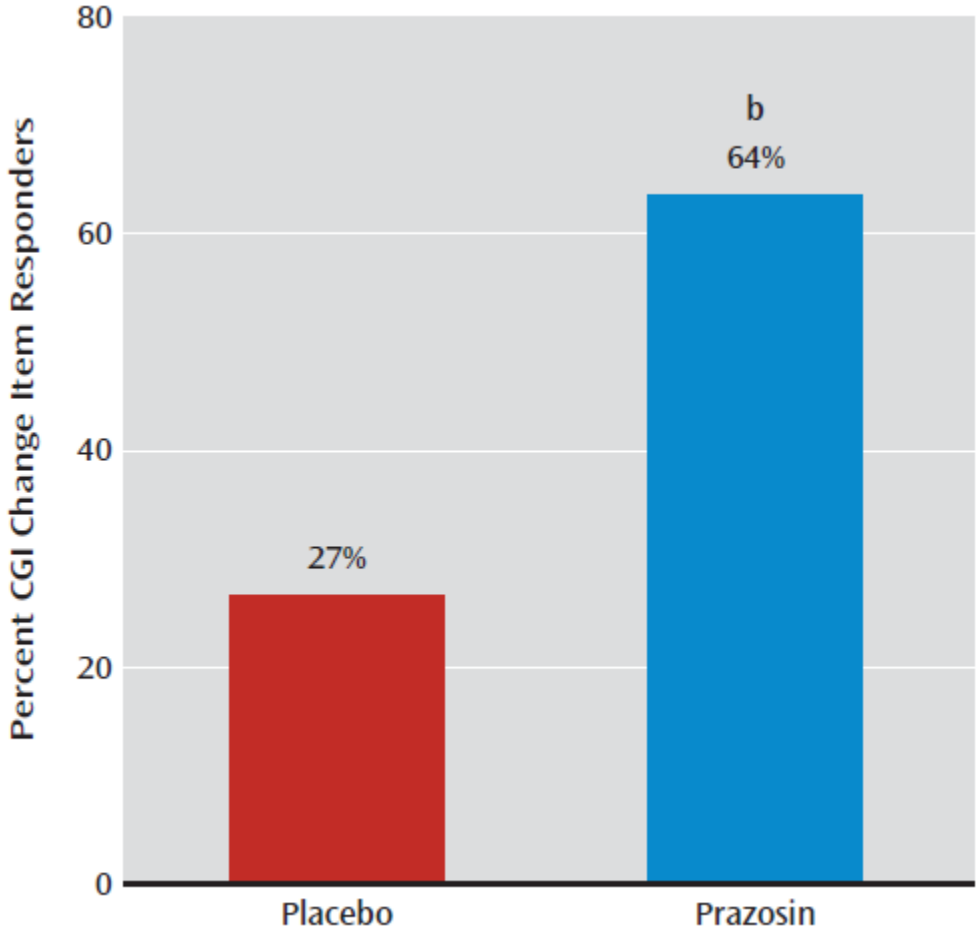
Stein MB, et al. Am J Psychiatry. 2002 Oct;159(10):1777-9.

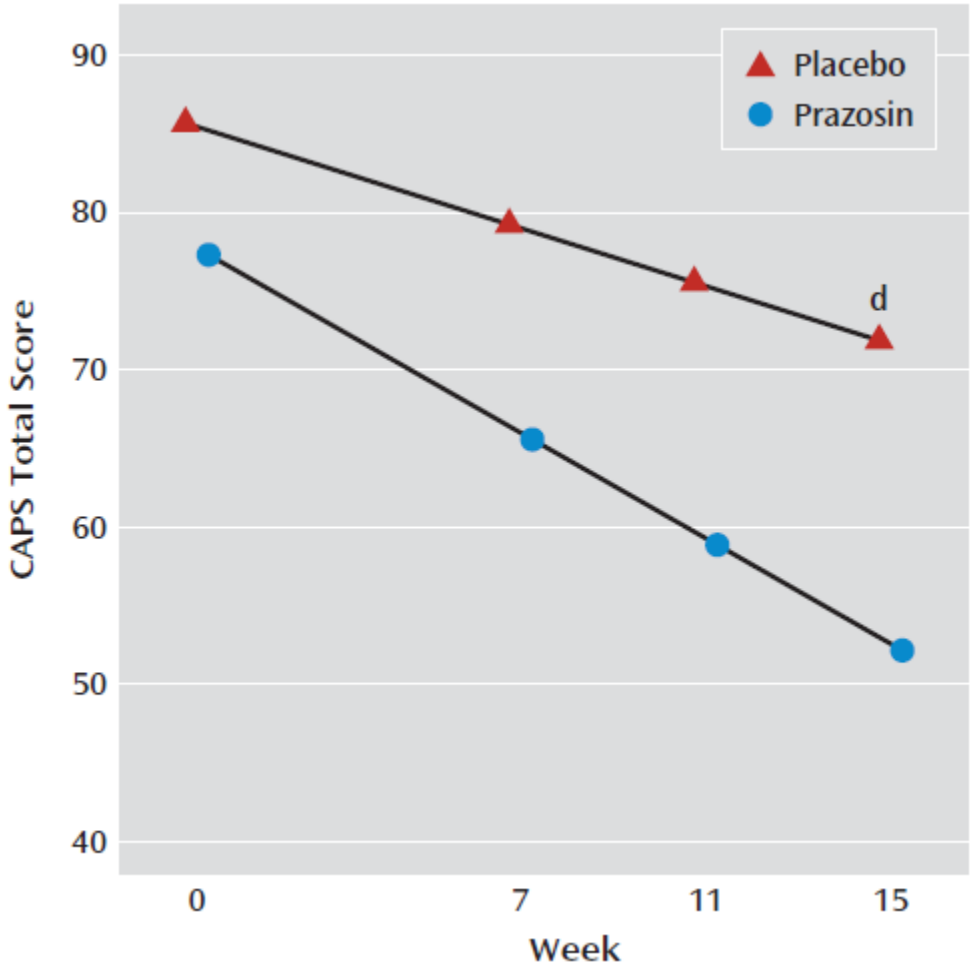
Sertraline-Mirtazapine vs Sertraline-Placebo in PTSD



Schneier et al – Depr Anx 2015

Prazosin vs Placebo in Active Duty Soldiers



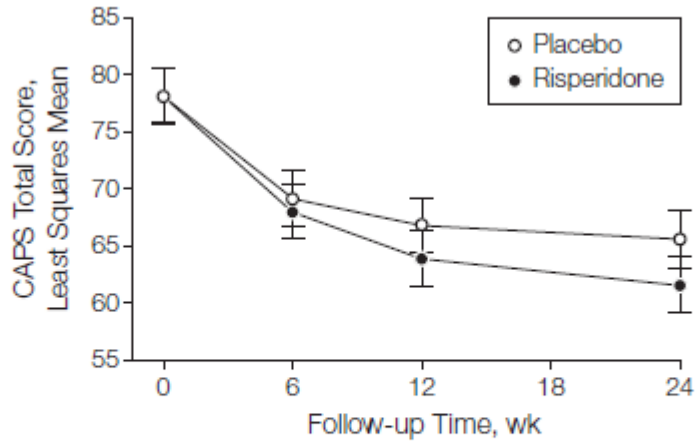


Raskind et al AJP 2013

Adjunctive Risperidone Treatment for Antidepressant-Resistant Symptoms of Chronic Military Service–Related PTSD

A Randomized Trial

Figure 2. Change in CAPS Total Score During Treatment



No. of patients				
Placebo	134	122	127	124
Risperidone	133	128	122	123

CAPS indicates Clinician-Administered Posttraumatic Stress Disorder Scale. Error bars indicate 95% confidence intervals.

Krystal et al JAMA 2011

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Relapse Prevention and SSRIs in PTSD*

	Rates of Relapse (%)		
	DRUG	PBO	NNT
Sertraline	5	26	4.8
Fluoxetine	6	16	9.7
Fluoxetine	22	50	3.6
All	9	27	5.6

* 12-15 month PBO-controlled relapse prevention; NNT, number needed to treat

Davidson JRT, et al. J Clin Psychopharmacology 2005

Conclusions

- Antidepressants > placebo
- Clear benefit but residual morbidity a problem
- Other drug groups uncertain benefit
- Atypical APs and prazosin still promising
- Long term Rx with SRIs prevent relapse
- Need exists for development of new treatments