POST-TRAUMATIC STRESS DISORDER

Comorbidity and Treatment

American Society of Clinical Psychopharmacology, Inc.
(ASCP)
Model Curriculum, 6th Edition 2010

Thomas A. Mellman, M.D.
Howard University, Washington DC

R. Bruce Lydiard PhD, MD
Clinical Professor of Psychiatry at the Medical University of South Carolina

Howard H. Fenn, MD
Clinical Associate Professor (affiliated), Stanford University

Major Teaching Points

- PTSD develops in a substantial minority of individuals exposed to severe trauma and is highly comorbid with other psychiatric disorders
- SSRI medications have FDA approval for PTSD and efficacy for some PTSD subpopulations
- An Alpha-1 adrenergic antagonist (prazosin) has been found beneficial in reducing PTSD symptoms which disrupt sleep
- Other antidepressants, new generation antipsychotic medications, noradrenergic antagonists, and mood stabilizers have a role in treating some PTSD cases
- Cognitive behavioral therapy is an important evidence-based intervention for PTSD

Pre-Lecture Exam
Question 1

True or False:

1. The prevalence of PTSD is higher in women than men.

Pre-Lecture Exam
Question 2

True or False:

1. All individuals exposed to severely threatening trauma will develop PTSD.

Pre-Lecture Exam Question 3

True or False:

1. Cortisol activity in chronic PTSD is similar to major depression.

Question 4

1. **The psychosocial PTSD treatment with the strongest evidence for efficacy is:**

A. EDMR

B. Breathing relaxation

C. Exposure

D. Thought-stopping

Question 5

1. **The weakest evidence for efficacy for PTSD is for which class of pharmacological agents:**

A. SSRI’s

B. TCA’s

C. MAOI’s

D. Benzodiazepines

E. Risperidone

Overview

I. Epidemiology
II. Diagnosis
III. Psychiatric Comorbidity
IV. Treatment

Post-Traumatic Stress Disorder (PTSD)

Lifetime prevalence in community of 1% to 14%, recent estimates from NCS of 7-8%; in US citizens lifetime prevalence: 8% (1)

PTSD is associated with sexual abuse, physical assault, military combat, torture, accidental trauma, natural or man-made disasters, diagnosis of threatening illness (2)

1. Vieweg WV, Julius DA, Fernandez A, Beatty-Brooks M, Hettema JM, Pandurangi AK. **Posttraumatic stress disorder: clinical features, pathophysiology, and treatment. Am J Med. May;119(5):383-90.**

2. American Psychiatric Association, 1994
Kessler et al., '95, 05

POST-TRAUMATIC STRESS DISORDER

A characteristic set of symptoms following exposure to extreme traumatic stress

1. **experience, witness, or confronted with actual or threatened death or injury**
2. **Response involves intense fear, helplessness, or horror**

Duration more than one month

Significant functional impairment

POST-TRAUMATIC STRESS DISORDER

Re-experiencing symptoms (need 1)

1. intrusive recollections
2. trauma-related nightmares
3. flashbacks
4. psychological distress with reminders
5. physiologic reactivity with reminders

POST-TRAUMATIC STRESS DISORDER

Avoidance symptoms (need 3)

1. avoid thoughts/feelings/conversations
2. avoid activities, places, people
3. inability to remember
4. diminished interest
5. feelings of detachment
6. restricted affect
7. foreshortened future

POST-TRAUMATIC STRESS DISORDER

Arousal symptoms (need 2)

1. impaired sleep initiation/maintenance
2. irritability
3. concentration
4. hypervigilance
5. exaggerated startle

PTSD

Associated Features

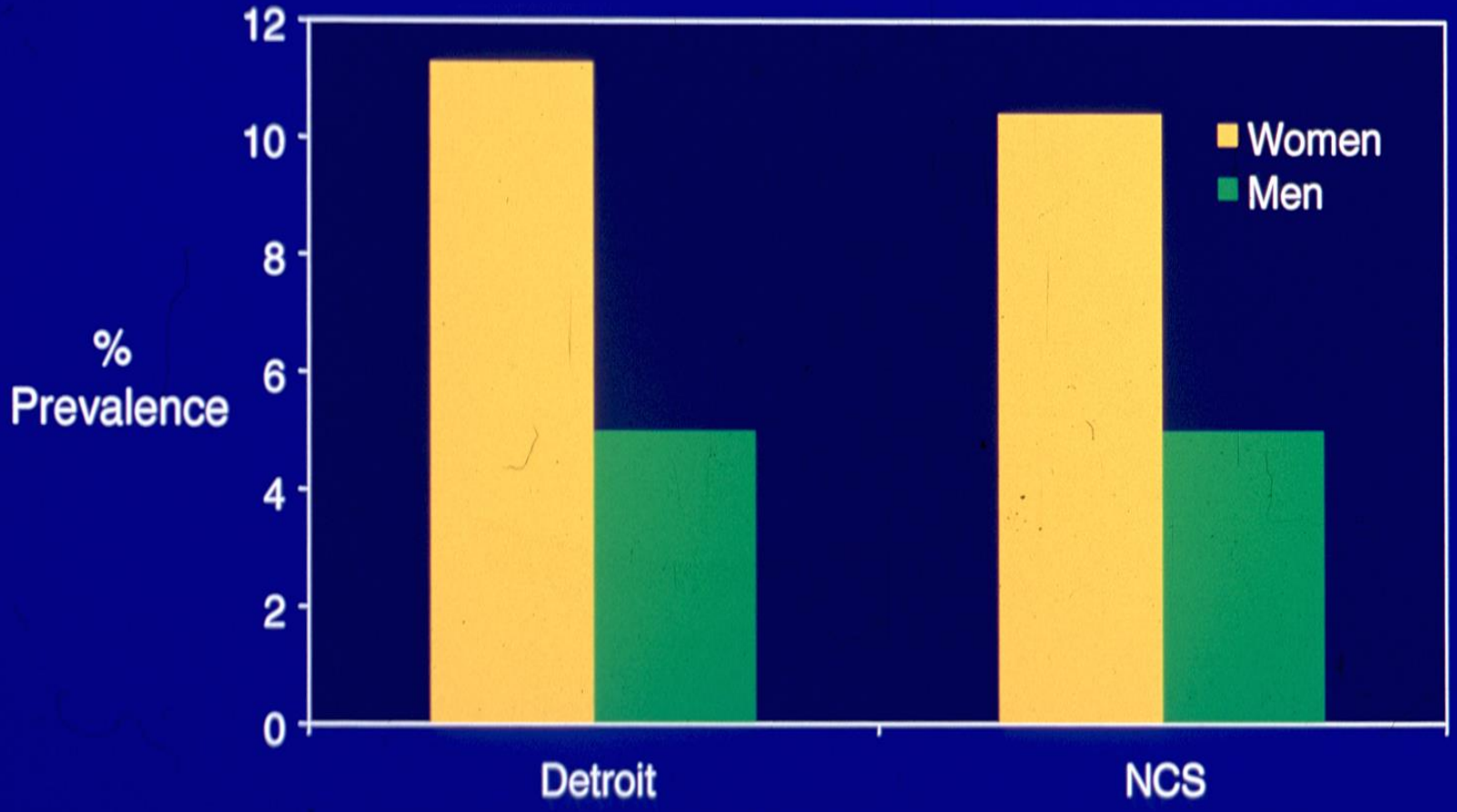
1. Alcohol/drug problems
2. Aggression/violence
3. Suicidal ideation, intent, attempts
4. Dissociation
5. Distancing
6. Problems at work
7. Marital problems
8. Homelessness

Lifetime Prevalence of DSM-III-R Major Psychiatric Disorders
NCS Data

	%
Mood Disorders	
Major depressive episode	17.1
Dysthymia	6.4
Manic episode	1.6
Anxiety Disorders	
Social phobia	13.3
Simple phobia	11.3
PTSD	7.8
Agoraphobia without panic	5.3
GAD	5.1
Panic disorder	3.5
Substance Use Disorders	
Alcohol abuse/dependence	23.5
Drug abuse/dependence	11.9

Adapted from: Kessler et al. Arch Gen Psychiatry. 1994;51:8–19.
Kessler et al. Arch Gen Psychiatry. 1995;52:1048–1060.

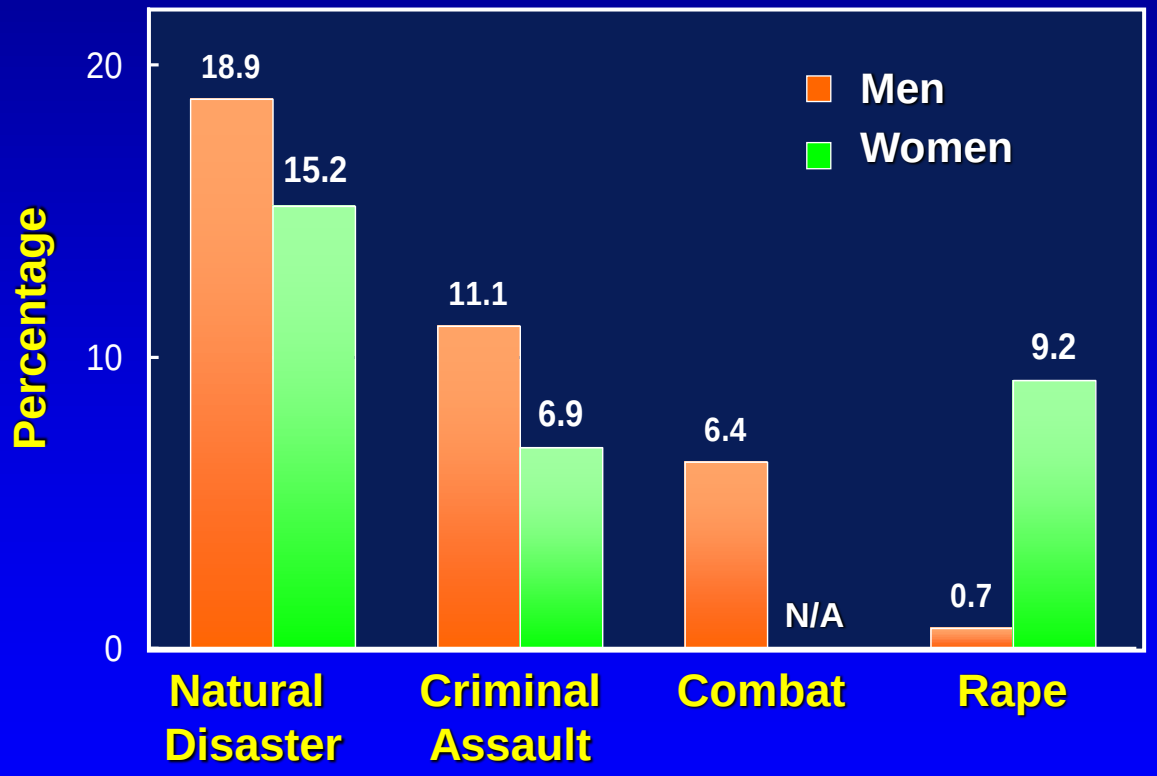
Lifetime Prevalence of PTSD



Breslau et al. *Arch Gen Psychiatry.* 1991;48:216-222.
Kessler et al. *Arch Gen Psychiatry.* 1995;52:1048-1060.

PTSD

Risks of Specific Traumas in the US Population



Kessler RC et al. *Arch Gen Psychiatry*. 1995;52:1048–1060.

PTSD

Risk Factors for PTSD

Severity of trauma (i.e., threat, duration, injury, loss)

Prior trauma

Gender

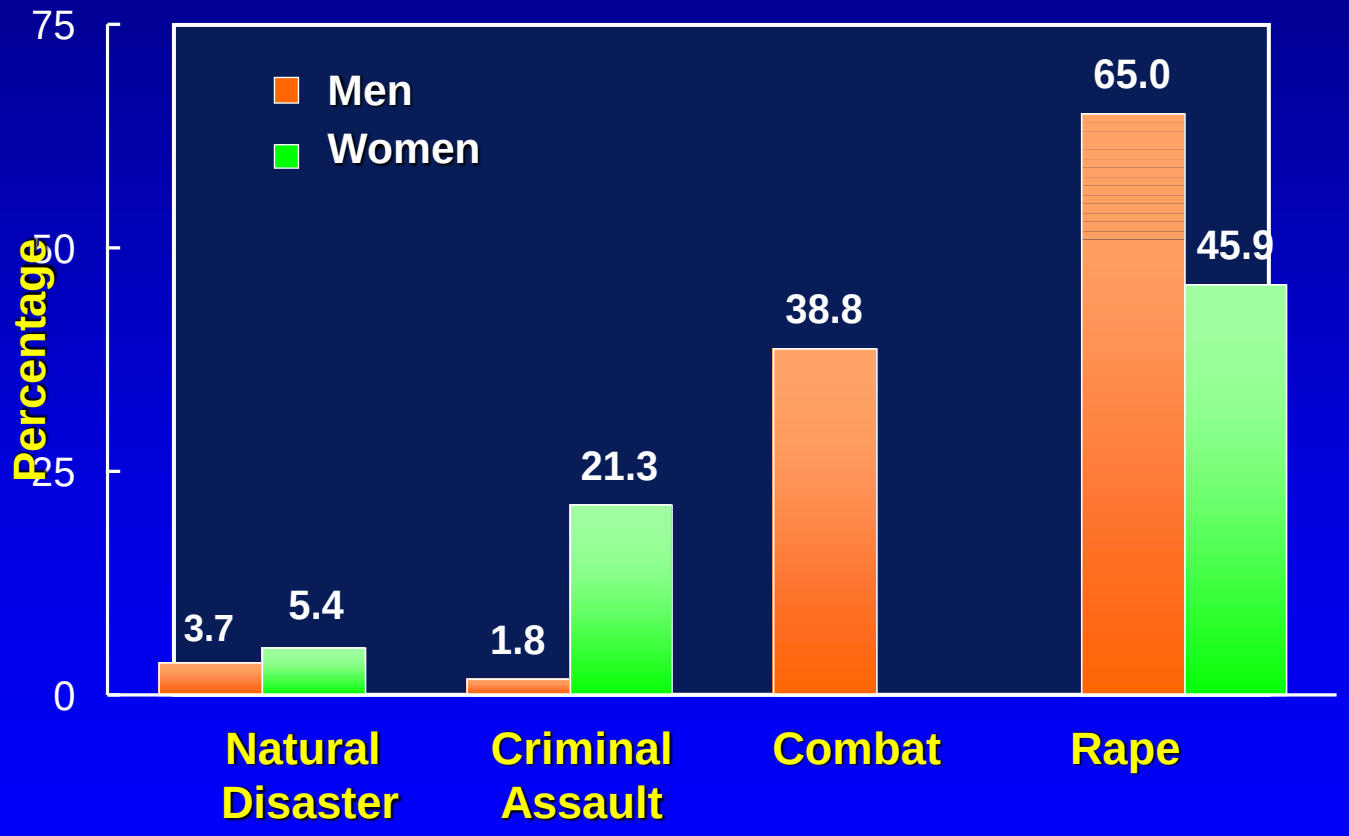
Prior mood and/or anxiety disorders

Family history of mood or anxiety disorders

Low Education

PTSD

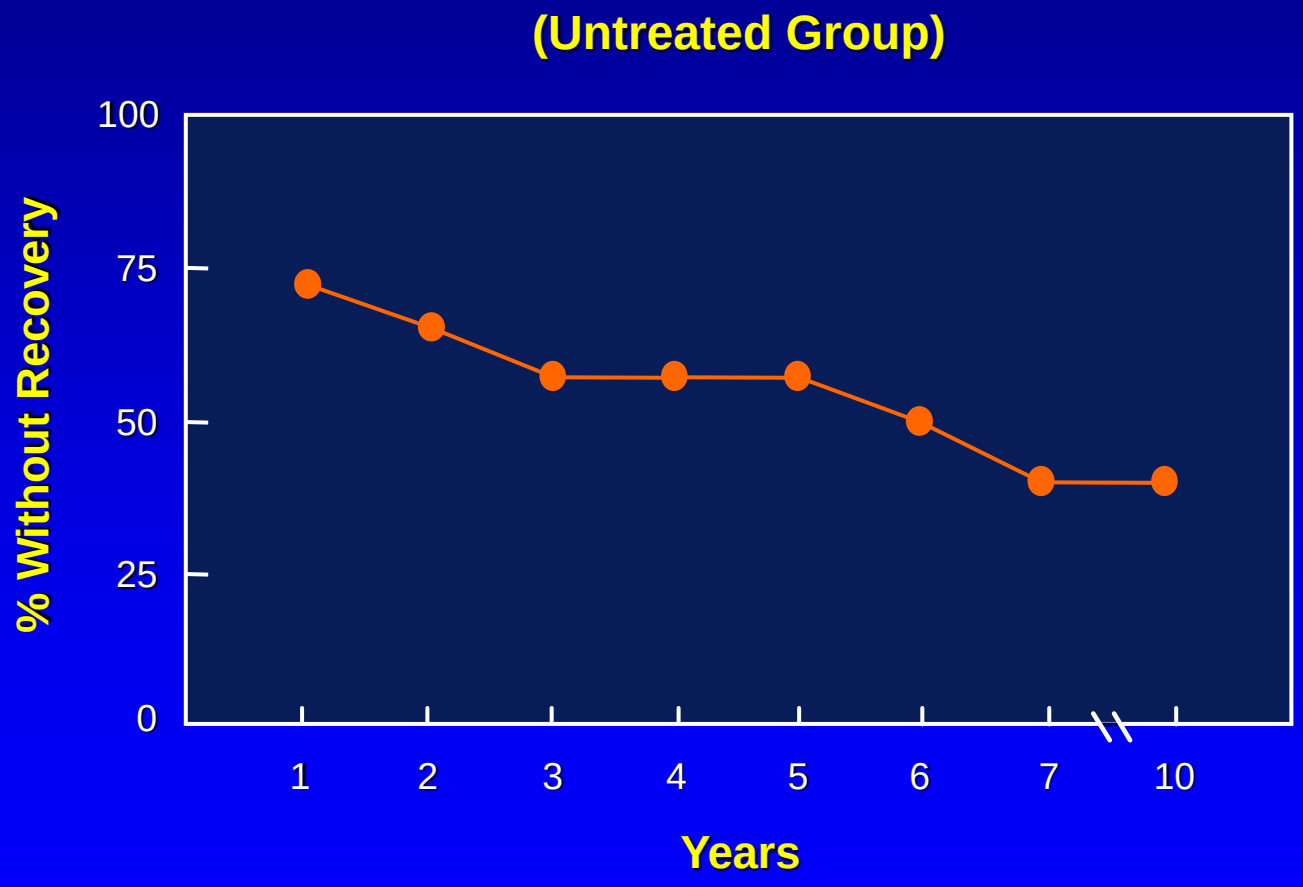
Rates Related to Specific Traumas



Kessler RC et al. *Arch Gen Psychiatry*. 1995;52:1048–1060.

PTSD

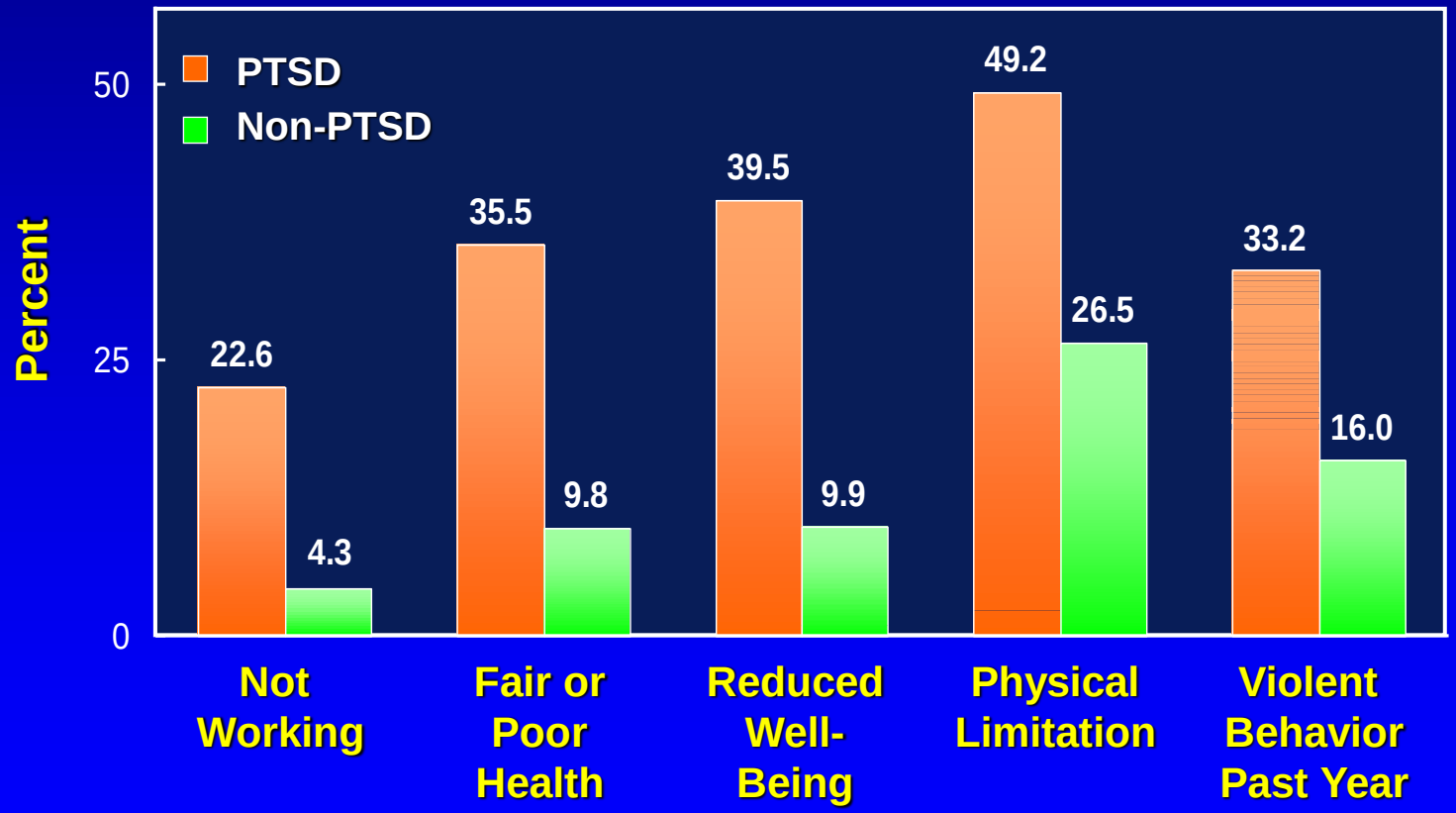
Persistence Over Time



Kessler RC et al. *Arch Gen Psychiatry*. 1995;52:1048–1060.

PTSD

Function and Quality of Life In VietnamVeterans With and Without PTSD



Zatzick DF et al. *Am J Psychiatry*. 1997;154:1690–1695.

PTSD

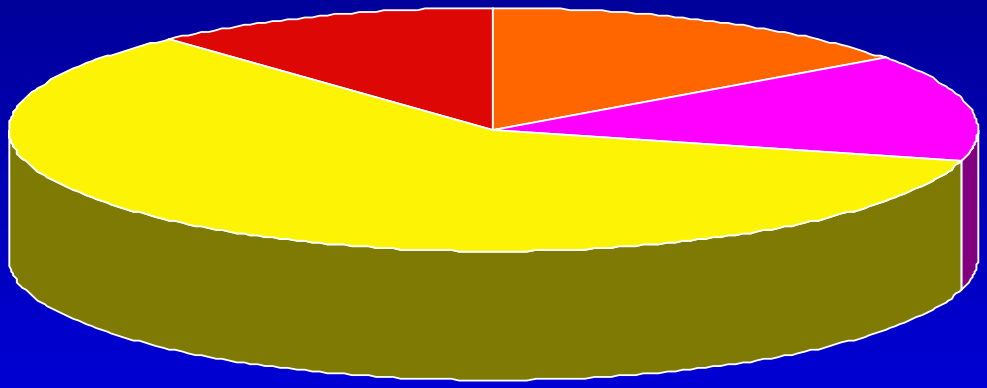
Psychiatric Comorbidity

	Lifetime Rates (%)			
	Men		Women	
	PTSD	Non-PTSD	PTSD	Non-PTSD
Depression	48	12	48	19
Mania	12	1	6	1
Panic Disorder	7	2	13	4
Social Phobia	28	11	28	14
GAD	17	3	15	6
Alcohol Abuse/Dependency	52	34	28	13
Substance Abuse/Dependency	34	15	27	8
Any Diagnosis	88	55	79	46

Kessler RC et al. *Arch Gen Psychiatry*. 1995;52:1048–1060.

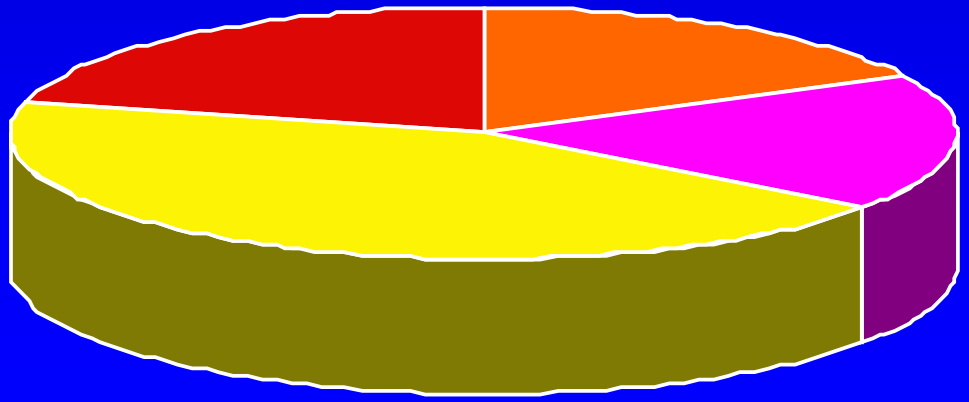
Comorbidity in PTSD
National Comorbidity Study

MEN



1 Other Diagnoses
2 Other Diagnoses
3 Other Diagnoses
No Other Diagnosis

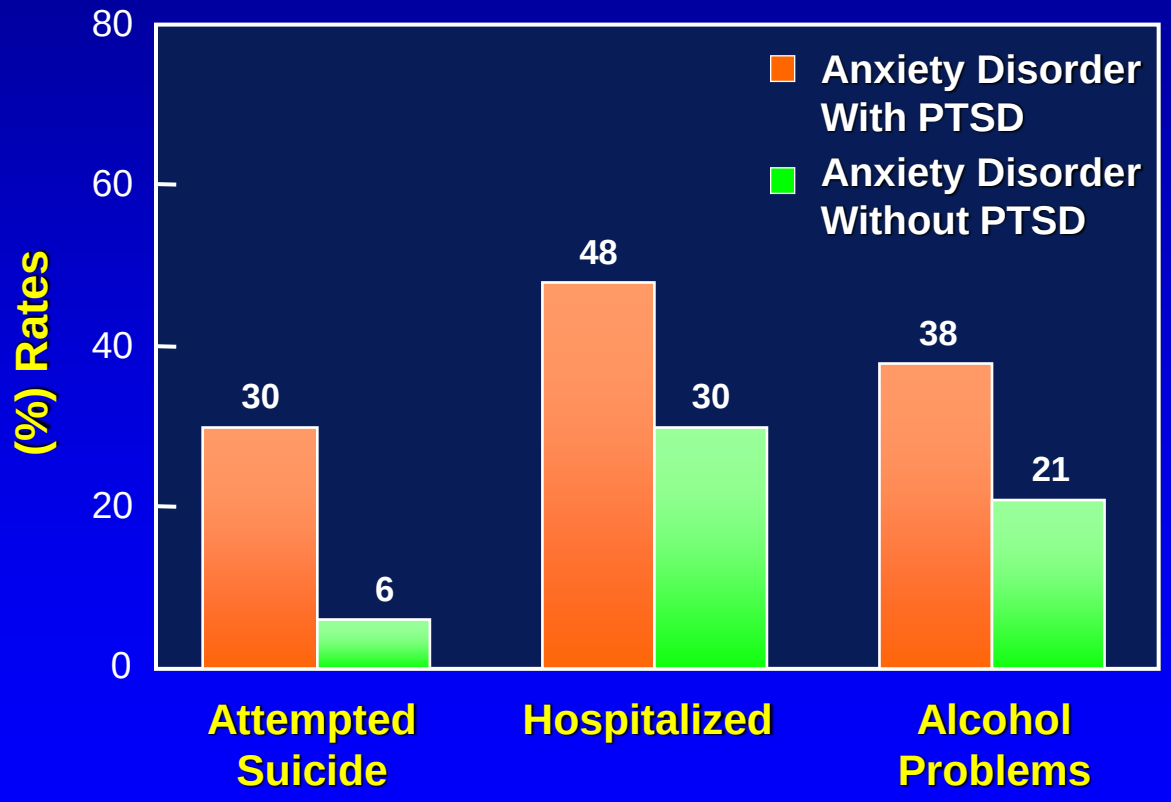
WOMEN



1 Other Diagnoses
2 Other Diagnoses
3 Other Diagnoses
No Other Diagnosis

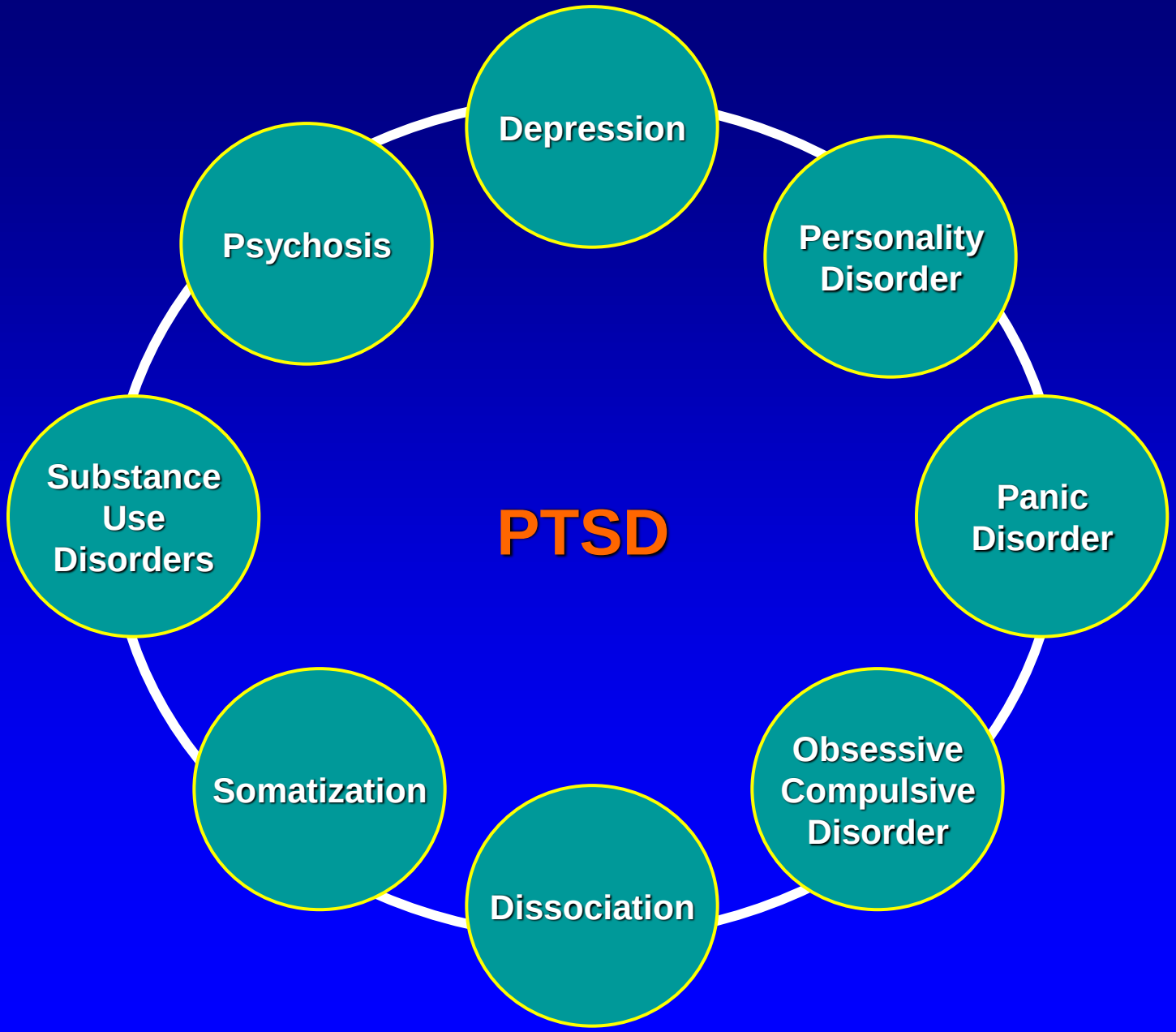
PTSD

Impact of Comorbid PTSD in Subjects With Other Anxiety Disorders



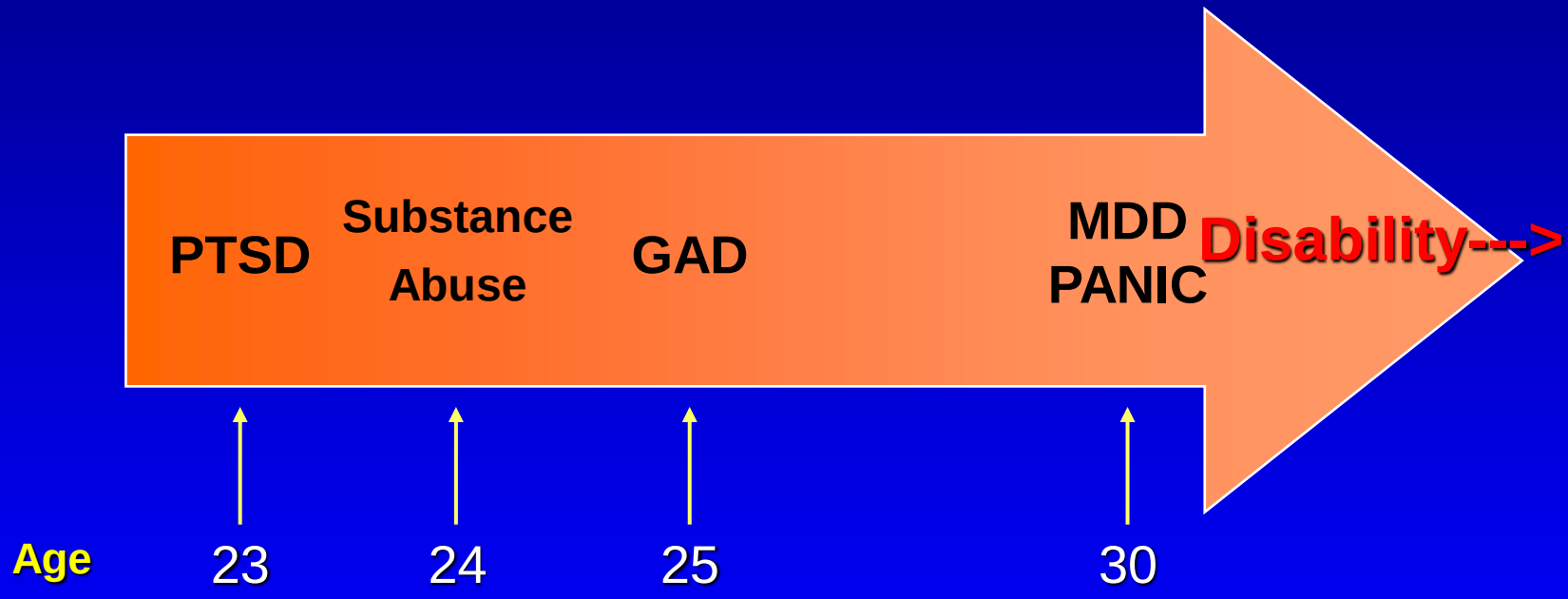
Warshaw MG et al. *Am J Psychiatry*. 1993;150:1512–1516.

DIAGNOSTIC SPECTRA



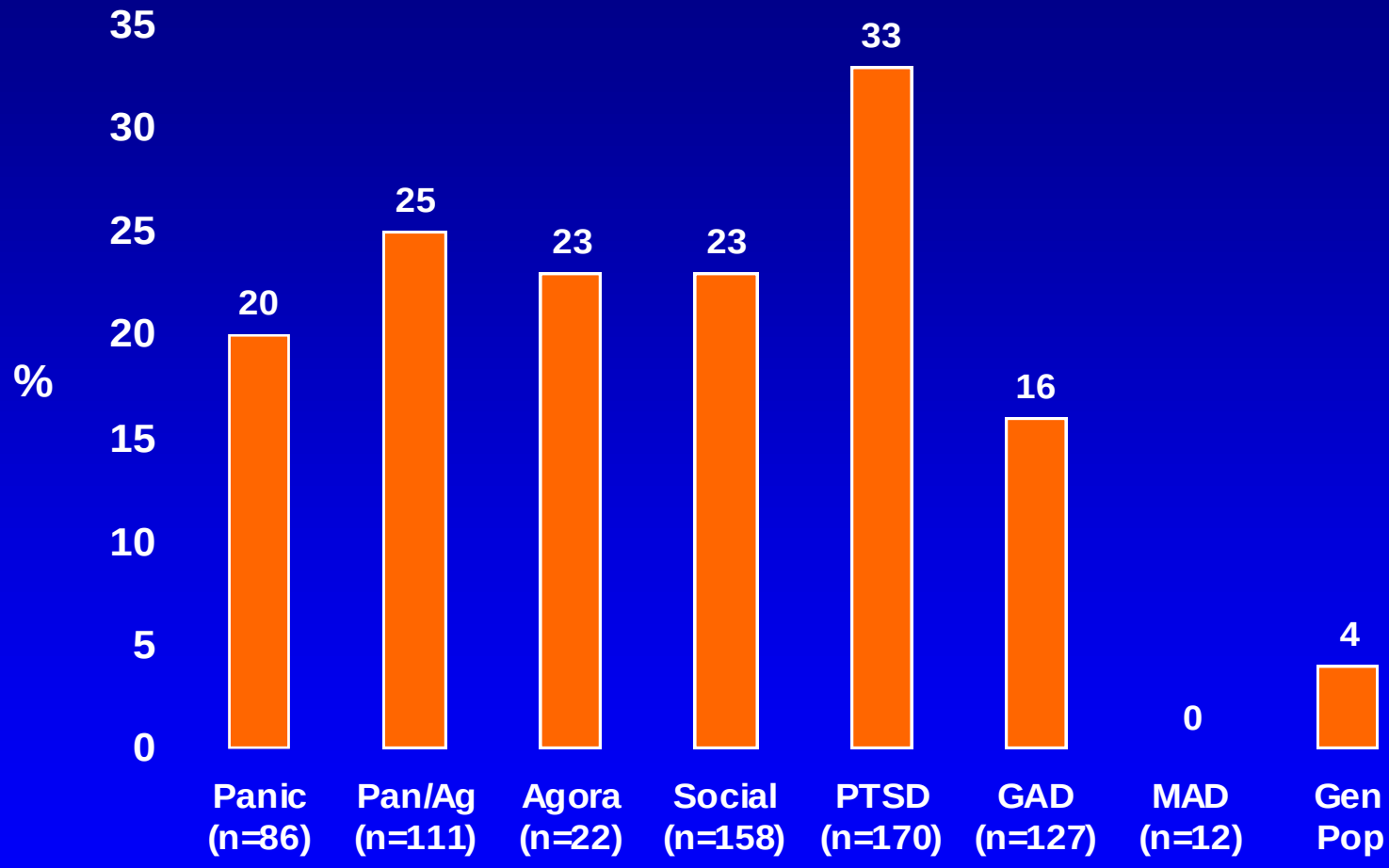
PTSD

Model Sequence of Comorbidity



Davidson JR et al. *Compr Psychiatry*. 1990;31:162–170.
Mellman TA et al. *Am J Psychiatry*. 1992;149:1568–1574.

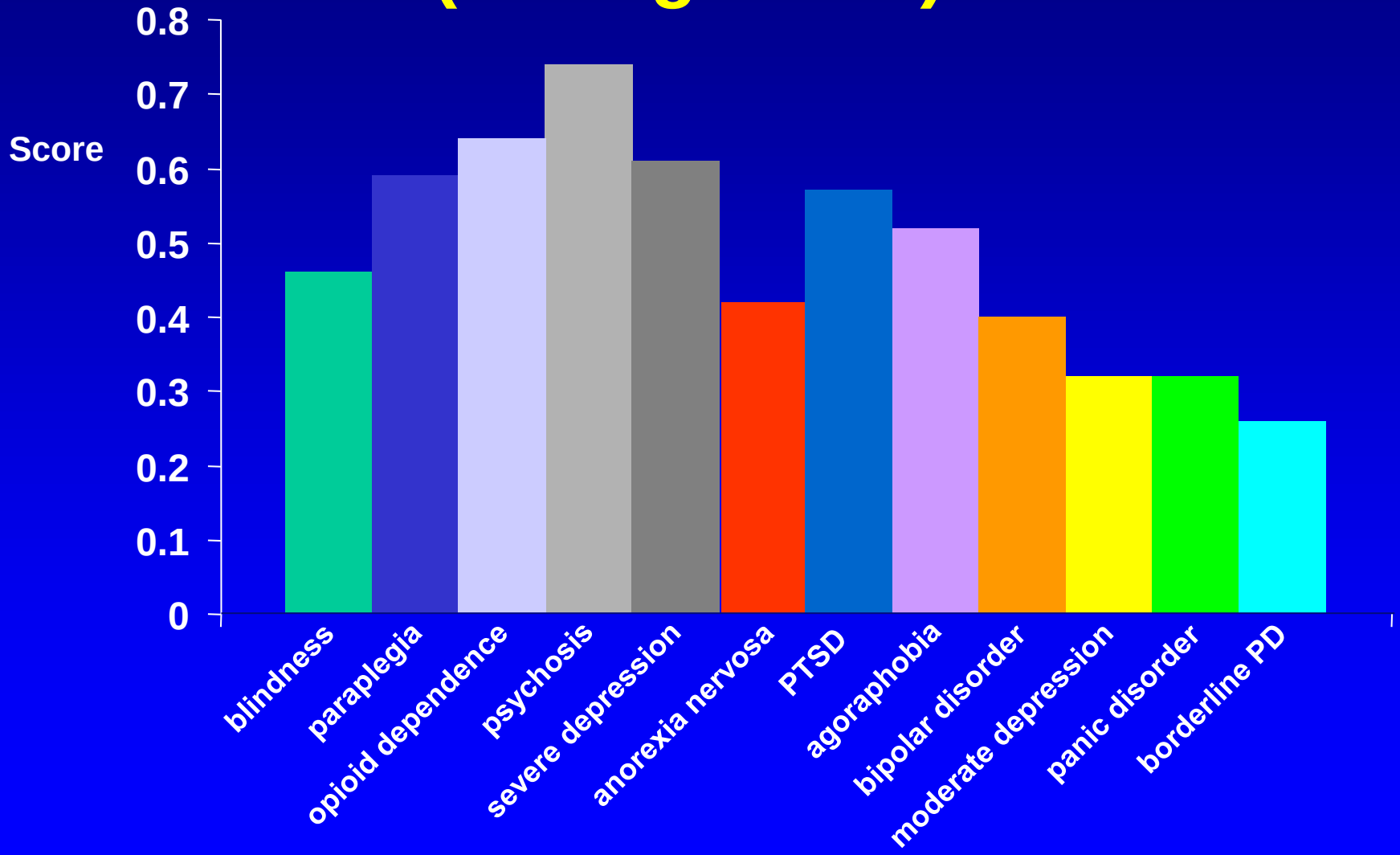
Lifetime History of Suicidal Attempts by Anxiety Disorder



General US population lifetime rates of suicide attempts range from 2.9% to 4.6%.

Kessler RC, *Archives of General Psychiatry*. 1999; Moscicki EK, *Yale Journal of Biology and Medicine*. 1988

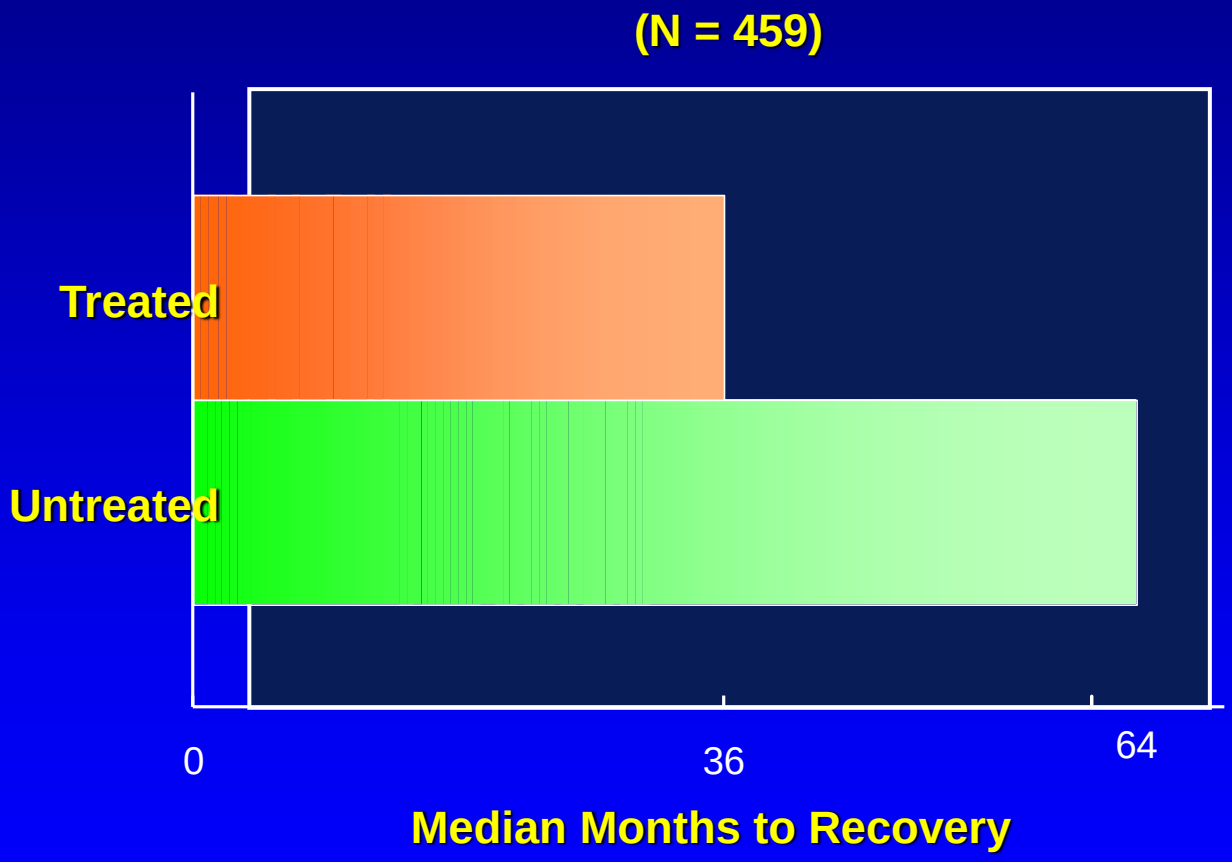
Disability Weights (Rating Scale)



Sanderson K and Andrews G, *Australian and New Zealand Jnl of Psych* 2001

PTSD

Impact of Treatment on Recovery



Kessler RC et al. *Arch Gen Psychiatry*. 1995;52:1048–1060.

PTSD

Overview of Treatment Options

- Psychotherapy
- Pharmacotherapy
- Combined treatments

PTSD

Considerations for Psychotherapy

1. Capacity to tolerate distress with exposure
2. Motivation/preference
3. Ability to participate and follow structure
4. Problems with interpersonal adjustment

Cognitive Restructuring and Combination Treatments

Study	Population	Comparison	Results
Marks et al., 1998	87 civilian trauma victims	Relaxation vs E vs cognitive restructuring (CR) vs combination	All superior to relaxation
Resick et al. 2002	120 F, sexual assault	Cognitive processing Tx (CPT) (elements of CR and E) vs E vs minimal contact	CPT = E > MC CPT superior for guilt
Monson et al., 2007	60 Male veterans	Cognitive processing CPT vs Present Centered (PC)	CPT superior to PC

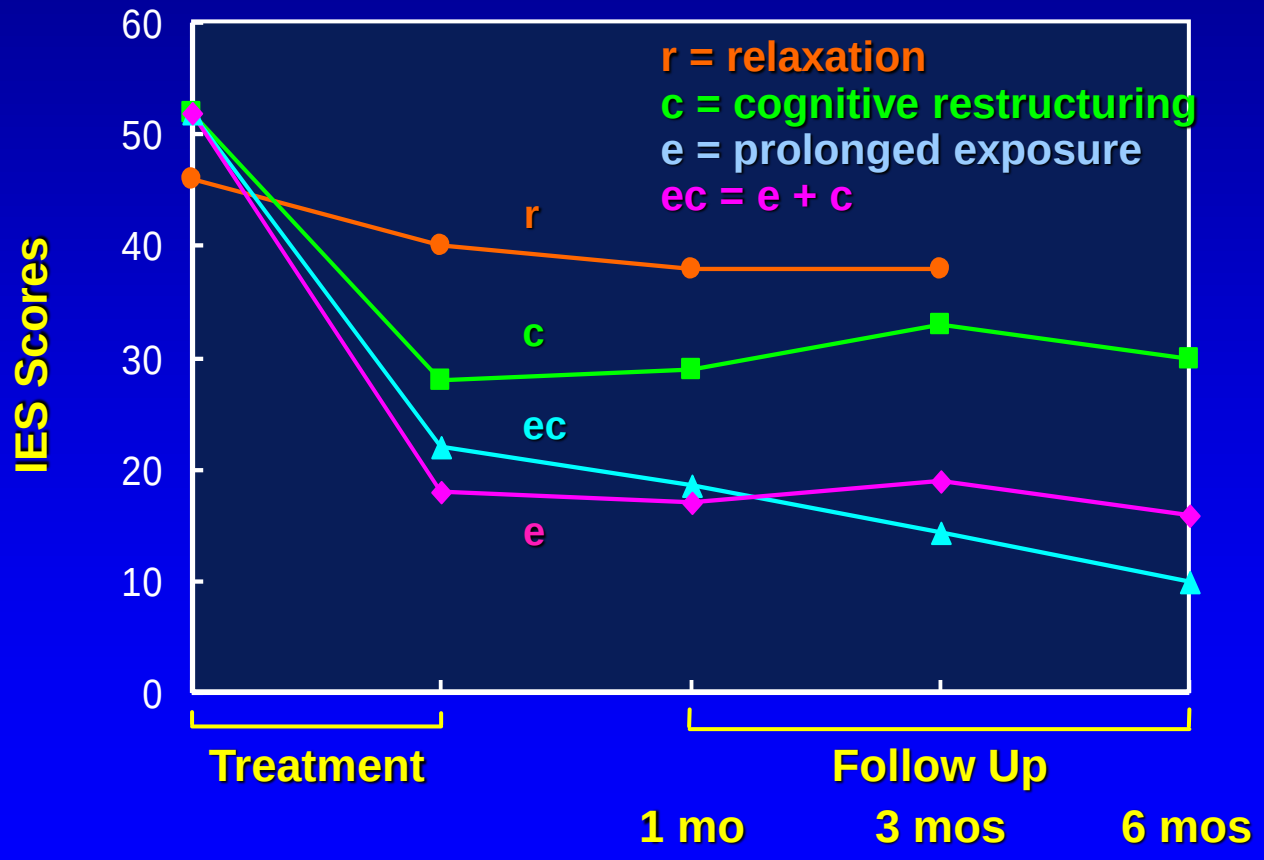
EXPOSURE STUDIES

Study	Population	Comparison	Results
Keane et al., 1989	24 Vietnam veterans	E vs WL	Exposure group more improved, especially re-experiencing
Foa et al., 2005	179 Women civilian trauma	E vs E+CR vs WL	E superior effective with all Sx clusters
Schnurr et al., 2007	Women veterans	E vs PC	E superior to PC

*E = exposure-based treatment
WL = wait list control
SIT = stress inoculation training

PTSD

Treatment of PTSD by Exposure and/or Cognitive Restructuring



Marks I et al. *Arch Gen Psychiatry*. 1998;55:317–325.

Conclusions of the IOM report on the Treatment of PTSD (2007)

"The evidence is sufficient to conclude the efficacy of (psychotherapy that utilize) exposure therapies in the treatment of PTSD" (PE, CPT)

PHARMACOTHERAPY

Neurobiological factors

Evidence of efficacy

What responds

PTSD

related pathology

Who responds

Type of trauma

comorbidity

gender

PTSD

Biological Evidence Update

High-resolution MRI brain imaging at 4T: (2010): first time in humans that PTSD associated/w selective volume loss of CA3/dentate gyrus subfields of hippocampus

Neurobiological evidence (1980 – 2006) for PTSD with Secondary Psychotic features (PTSD-SP)

- **Cortisol**
- **Corticotrophin releasing hormone**
- **Dopamine beta-hydroxylase**
- **Smooth pursuit eye movements**
- **Psychopharmacological and pathophysiological mechanisms for PTSD-SP**

PTSD: Neurobiological Alterations of Memory Processing

Greater physiologic reactivity to trauma-related stimuli

Selective attention to trauma stimuli

Fragmentary trauma narratives

Deficits in standard tests of verbal memory

Suggested abnormalities from structural and functional brain imaging

PTSD: Hormones and Neurotransmitters

Cortisol: reduced secretion and increased sensitivity to feedback inhibition with PTSD (Yehuda et al., 1993)

Role of noradrenergic activity in fear-enhanced learning (Cahill, 1997)

Noradrenergic and serotonergic probes stimulate panic and flashback symptoms in combat-related PTSD (Southwick et al., 1997)

PTSD: Dysregulated sleep

Subjective

- Trauma-related nightmares
- Insomnia/nonrestorative sleep

Objective (EEG findings)

- Mixed findings regarding sleep maintenance and duration
- Increased REM density/ Disrupted REM sleep continuity
- Increased motor activity

Ross et al., 1994; Mellman et al., 1997, 2002, Breslau et al., 2004

AIMS OF PHARMACOTHERAPY

Reduce core symptoms

Reduce associated symptoms

Facilitate non-pharmacologic therapies

Medication Treatment for PTSD: Nature of the Evidence

At least 7 published RCTs supporting efficacy of SSRIs for acute Rx of PTSD

Mean N participants = 236.3 (range: 47-551)

FDA approval for sertraline (’99), paroxetine (’01)

Maintenance efficacy established for sertraline for up to 52 weeks (Davidson et al. ‘01)

Improvement in all 3 sx clusters and QOL measures, treatments safe

Medication Treatment for PTSD: Nature of the Evidence

Additional RCTs not demonstrating benefit for SSRIs. Some are underpowered. The one large and well designed negative study featured male combat veterans with chronic PTSD treated in VA settings (Friedman et al., 2007)

Medication Treatment for PTSD: Nature of the Evidence

Efficacy supported by smaller RCTs

TCAs, MAOIs, lamotrigine; adjunctive olanzapine and risperidone, prazosin for sleep disturbances

Efficacy not supported by trials

benzodiazepines

Benefits suggested in open trials

Other SSRIs, Novel APs, AEDs, trazodone, nefazodone, noradrenergic suppressor/antagonists (eg prazocin)

Medication Treatment for PTSD: Recommendations

1st Line

SSRIs (sertraline, paroxetine, fluoxetine)

2nd Line

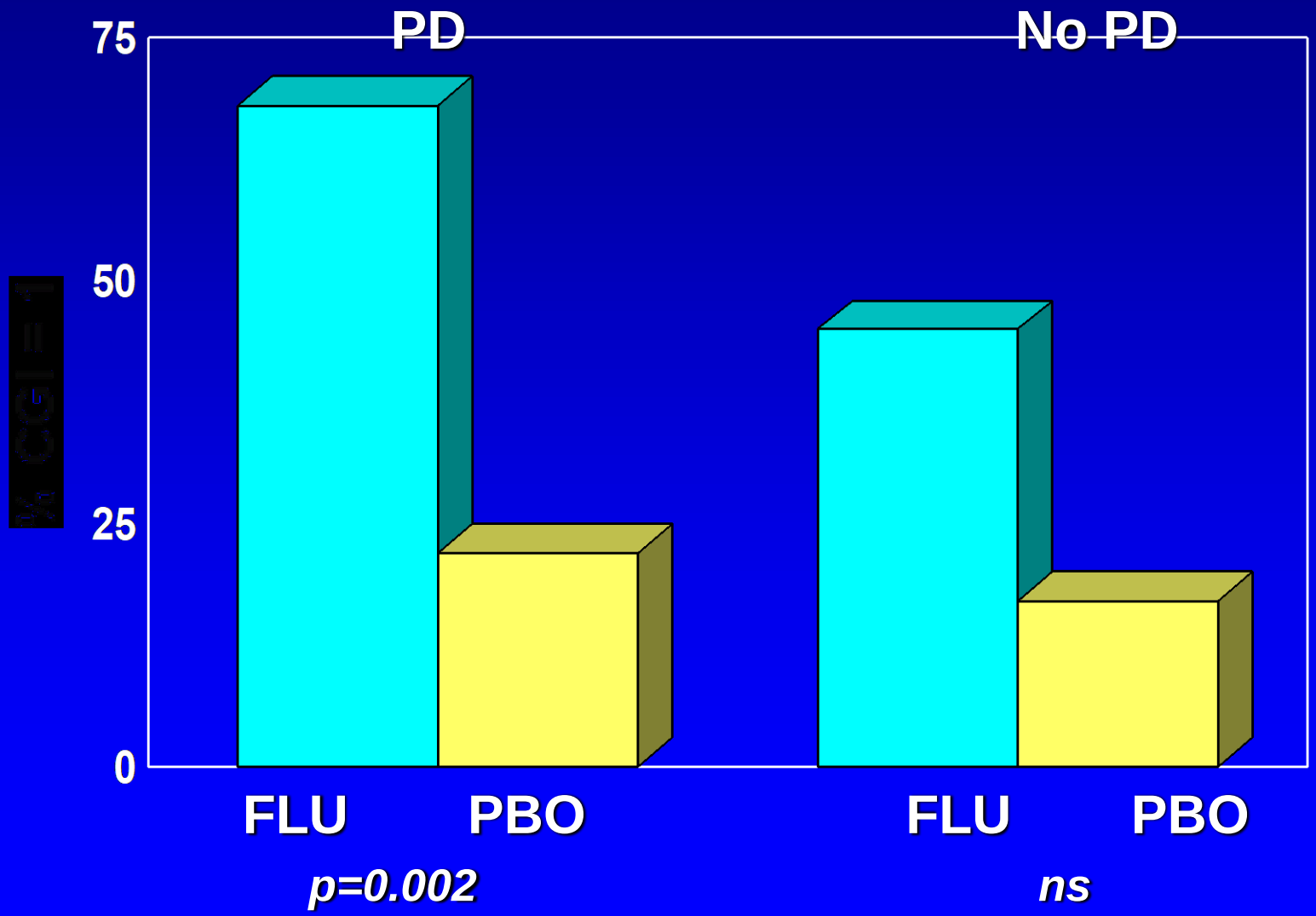
Noradrenergic agents; anticonvulsant/mood stabilizers; novel AP medications

Not recommended

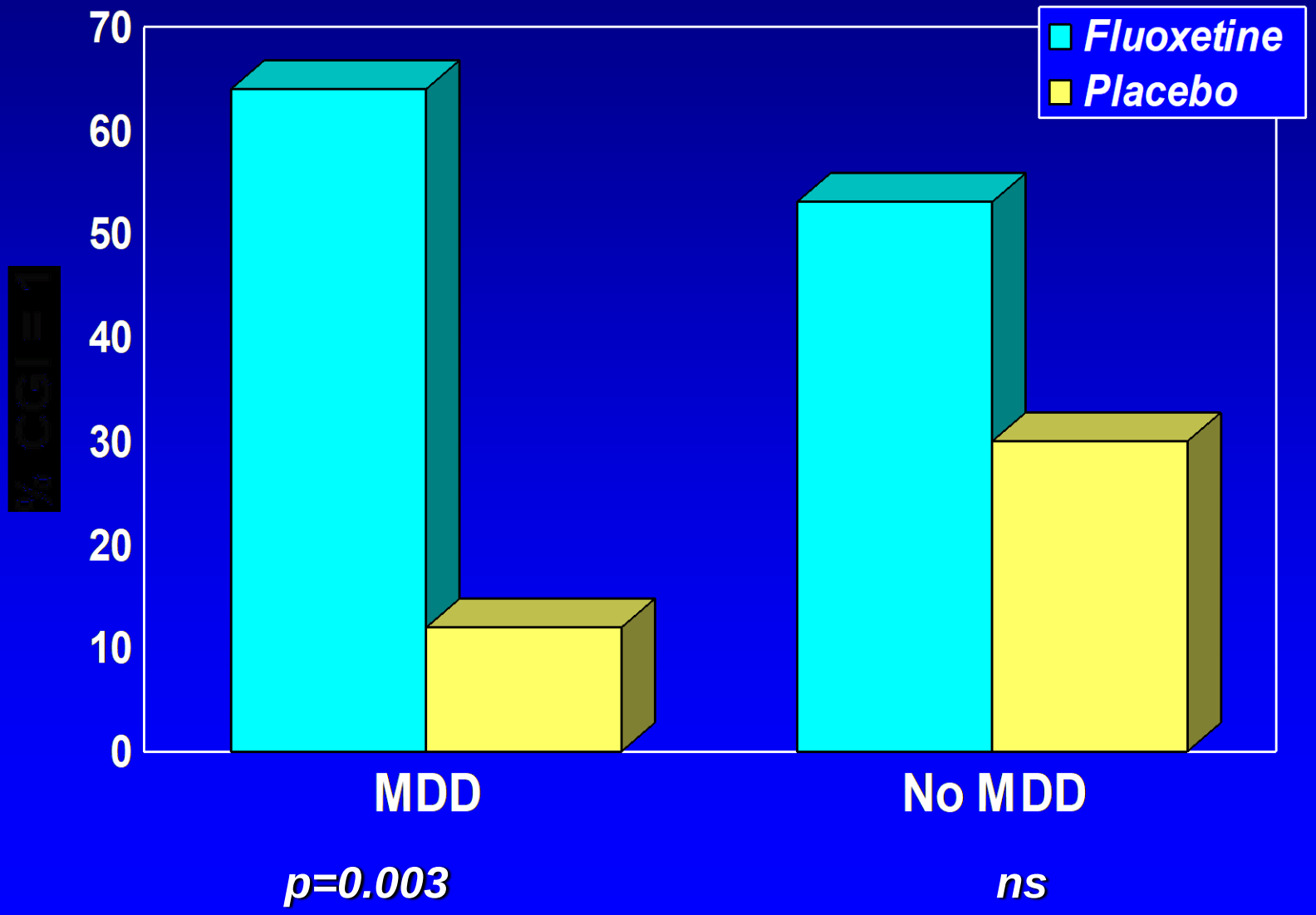
Conventional APs, benzodiazepines*

Friedman et al., 2000

DOES COMORBID PERSONALITY DISORDER AFFECT THE RESPONSE TO AN SSRI?

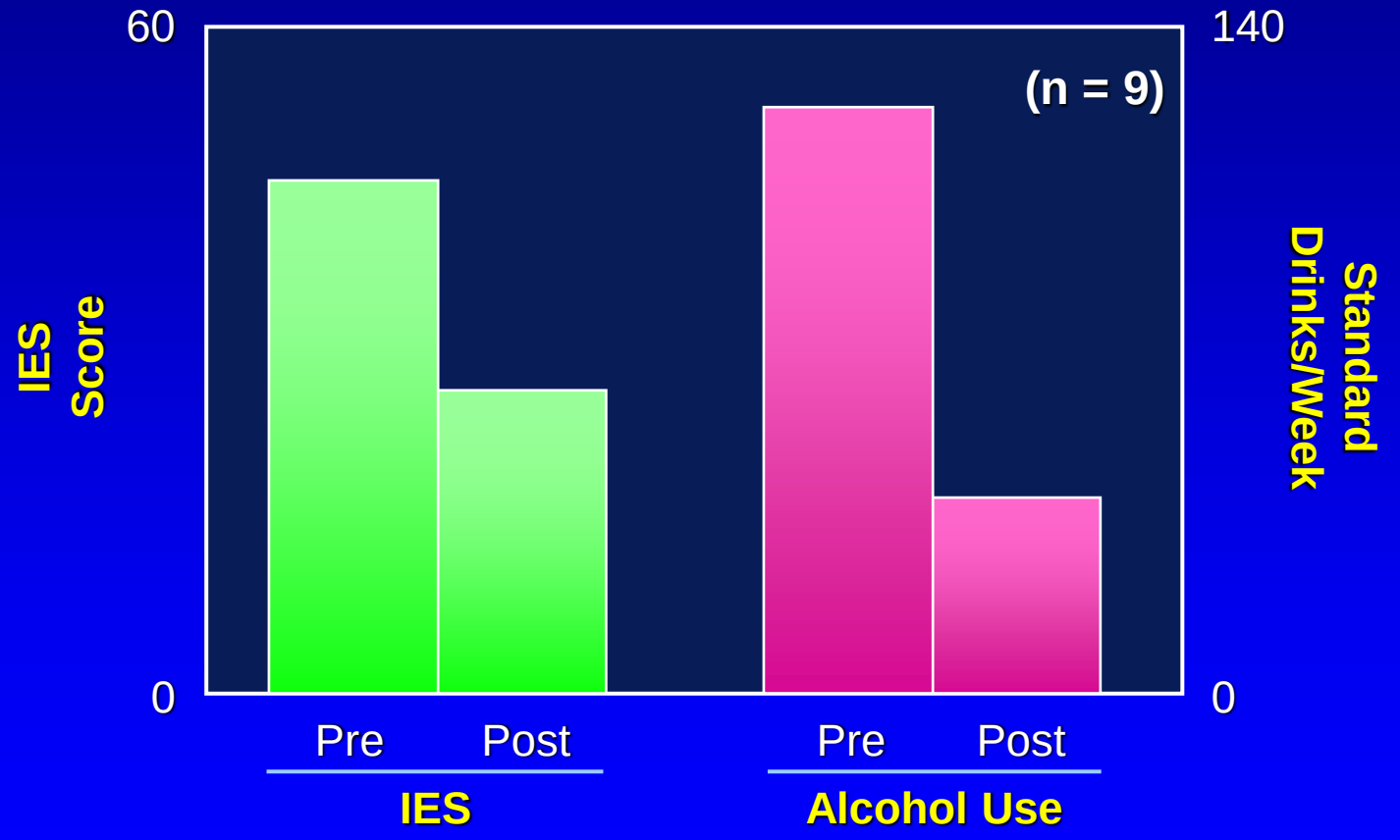


DOES COMORBID DEPRESSION AFFECT THE RESPONSE TO AN SSRI?



PTSD Treatment With SSRIs

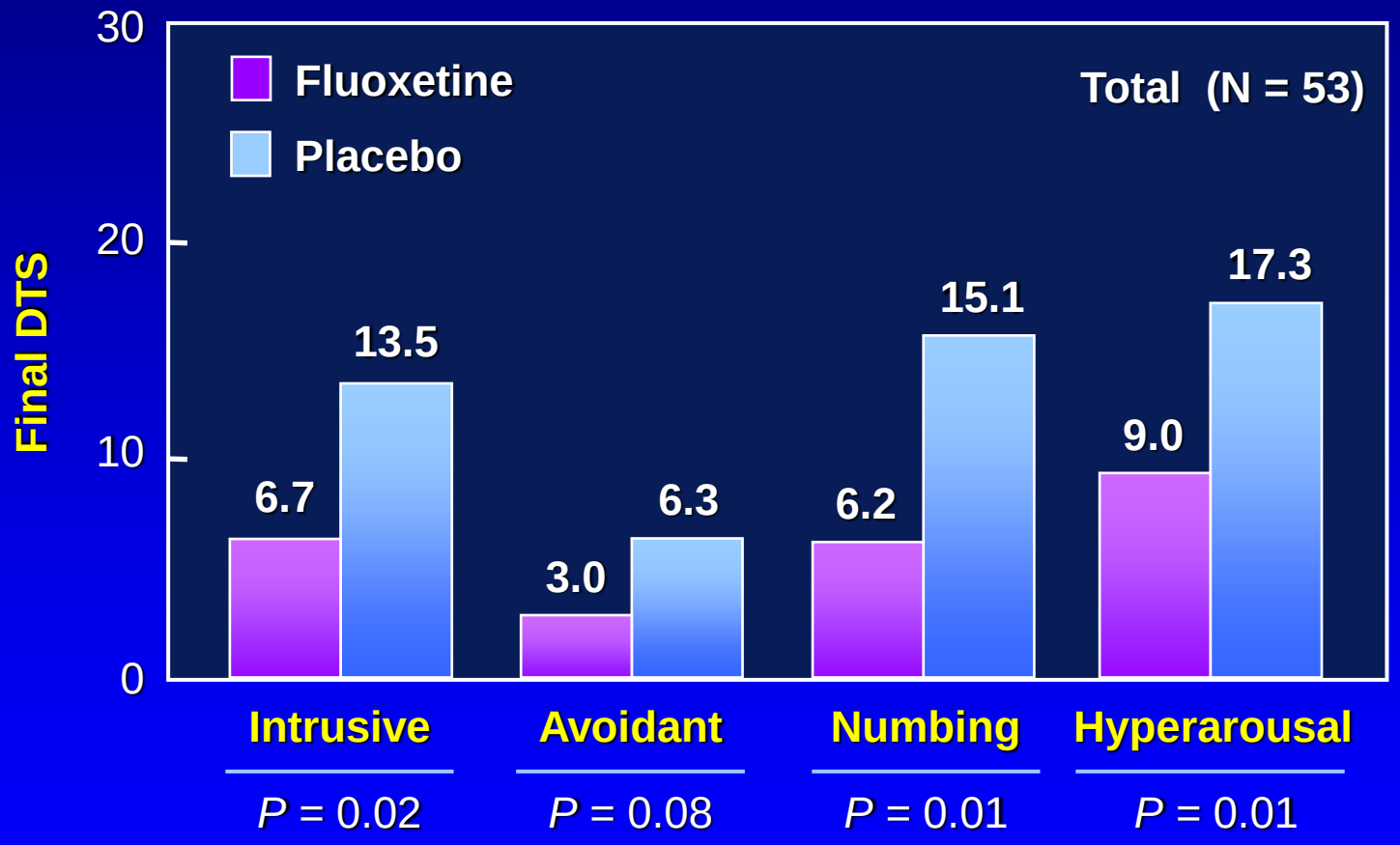
Open-Label Sertraline in Comorbid PTSD and Alcoholism



Brady KT et al. *J Clin Psychiatry.* 1995;56:502–505.

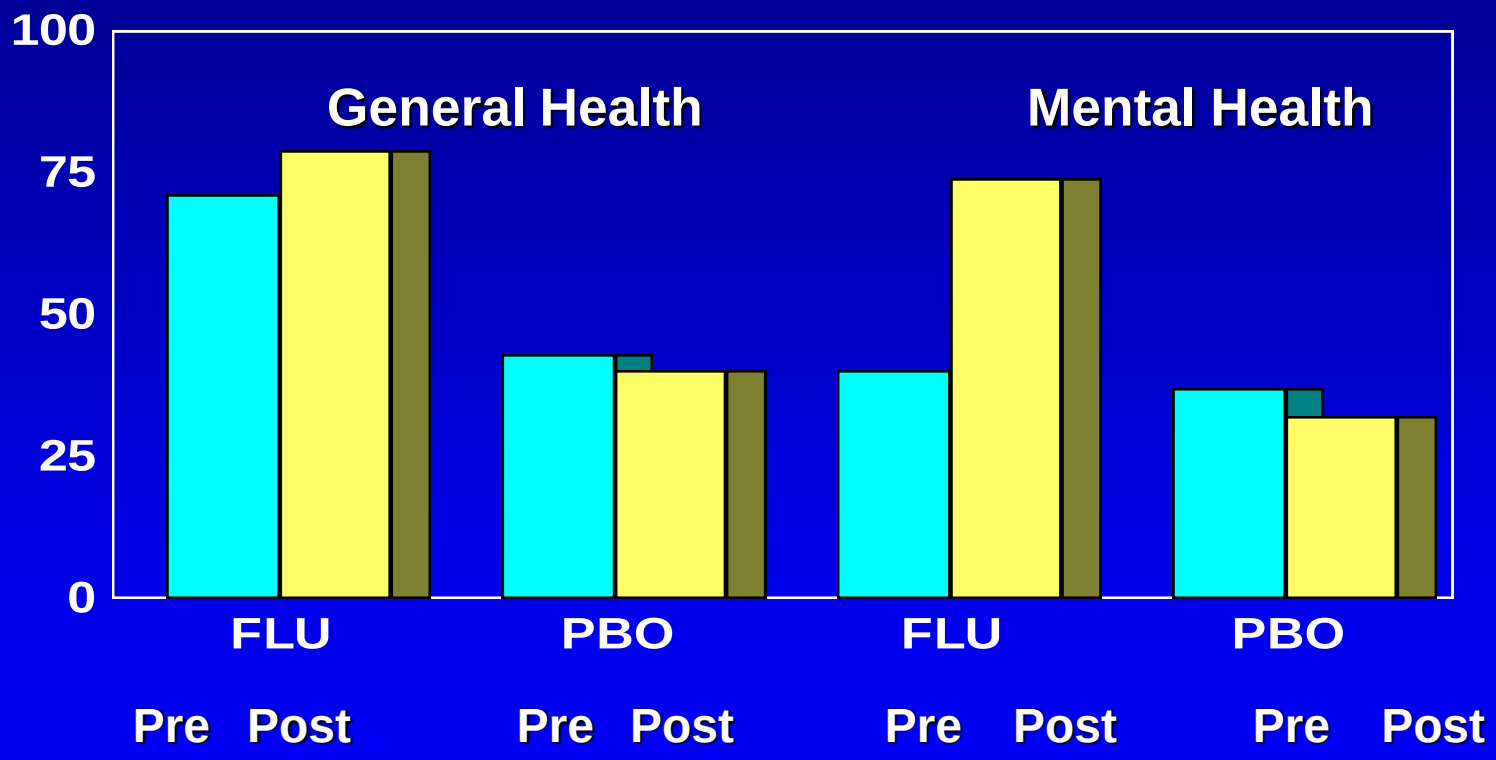
PTSD Treatment With SSRIs

Effect of Fluoxetine in Symptom Clusters



Davidson JR et al. *Int Clin Psychopharmacol*. 1997;12:291–296.

EFFECT OF FLUOXETINE ON QUALITY OF LIFE (SF36) IN PTSD: Pre- to Post-Treatment

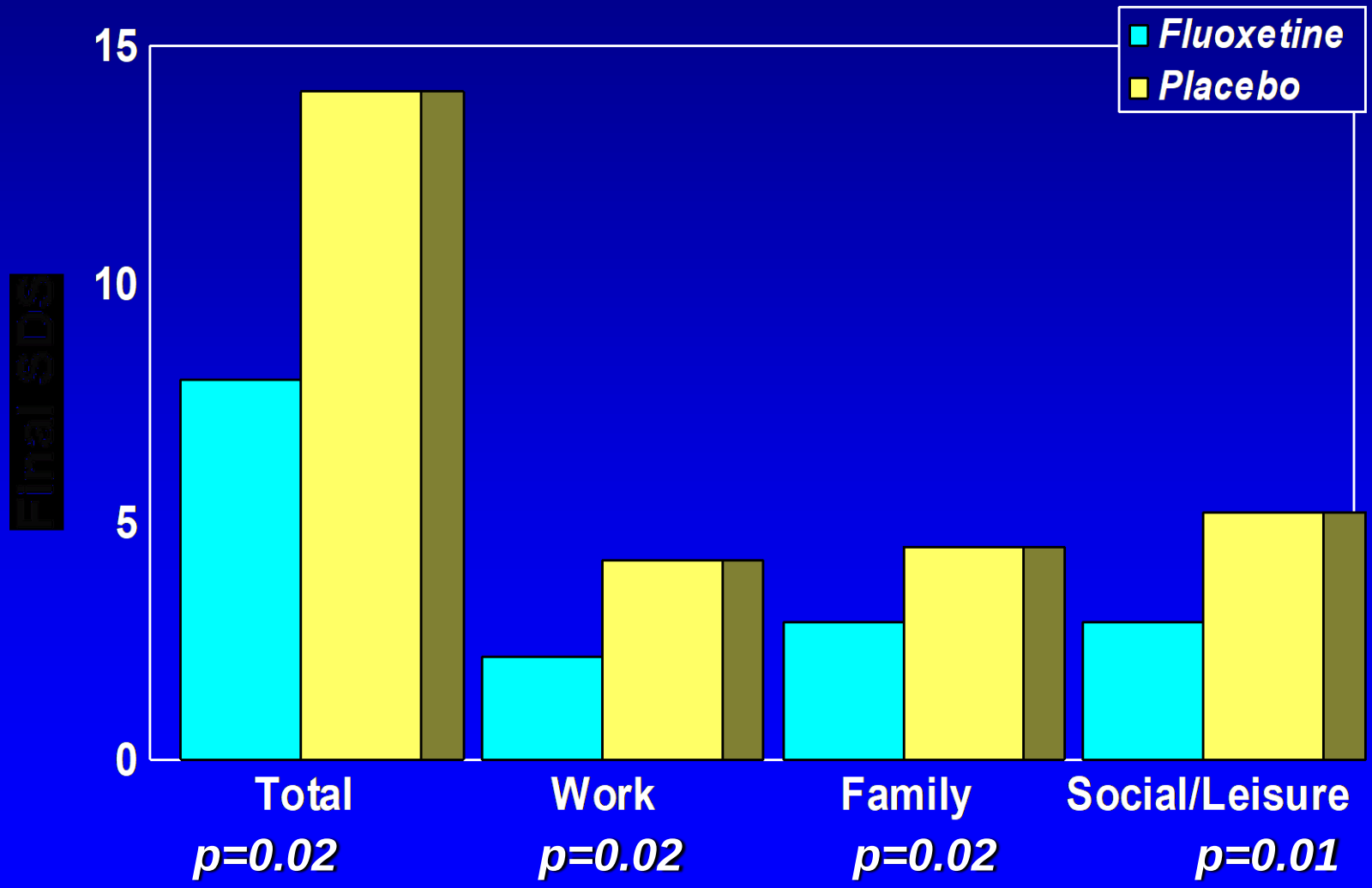


p=0.006

ns

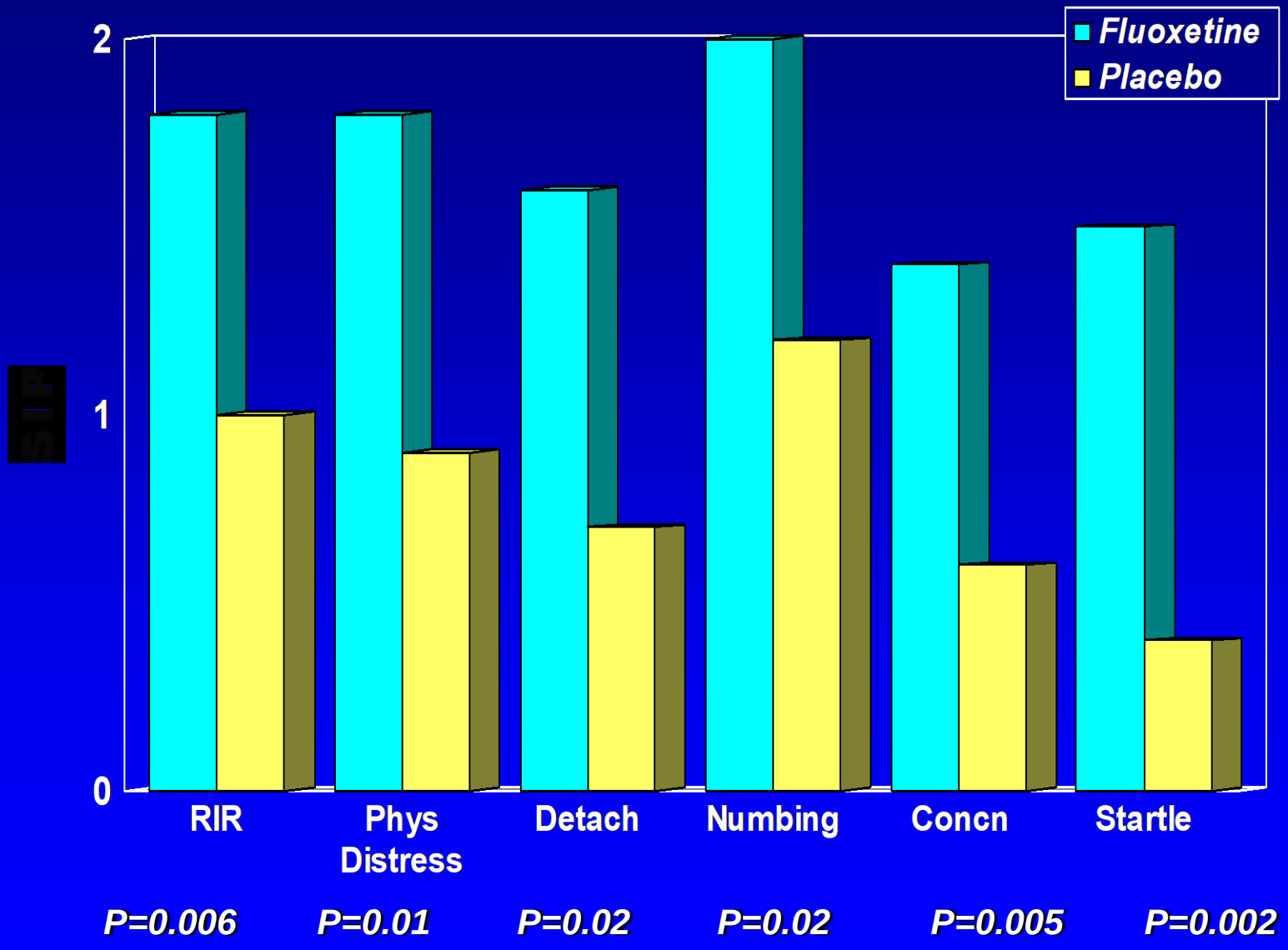
Davidson et al., 1997

IMPROVEMENT IN DISABILITY: Fluoxetine vs Placebo



Davidson et al., 1997

WHICH SYMPTOMS RESPOND TO AN SSRI?



Davidson et al., 1997

SEQUENCE OF SYMPTOM IMPROVEMENT WITH FLUOXETINE (SIP)

	Week		
	4	8	12
Startle	**	*	**
Concentration	**		**
Intrusive recollections	**		**
Physiological symptoms		**	**
Estrangement			*
Numbing			*

*p<0.05 *p<0.01

SEQUENCE OF SYMPTOM IMPROVEMENT WITH FLUOXETINE (DTS)

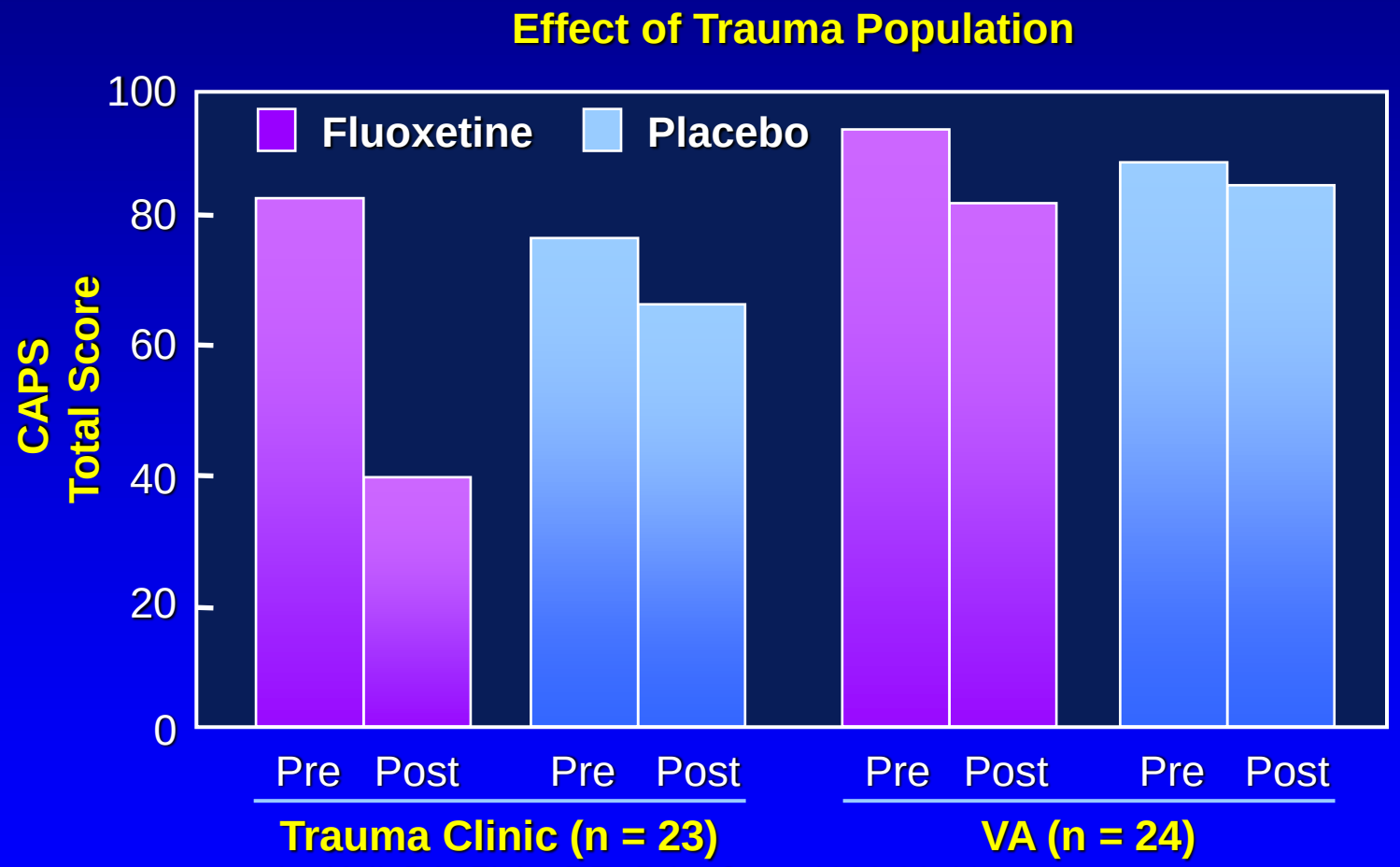
	Week					
	2	4	6	8	10	12
Hypervigilance	**	***	***	*	**	***
Poor concentration	**	***	***	*	***	**
Upset by reminders	*	*			*	*
Estrangement		**	**	*	**	**
Anhedonia					*	**
Avoid thoughts				*		*
Foreshortened future						*

*p<0.05 **p<0.01 ***p<0.001

Davidson et al., 1997

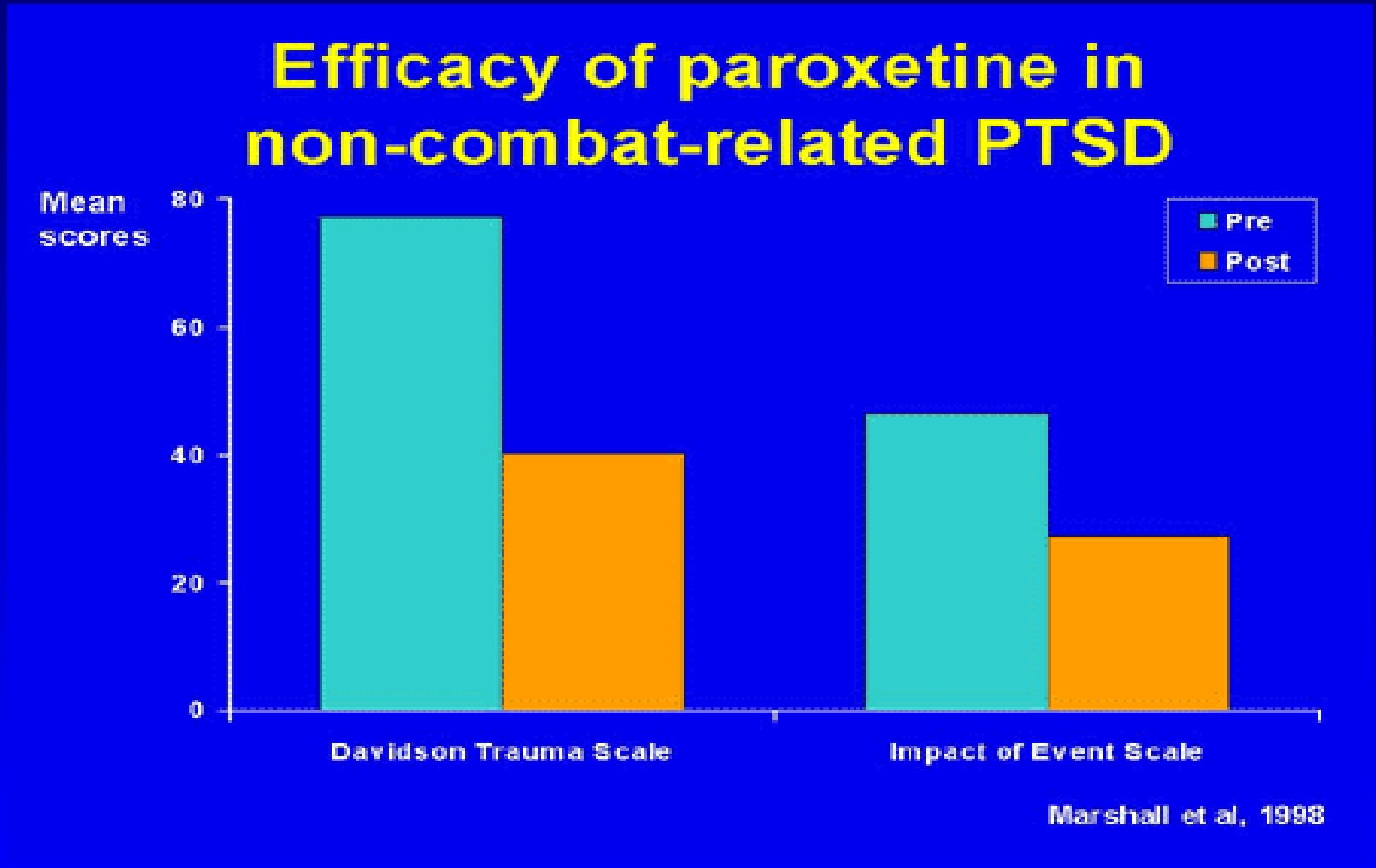
PTSD Treatment With SSRIs

Effect of Fluoxetine

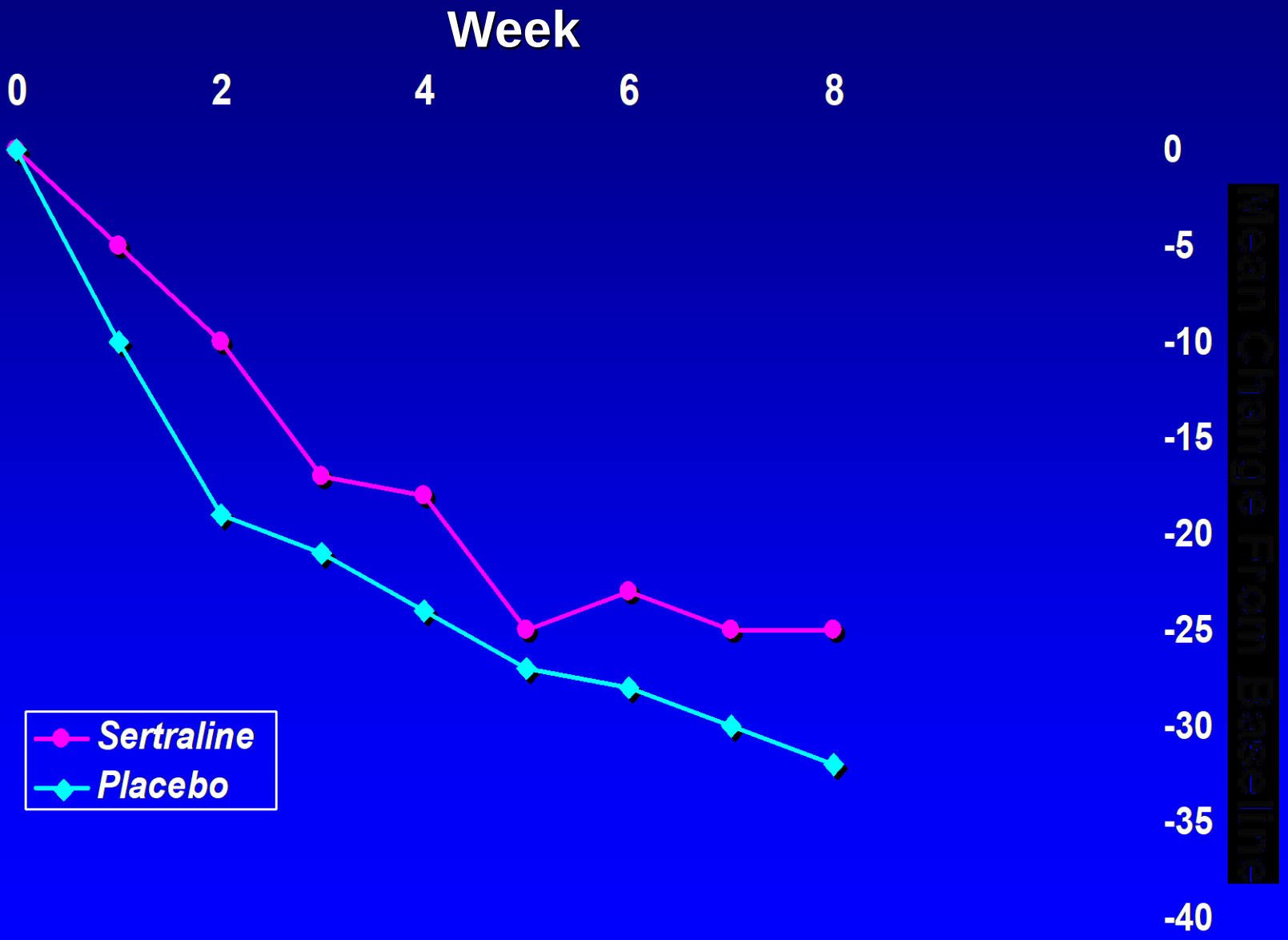


van der Kolk BA, Fisler RE. *Prim Care*. 1993;20:417–432.

Paroxetine in PTSD



Sertraline vs Placebo in Non-Combat-related PTSD



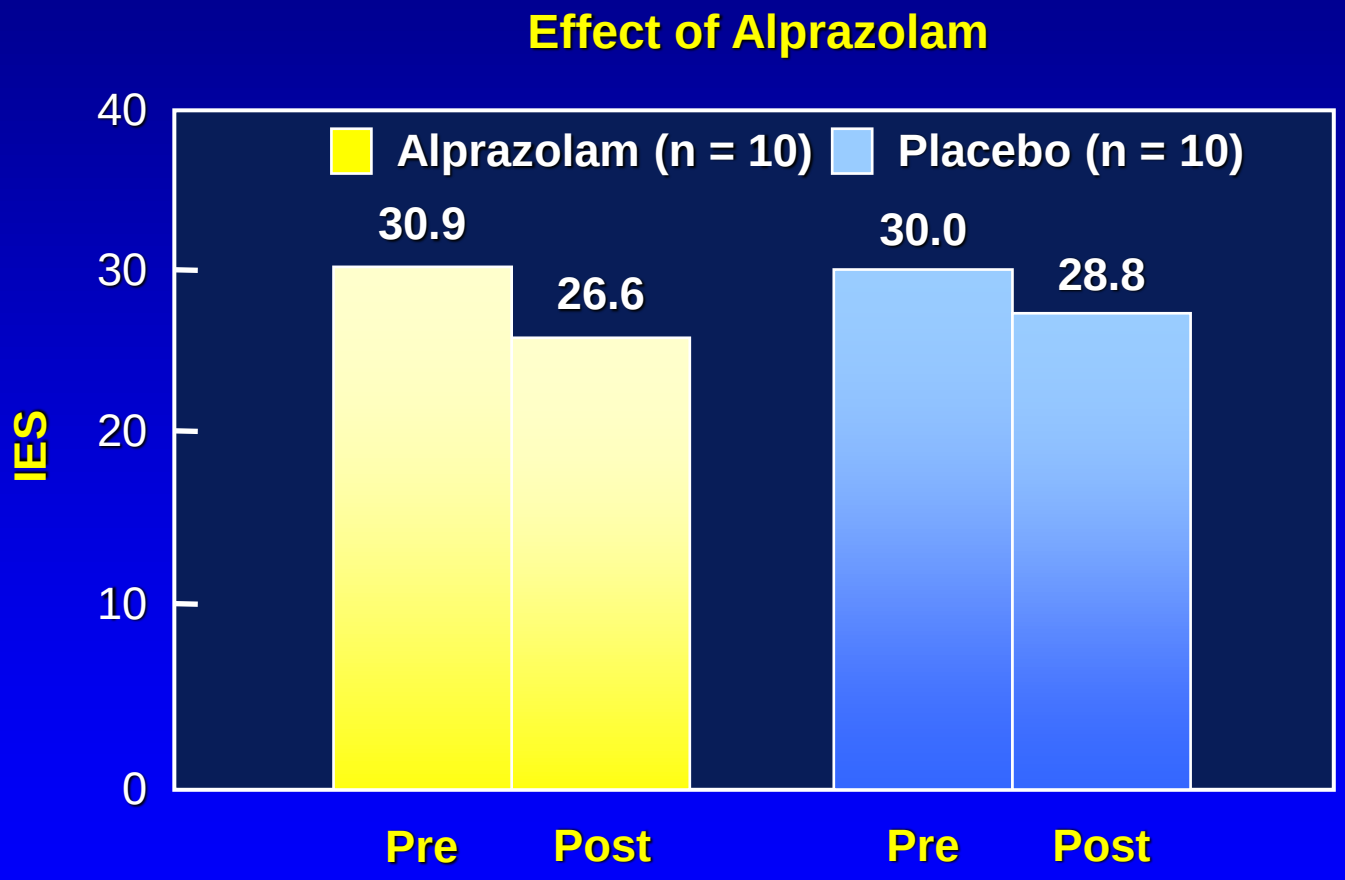
Brady et al.. JAMA 2000

ADVANTAGES AND DISADVANTAGES OF SSRIs

Advantages	Disadvantages
Effective on all PTSD symptoms	Unproven in Combat Veterans
Abuse-free	GI, sexual, activating side effects
Once daily	Medication interactions

PTSD

Treatment With Benzodiazepines



Braun P et al. *J Clin Psychiatry*. 1990;51:236–238.

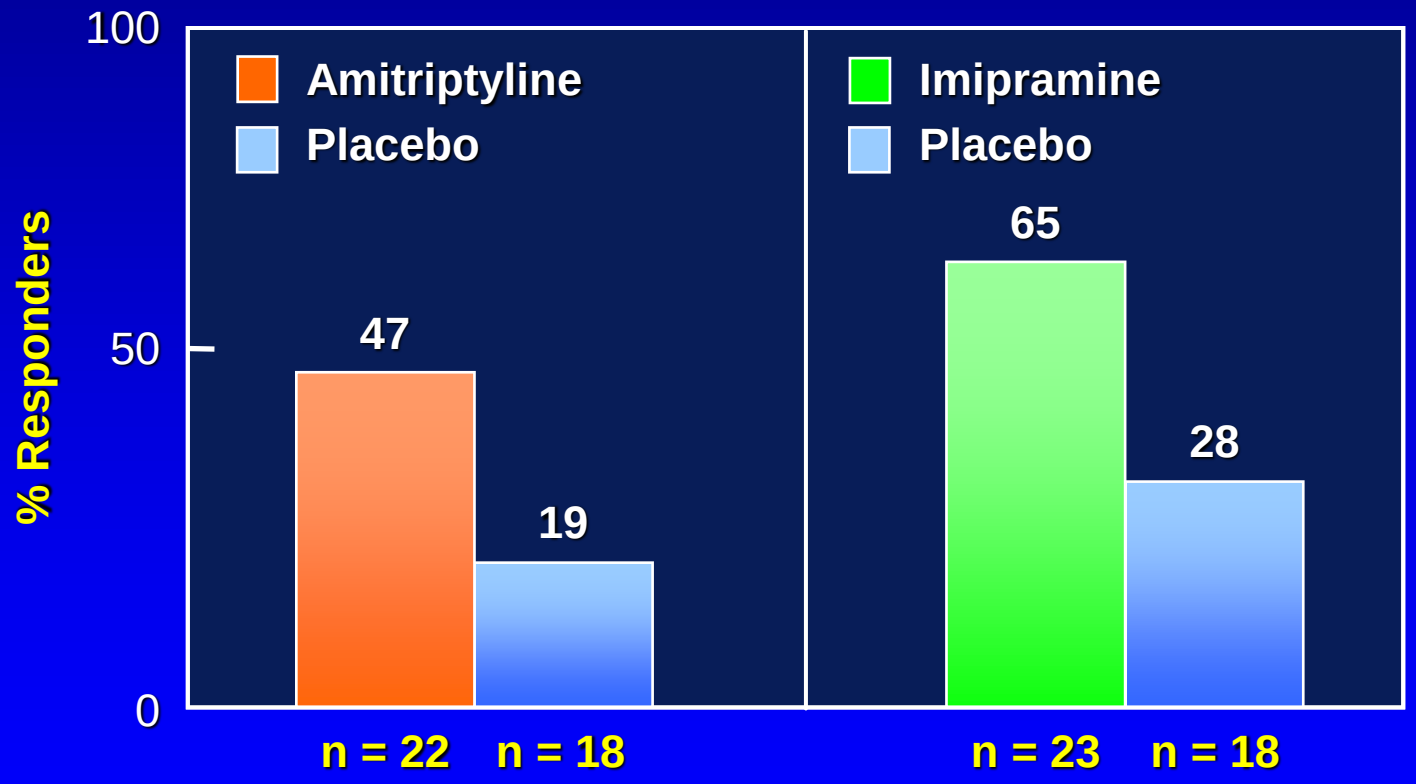
ADVANTAGES AND DISADVANTAGES OF BZDs

Advantages	Disadvantages
Acute relief of non-specific anxiety	No evidence of efficacy for PTSD Possible disinhbition Possible dependence

PTSD

Treatment With Tricyclics

Studies Comparing Amitriptyline and Imipramine With Placebo



Davidson J et al. *Arch Gen Psychiatry*. 1990;47:259-266.

Kosten TR et al. *J Nerv Ment Dis*. 1991;179:366–370.

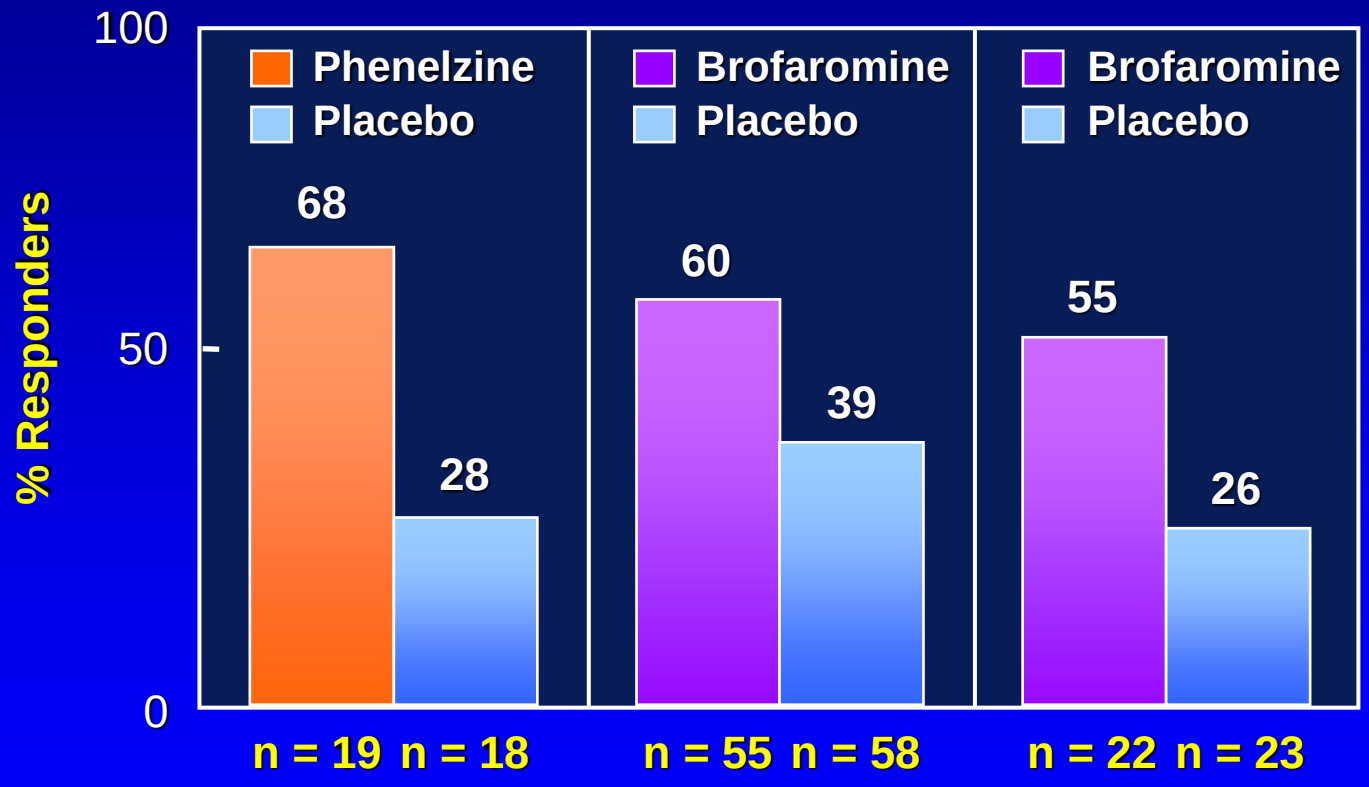
ADVANTAGES AND DISADVANTAGES OF TCAs

Advantages	Disadvantages
Effective in PTSD	Numerous side effects
Abuse-free	Poorly tolerated
Once daily	Dangerous in overdose
Hypnotic effects	Wide dose range

PTSD

Treatment With MAOIs

Studies Comparing Phenelzine and Brofaromine With Placebo



Kosten TR et al. *J Nerv Ment Dis*. 1991;179:366–370.

Baker DG et al. *Psychopharmacology* . 1995;122:386–389.

Katz RJ et al. *Anxiety*. 1994–95;1:169–174.

ADVANTAGES AND DISADVANTAGES OF MAOIs

Advantages	Disadvantages
Effective in PTSD	Numerous side effects
May be particularly useful in complex cases	Poor tolerance
	Dietary & other restrictions
	Dangerous in overdose

Antipsychotic Medications

- **Support for risperidone as add on Rx** (Bartzokis et al., 2005; Reich et al., 2004
- **olanzapine 1 small study supporting adjunct efficacy, benefit to sleep** (Stein et al., 2002)
- **Traditional Antipsychotic medications "not recommended"**
  - (Friedman et al. ISTSS Treatment Guidelines, 2000)

Mood Stabilizers

- **Carbamazepine**
  - Open clinical trial: decreased intrusions, flashbacks, insomnia, irritability, impulsivity, and violent behavior (Lipper et al., Psychosomatics, 1986)
- **Valproic acid**
  - Open trial: decreased hyperarousal and avoidance (Stein, J Clin Psych, 1995)
- **Lamotrigine**
  - Small controlled trial: decreased re-experiencing, numbing and avoidance (Hertzberg et al., Biol Psychiatry, 1999)

Alpha 1 Antagonist (Prazosin)

At Doses of 1-20 mg/day, Prazosin reduced:

- **Combat-related nightmares**
- **Recurrent distressing dreams**
- **Re-experiencing traumatic event in sleep**

PTSD

Unique Populations: the Elderly

1. Persistence of traumatic memories in World War II prisoners of war.
2. Traumatic memories and clinical levels of PTSD persist for WWII POWs as long as 65 years after their captivity.
3. Rumination about these experiences, including flashbacks and persistent nightmares, may increase after retirement, particularly for those held in the Pacific theater.

PTSD

Summary

1. PTSD is common, usually chronic, Presentation varies, comorbidity is the rule
2. Comprehensive assessment of patients is critical to develop an individualized treatment plan
3. Treatment often involves multiple modalities

PTSD Treatment Recommendations

CBT effective

Antidepressant agents can be effective

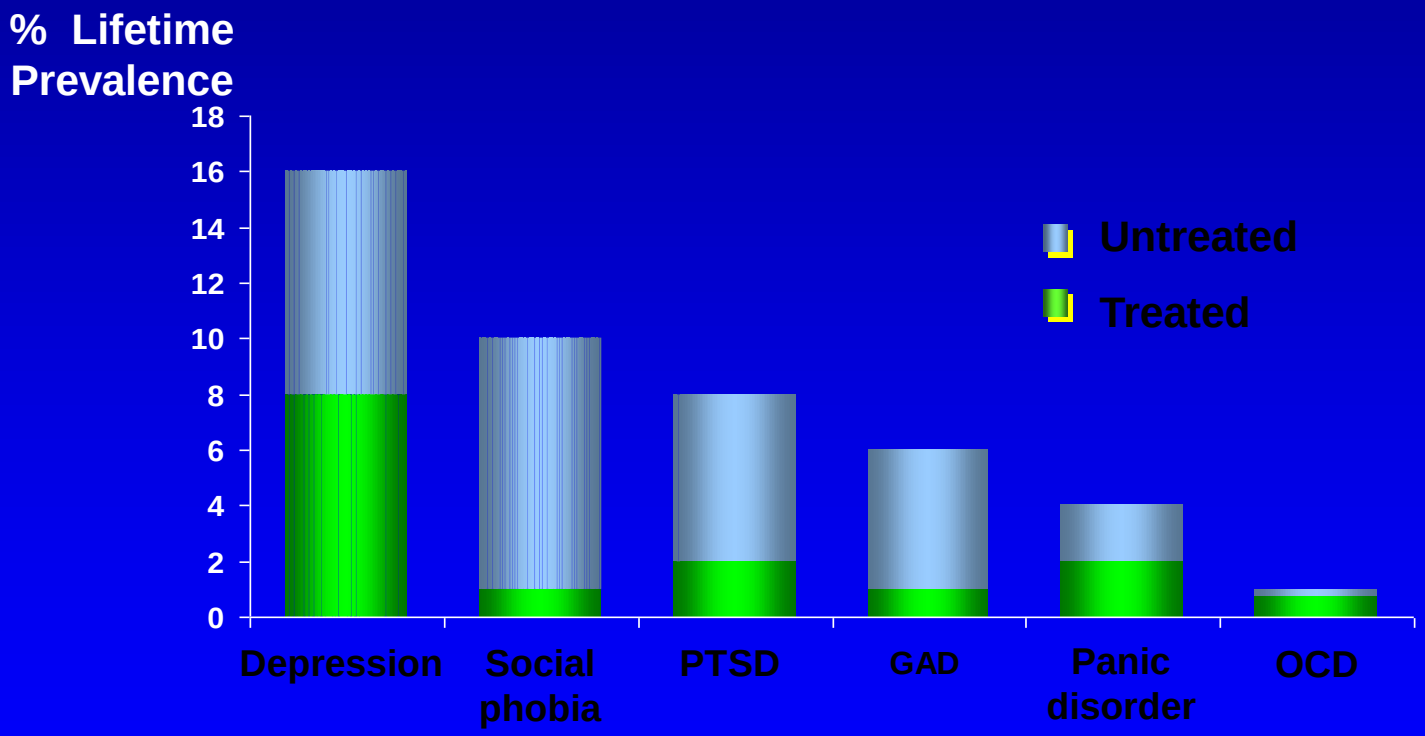
SSRI, MAOI, TCA

Combine CBT & pharmacotherapy

Treat sleep-disruptive symptomatology

PTSD: Unmet Medical Need

Few Are Treated



% untreated	50%	90%	75%	80%	50%	30%

Question 1

True or False:

1. The prevalence of PTSD is higher in women than men.

Question 2

True or False:

1. All individuals exposed to severely threatening trauma will develop PTSD.

Question 3

True or False:

1. Cortisol activity in chronic PTSD is similar to major depression.

Question 4

1. **The psychosocial PTSD treatment with the strongest evidence for efficacy is:**

A. EDMR

B. Breathing relaxation

C. Exposure

D. Thought-stopping

Question 5

1. **The weakest evidence for efficacy for PTSD is for which class of pharmacological agents:**

A. SSRI’s

B. TCA’s

C. MAOI’s

D. Benzodiazepines

E. Risperidone

Answers to Pre & Post Competency Exams

1. True
2. False
3. False
4. C
5. D