POST-TRAUMATIC STRESS DISORDER
Comorbidity and Treatment

Thomas A. Mellman, M.D.

Kathleen T. Brady, M.D., Ph.D.

R. Bruce Lydiard, M.D., Ph.D.

Howard University, Washington DC and
Medical University of South Carolina
Charleston, SC

Major Teaching Points

- PTSD develops in a substantial minority of individuals exposed to severe trauma
- PTSD is highly comorbid with other psychiatric disorders
- SSRI medications have FDA approval for PTSD and efficacy for some PTSD subpopulations
- Other antidepressants, mood stabilizers and new generation antipsychotic medications have a role in treating some PTSD cases
- Psychotherapy is an important intervention for PTSD

Pre-Lecture Exam
Question 1

True or False:

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

Question 2

True or False:

2. Combat-related PTSD is not responsive to treatment.

Question 3

1. **Pharmacological agents that have evidence for efficacy in PTSD include all but which of the following:**

A. SSRI’s

B. TCA’s

C. MAOI’s

D. Benzodiazepines

E. Anticonvulsants

Question 4

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

A. EDMR

B. Breathing relaxation

C. Exposure

D. Thought-stopping

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%

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

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

Experiencing symptoms (1 necessary)

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 (3 necessary)

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 (2 necessary)

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

PTSD

Associated Features

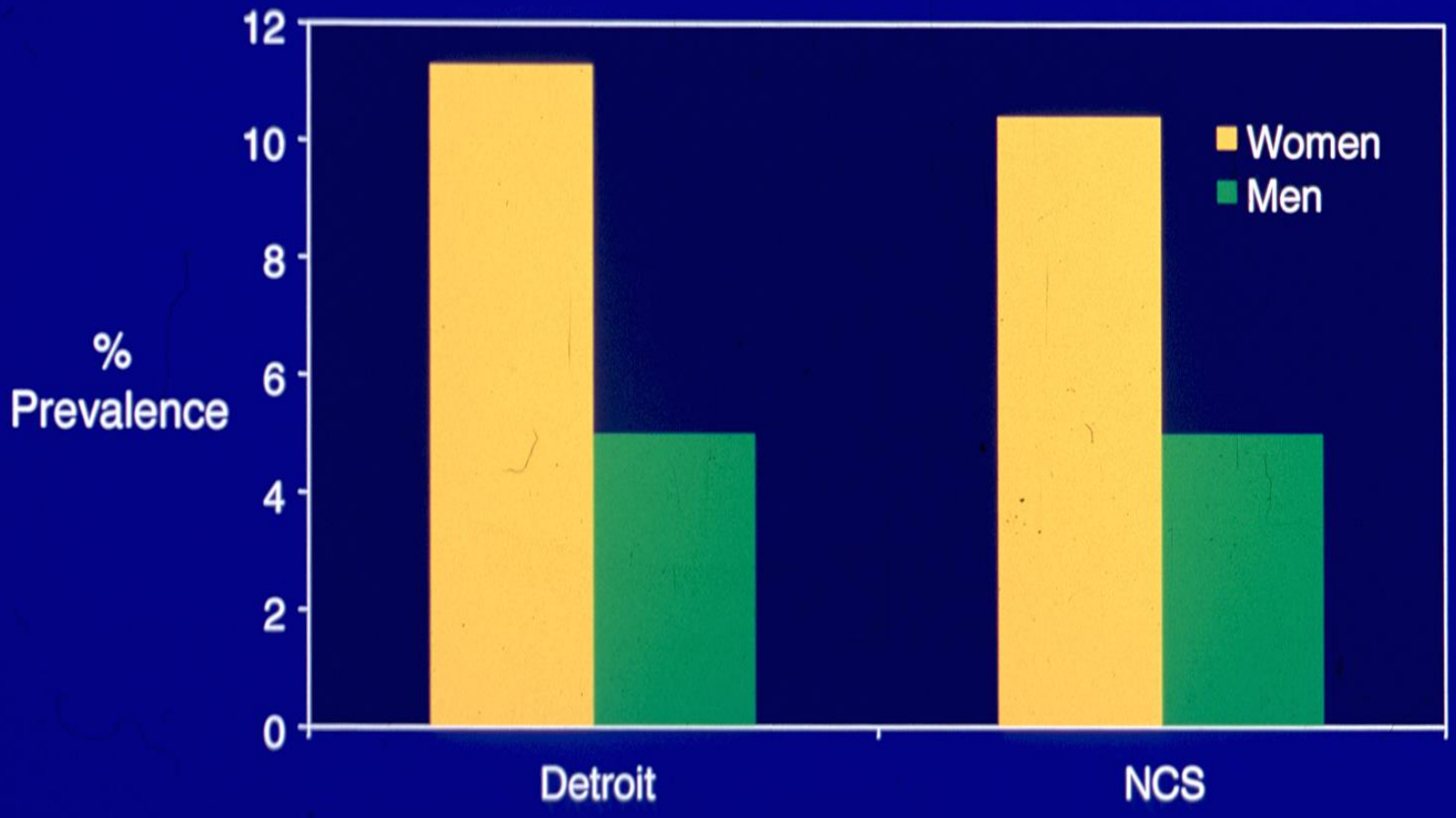
1. Alcohol/drug problems
2. Aggression/violence
3. Suicidal ideation, intent, attempts
4. Dissociation
5. Distancing
6. Problems at work
7. Marital problems
8. Homelessness

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.

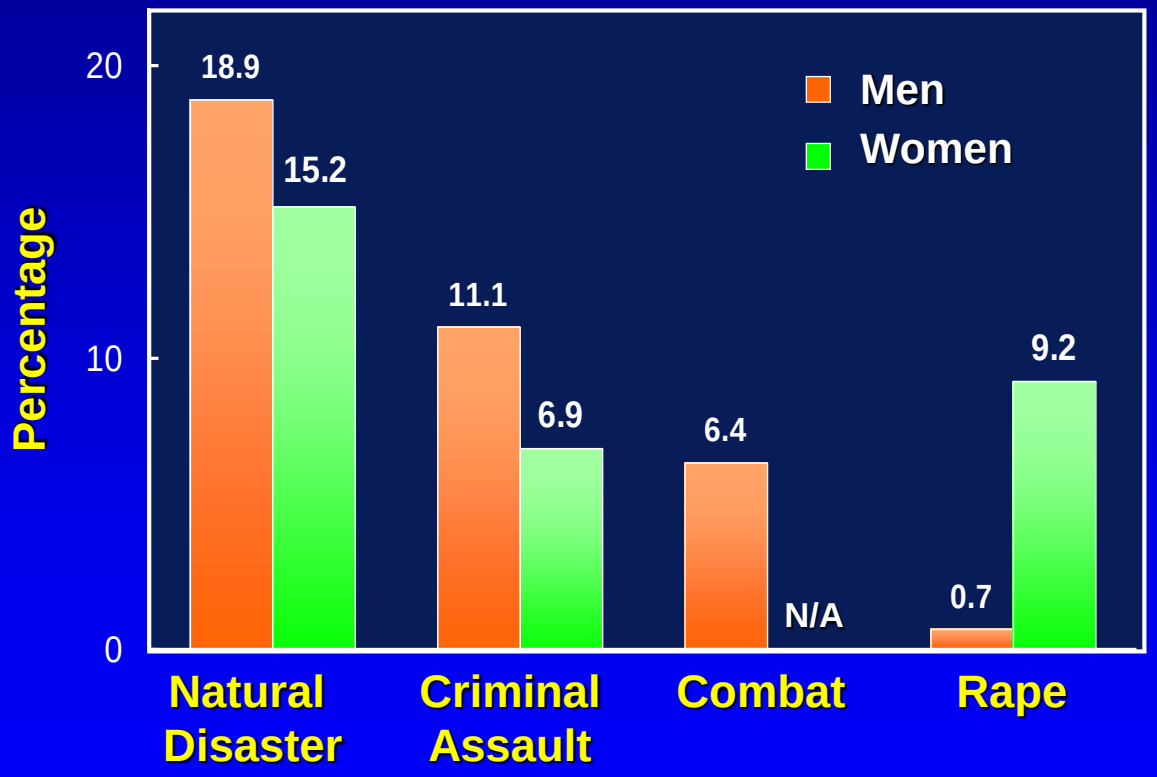
Lifetime Prevalence of PTSD



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



5. **About 30% of people exposed to trauma developed PTSD**

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

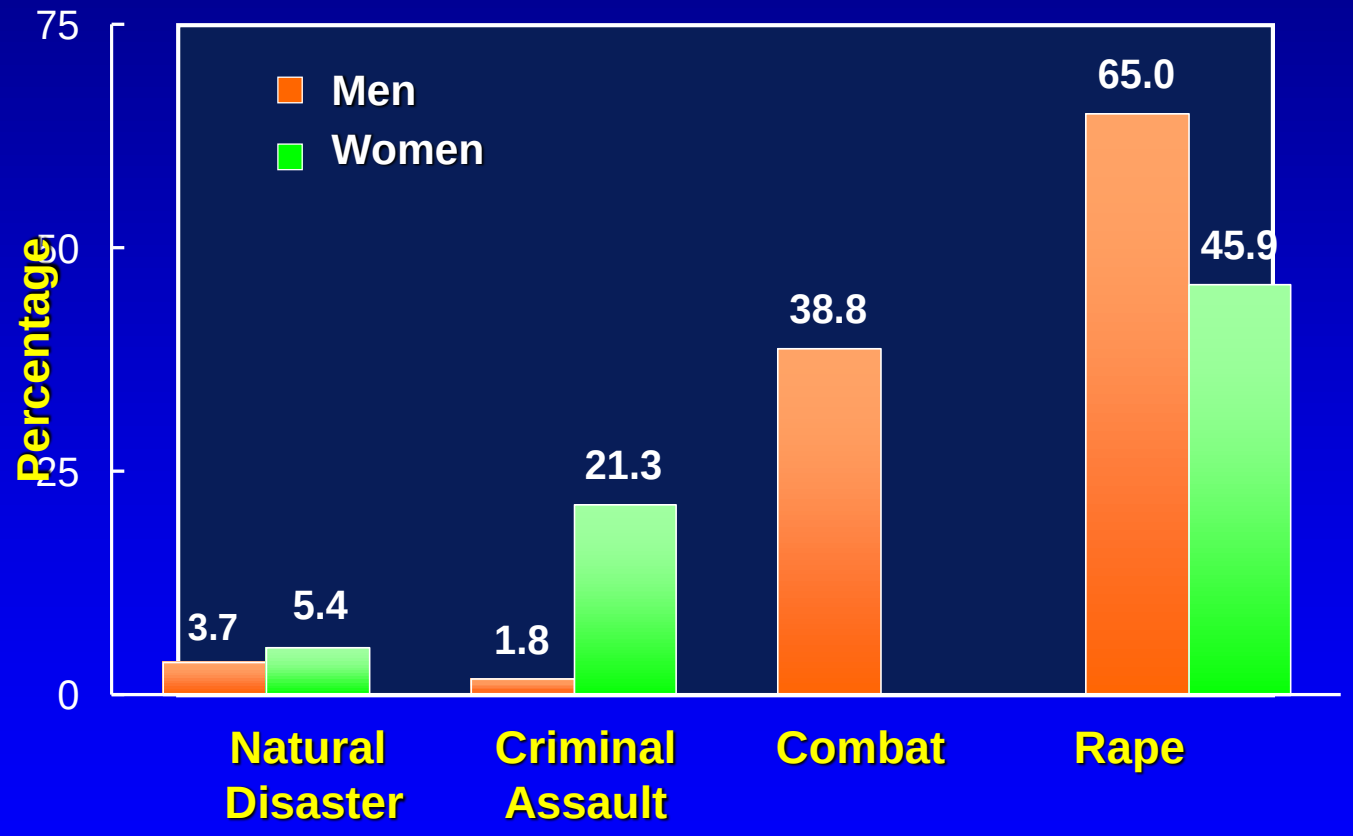
PTSD

Risk Factors for PTSD

- Severity of trauma (ie, threat, duration, injury, loss)
- Prior trauma
- Gender
- Prior mood and/or anxiety disorders
- Family history of mood or anxiety disorders
- Education

PTSD

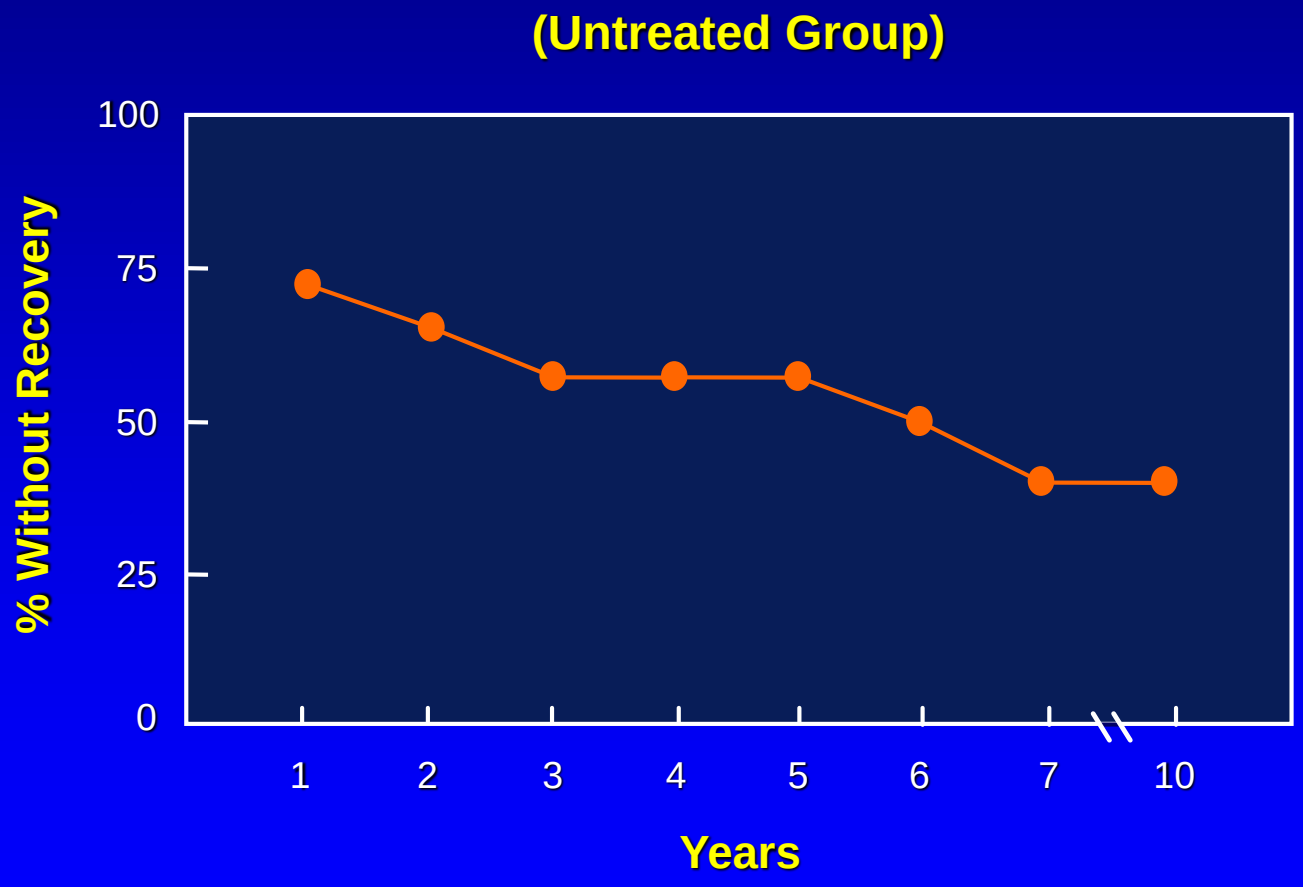
Rates Related to Specific Traumas



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

PTSD

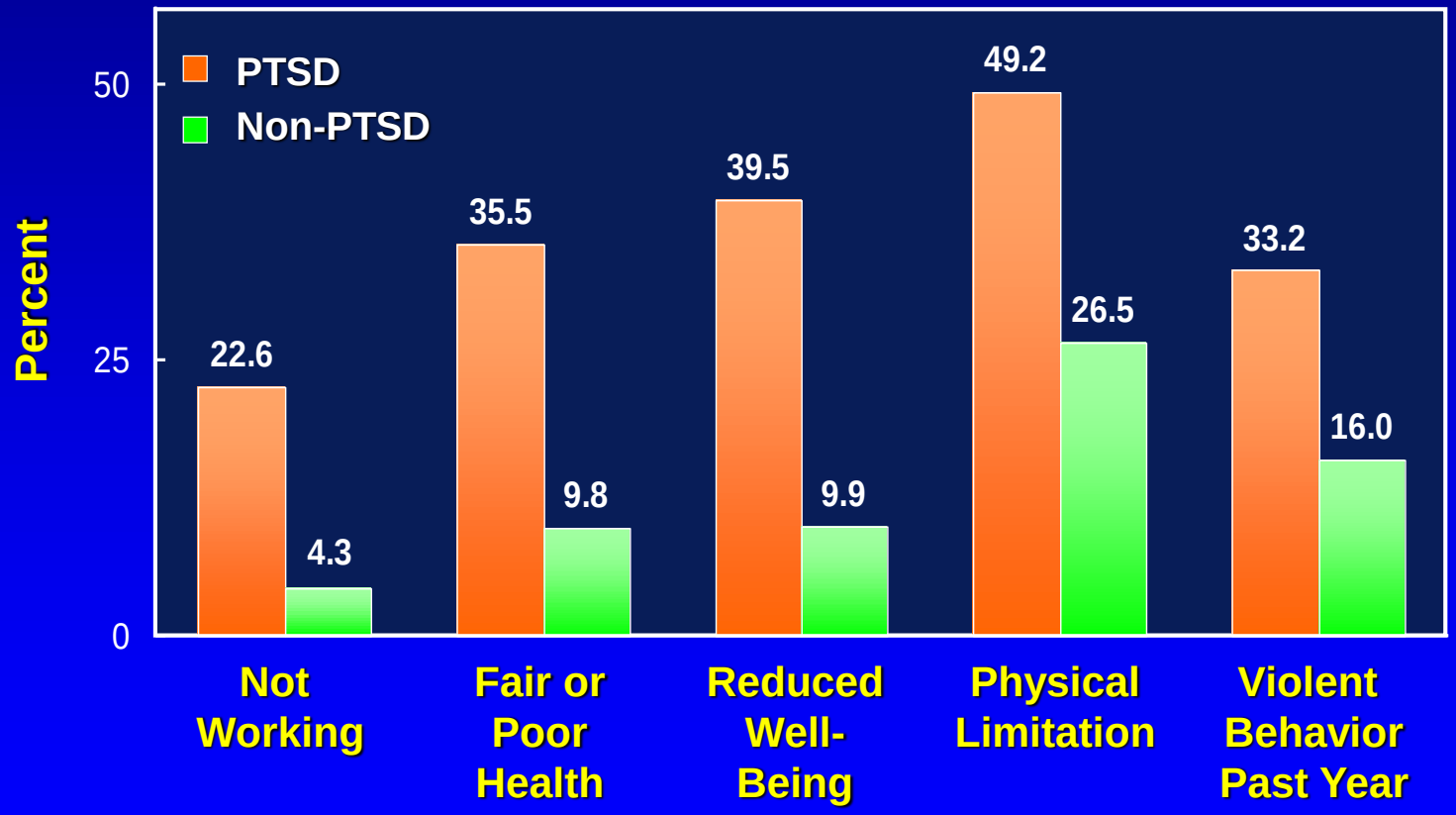
Persistence Over Time



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

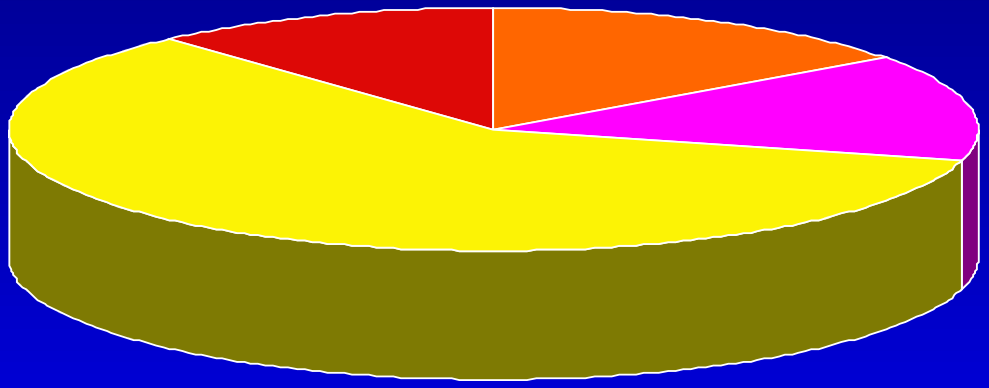
Psychiatric Comorbidity

	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.

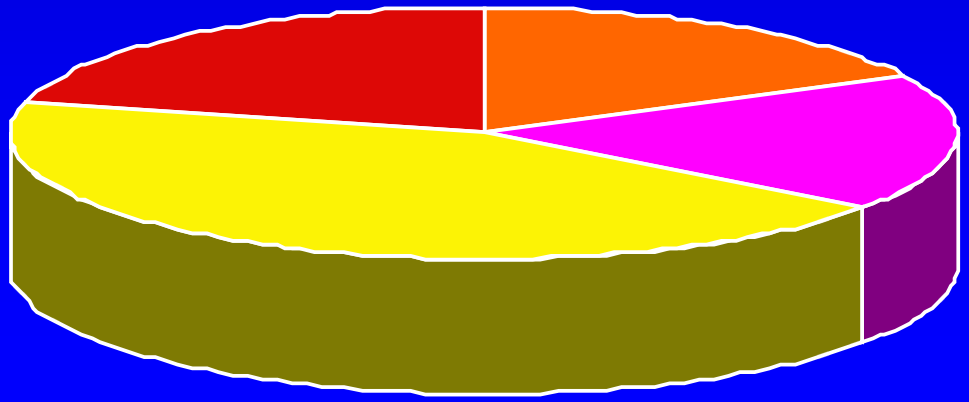
Comorbidity in PTSD
National Comorbidity Study

MEN



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

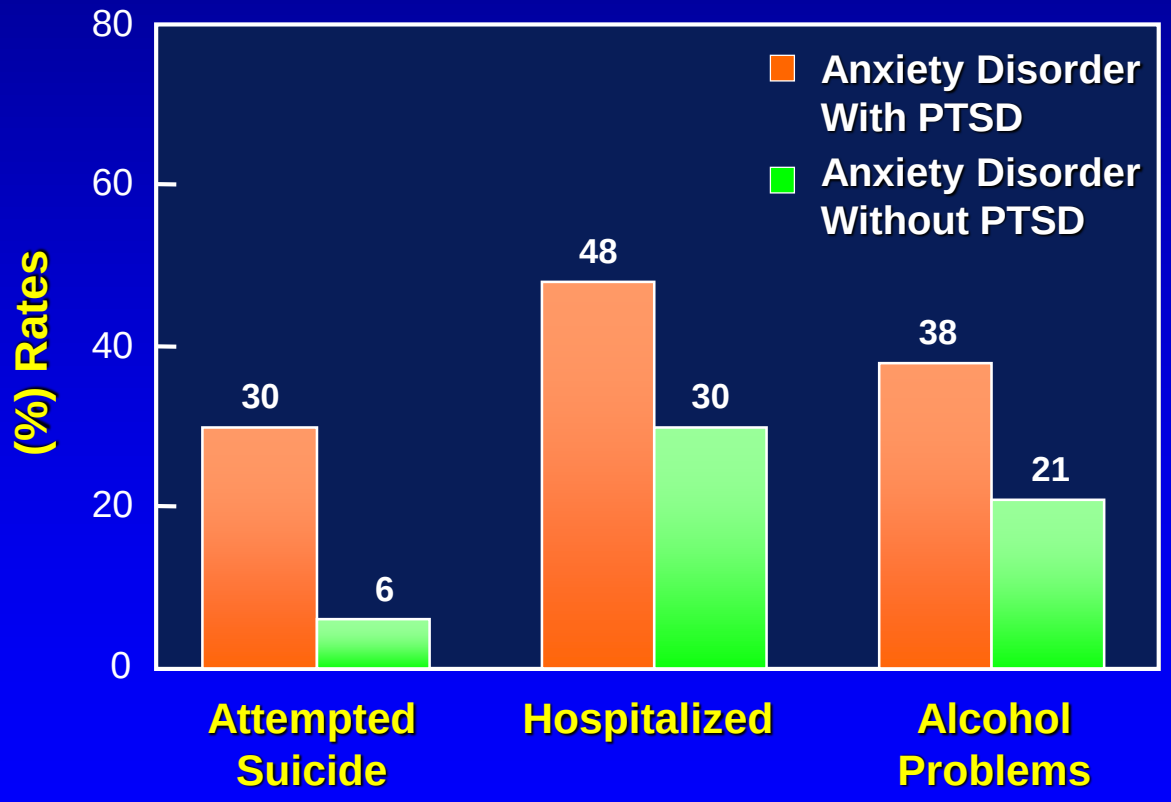
WOMEN



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

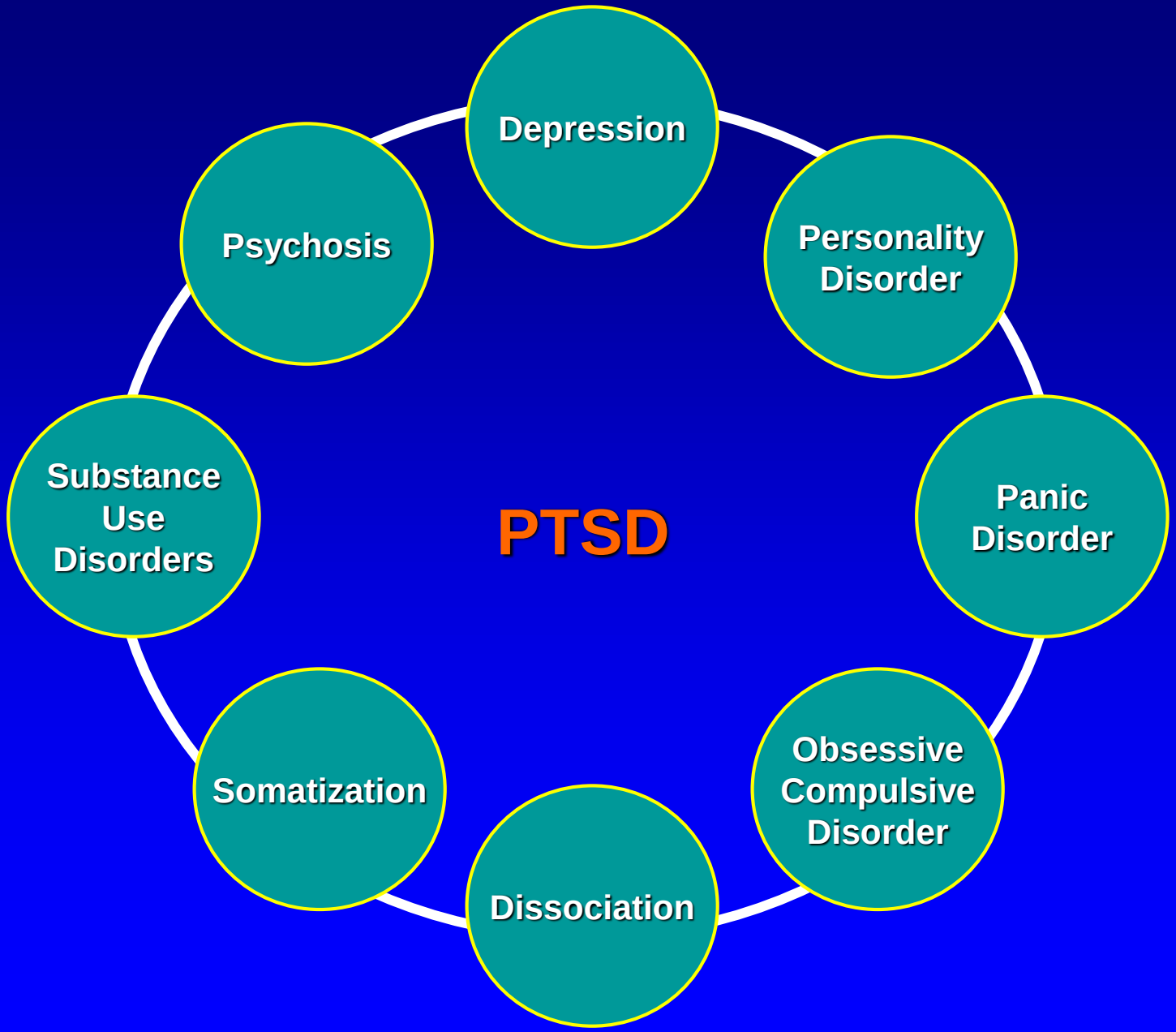
PTSD

Impact of Comorbid PTSD in Subjects With Other Anxiety Disorders



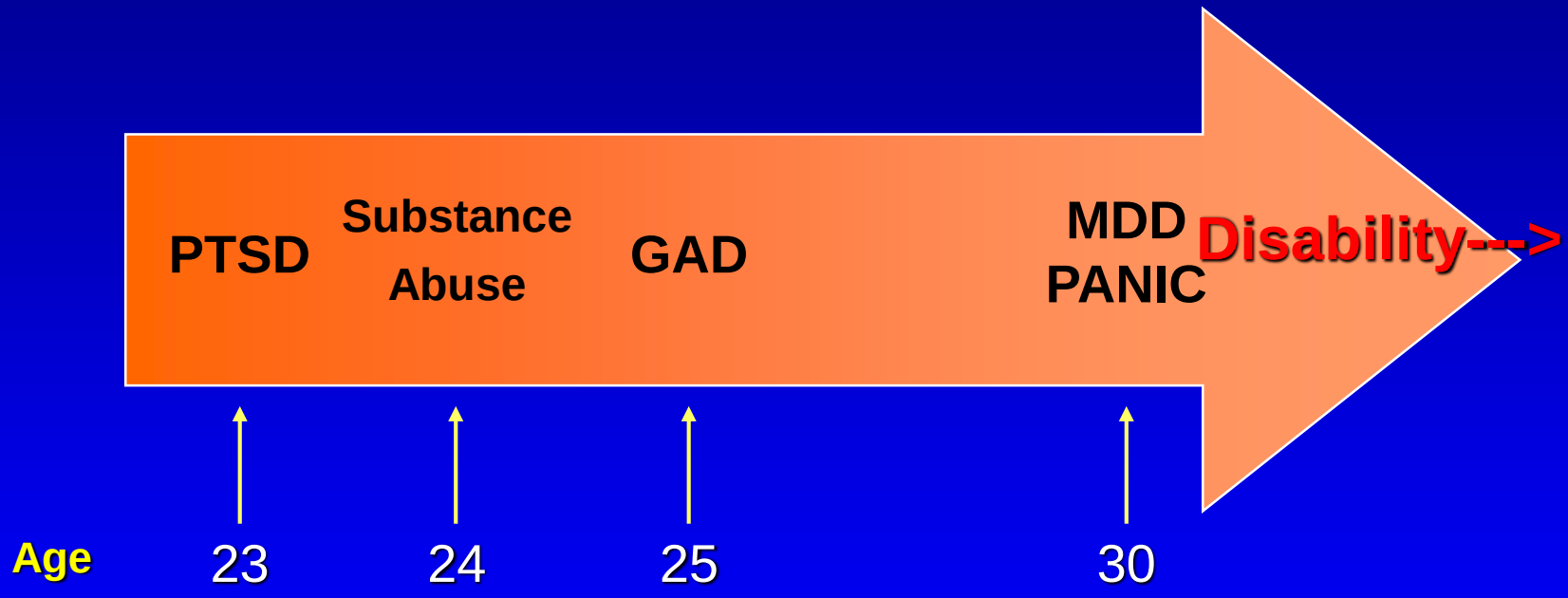
Warshaw MG et al. *Am J Psychiatry*. 1993;150:1512–1516.

DIAGNOSTIC SPECTRUMS



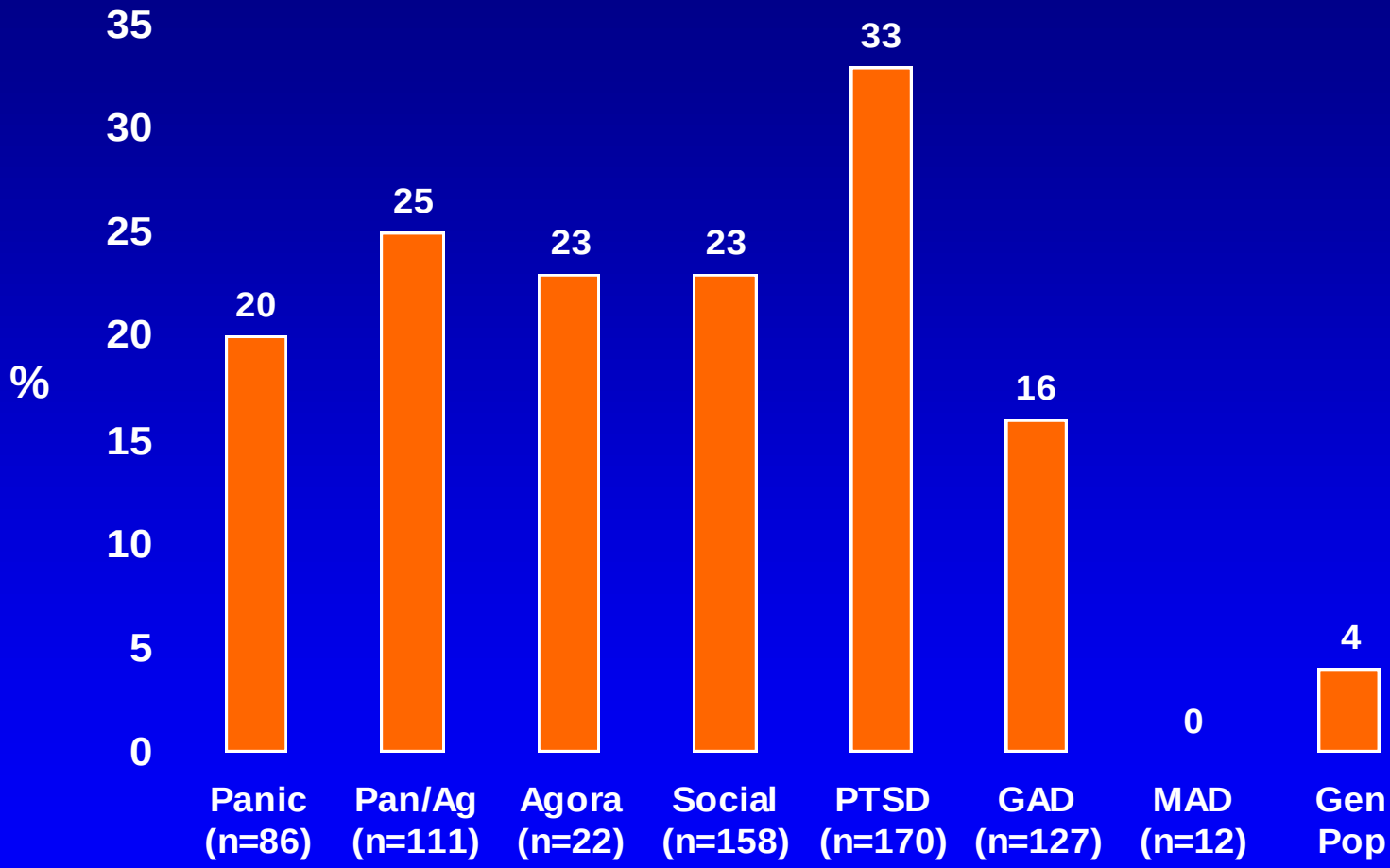
PTSD

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.

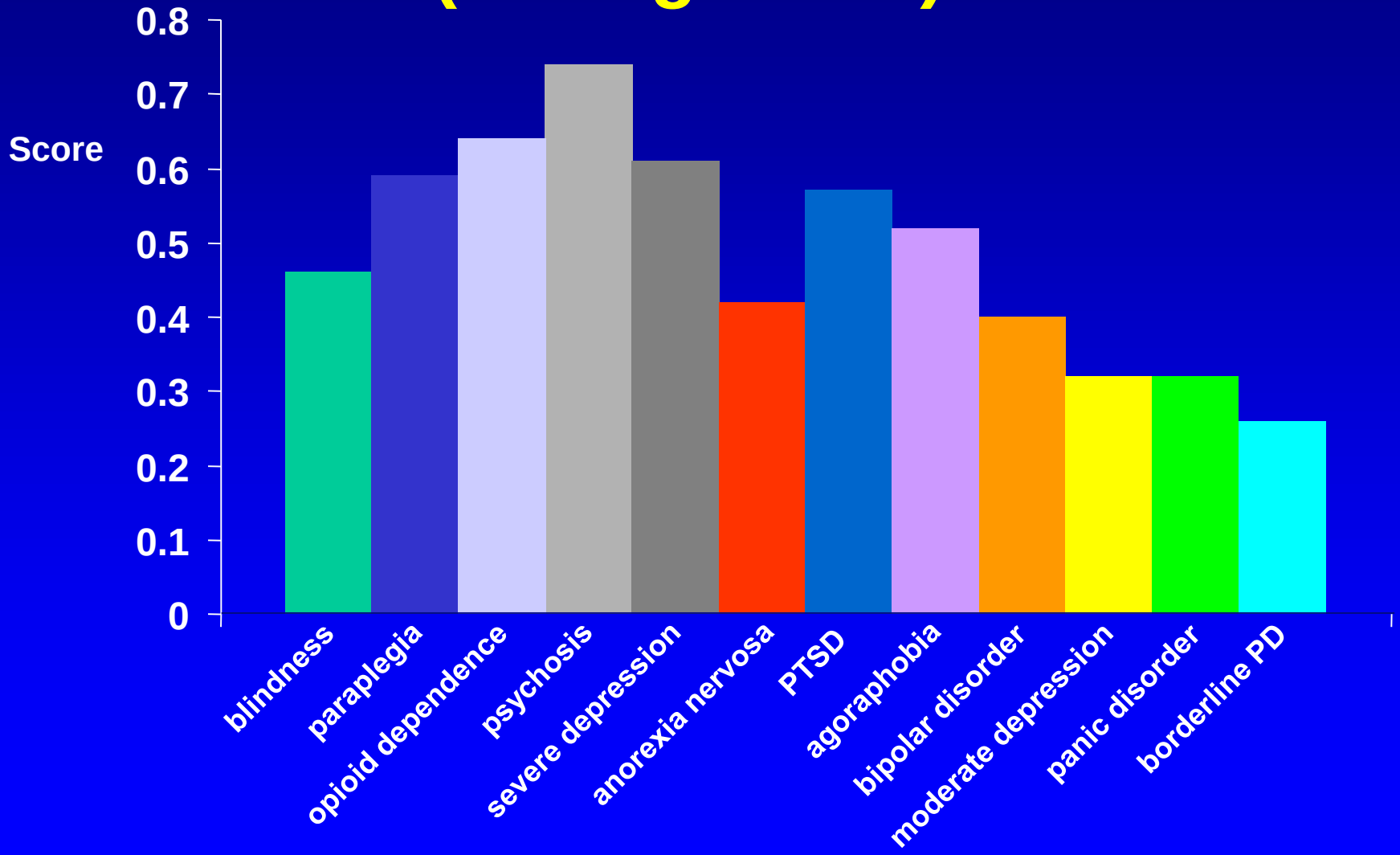
Lifetime History of Suicidal Attempts by Anxiety Disorder



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

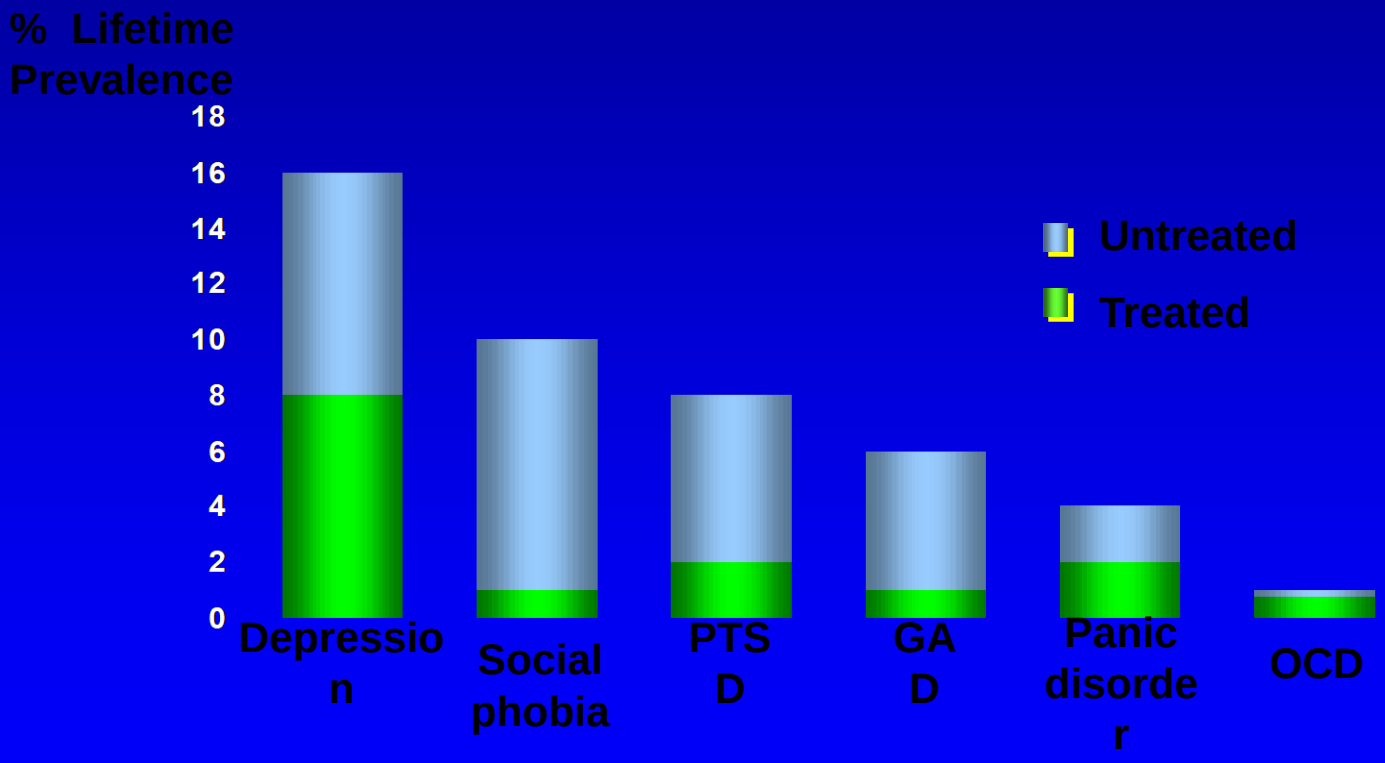
Disability Weights (Rating Scale)



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

PTSD: Unmet Medical Need

Few Are Treated



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

PTSD

Treatment Options

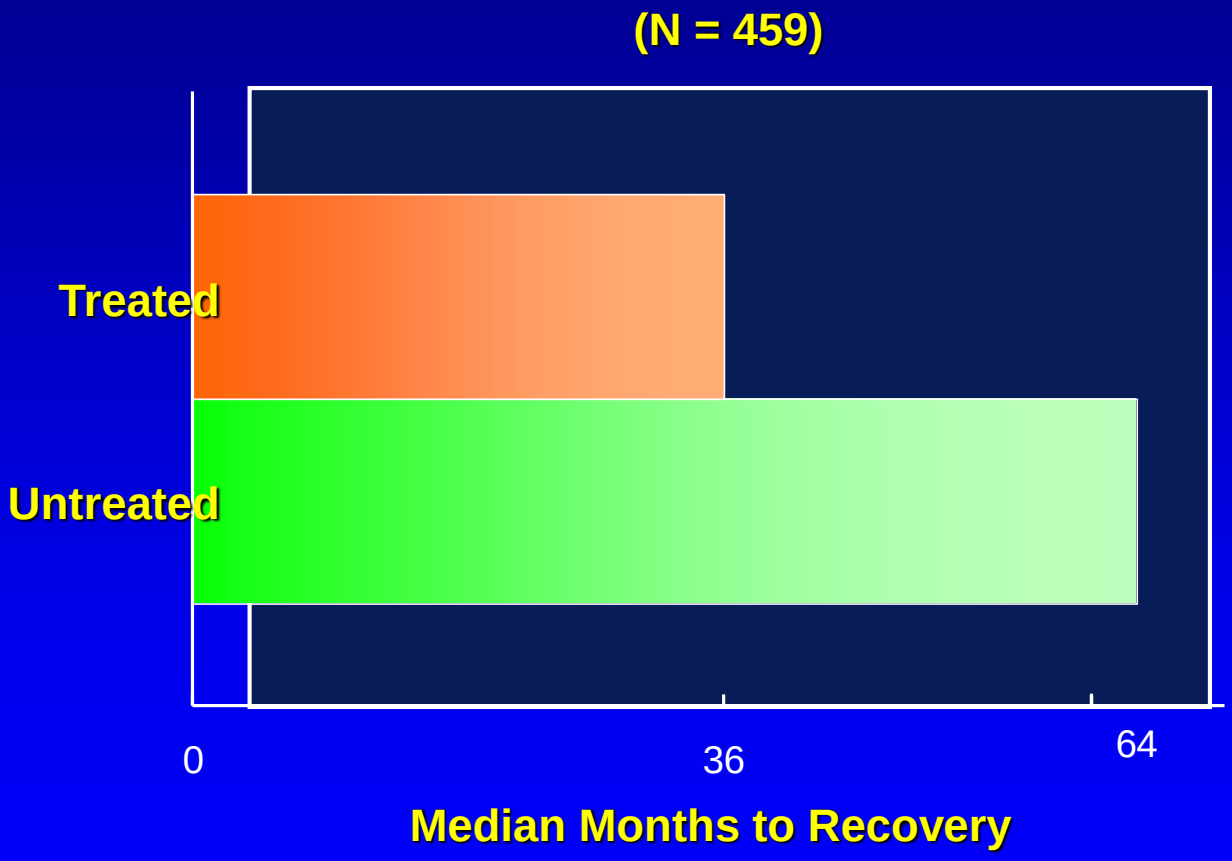
Psychotherapy

Pharmacotherapy

Multimodal treatment

PTSD

Impact of Treatment on Recovery



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

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

ANXIETY MANAGEMENT TREATMENT/COMBINATIONS*

Study	Population	Comparison	Results
Resick et al., 1988	Female rape victims	WL vs SIT vs supportive vs assertion training	All active treatments superior to PBO
Resick & Schnicke, 1992	19 rape victims	Combined vs WL	Combined superior to wait list
Foa et al., 1995	Women rape victims	E vs SIT vs combined	All 3 effective
Marks et al., 1998	87 civilian trauma victims	Relaxation vs SIT vs cognitive restructuring vs combination	All superior to relaxation

*Combined = exposure + anxiety management techniques

EYE MOVEMENT DESENSITIZATION AND REPROCESSING

Study	Population	Comparison	Result
Boudewyns et al., 1993	Veterans	EMDR vs E vs milieu	All negative
Pitman et al., 1996	17 Vietnam veterans	EMDR vs EMDR without eye movement	No difference between groups
Wilson et al., 1995	80 male & female trauma victims	EMDR vs delayed treatment	EMDR superior
Vaughan et al., 1994	36 male & female with PTSD	EMDR vs E vs muscle relaxation vs WL	All active treatments effective
Jensen et al., 1994	25 Vietnam veterans	EMDR vs milieu	No difference
Rothman, 1995	21 female victims	EMDR vs WL	EMDR superior

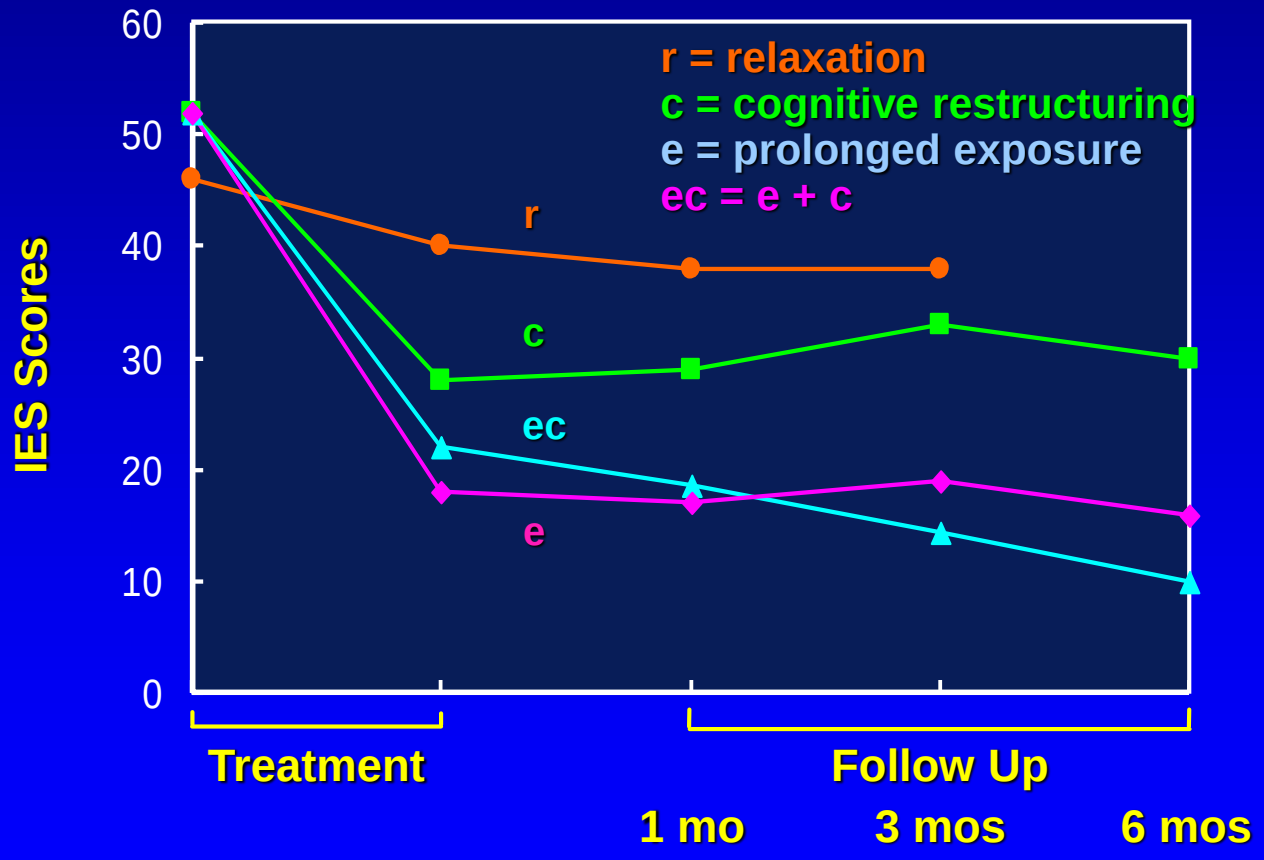
EXPOSURE STUDIES

Study	Population	Comparison	Results
Brom et al., 1989	112 males & females	E* vs psychodynamic vs hypnosis vs WL*	All active treatments superior to waitlist
Cooper & Clum, 1987	26 Vietnam veterans	Standard treatment vs standard treatment + E	Exposure group increased improvement
Keane et al., 1989	24 Vietnam veterans	E vs WL	Exposure group more improved, especially re-experiences
Boudewyns et al., 1990	Vietnam veterans	E vs individual counseling	Exposure improved psychologically but not physiologically or PTSD symptoms
Foa et al., 1991	Women civilian trauma	Supportive vs E vs WL vs SIT*	SIT & exposure improved on all PTSD clusters

*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.

PHARMACOTHERAPY

Neurobiological basis

Evidence of efficacy

What responds

PTSD

related pathology

Who responds

Type of trauma

comorbidity

gender

culture

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., '04

AIMS OF PHARMACOTHERAPY

Reduce core symptoms

Reduce associated symptoms

Facilitate other therapy

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

Efficacy supported by smaller RCTs

TCAs, MAOIs, lamotrigine; adjunctive olanzapine, risperidone, prazosin

Efficacy not supported by trials

benzodiazepines

Benefits suggested in open trials

Other SSRIs, Novel APs, AEDs, trazodone, nefazodone, noradrenergic suppressor/antagonists

Medication Treatment for PTSD: Recommendations

1st Line

SSRIs (sertraline, paroxetine, fluoxetine)

2nd Line

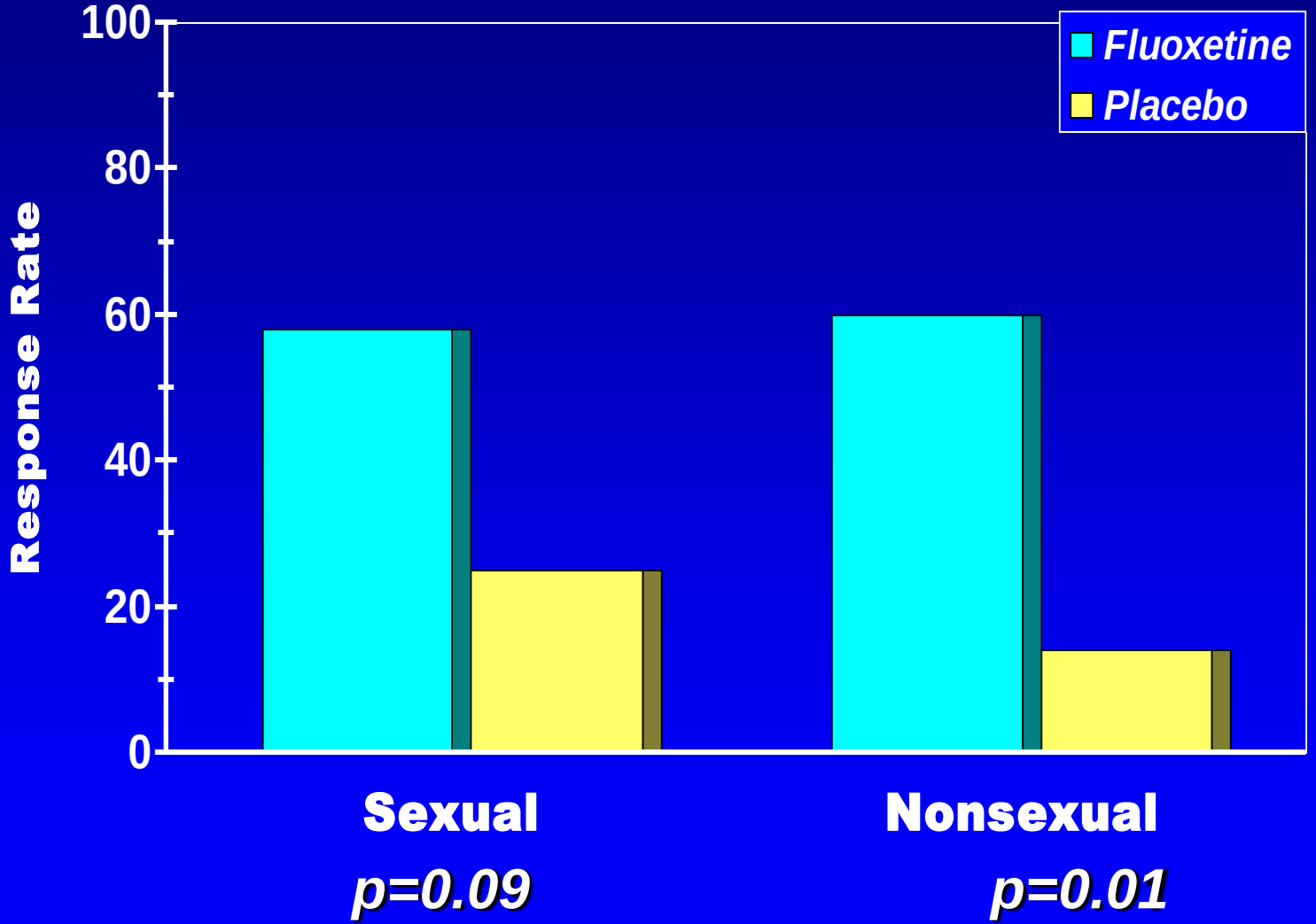
other novel and traditional ADs; noradrenergic agents; anticonvulsant/mood stabilizers; novel AP medications

Not recommended

traditional APs, benzodiazepines*

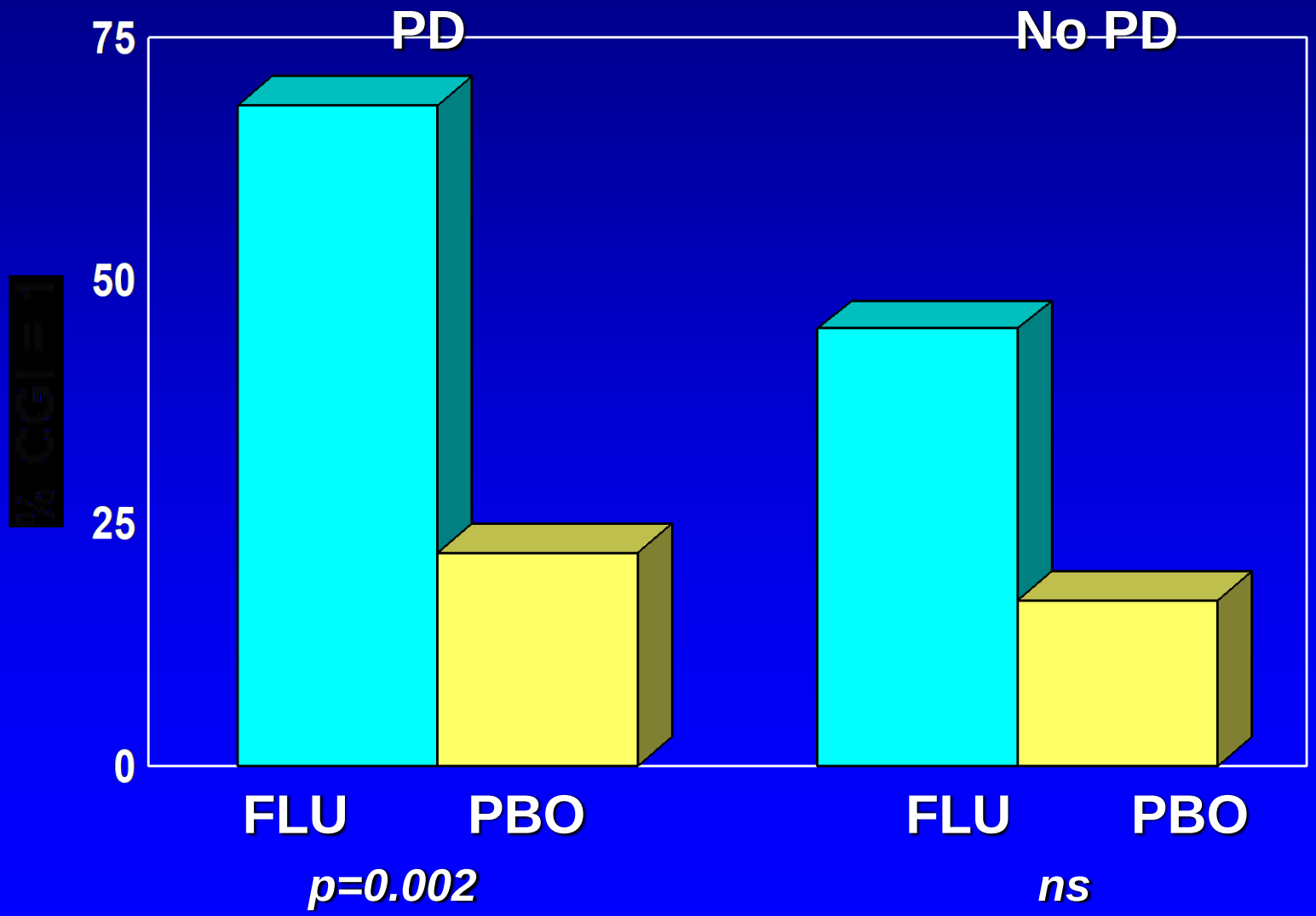
Friedman et al., 2000

SEXUAL TRAUMA-RELATED PTSD

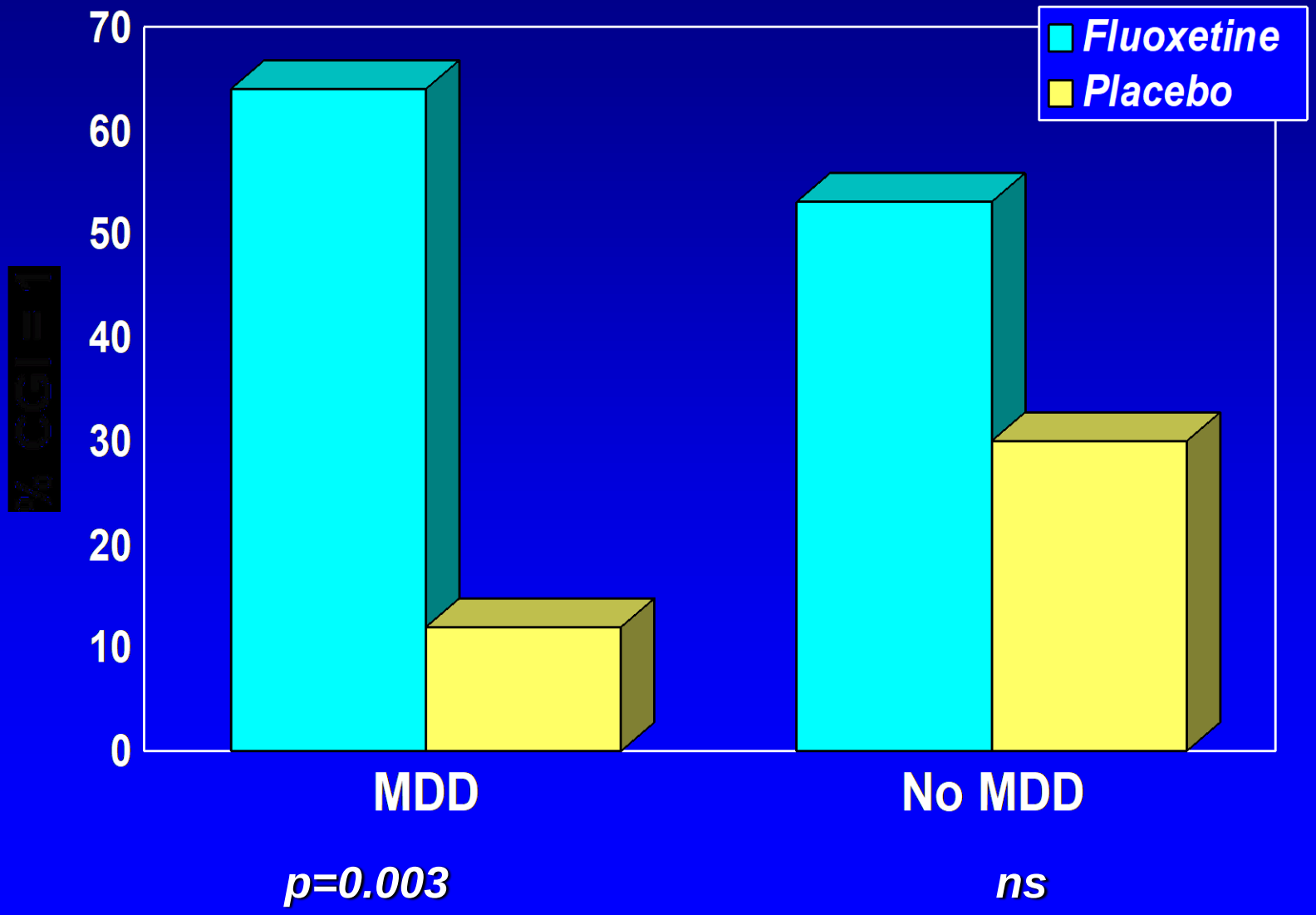


Davidson et al., 1997

DOES COMORBID PERSONALITY DISORDER AFFECT THE RESPONSE TO AN SSRI?

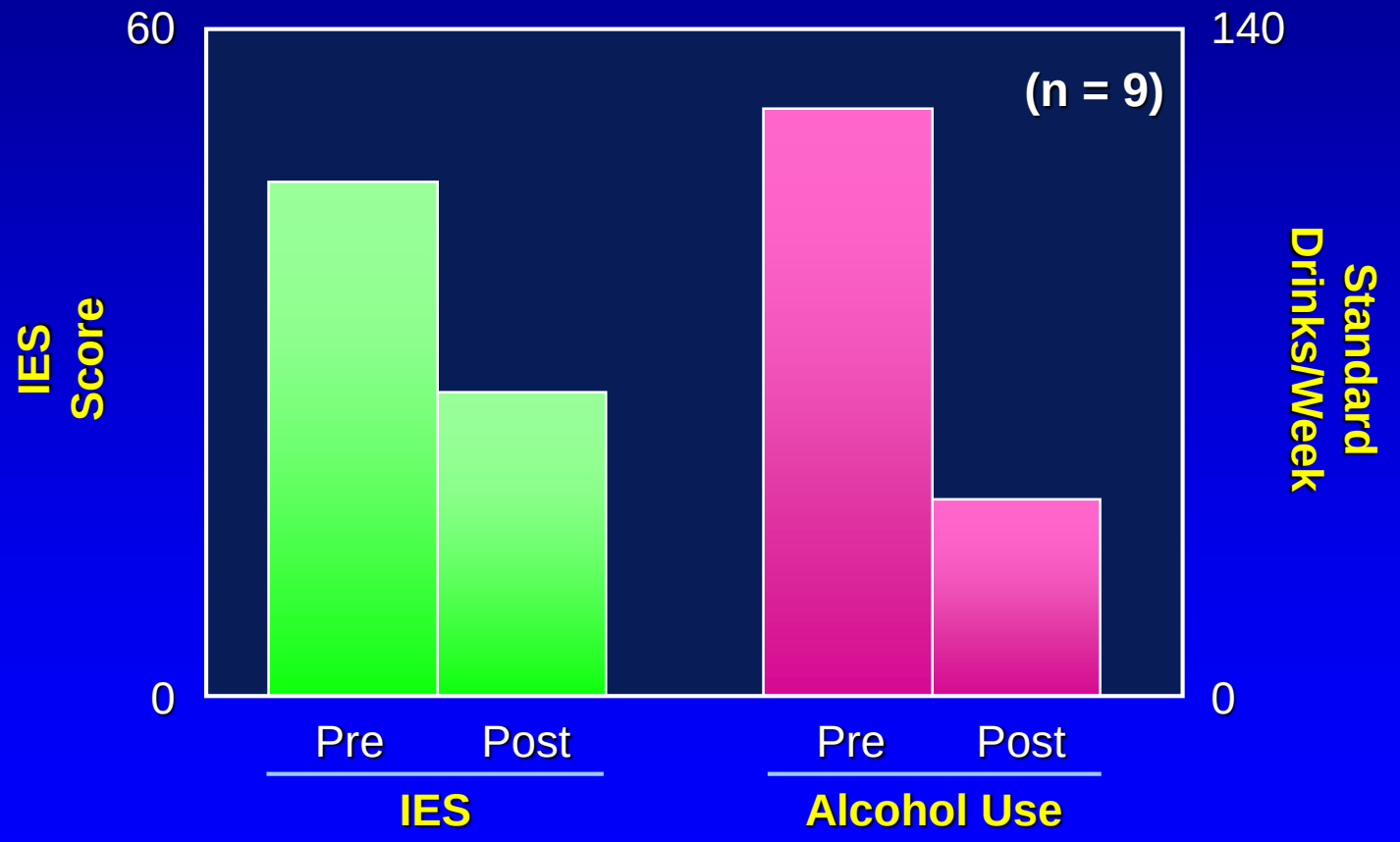


DOES COMORBID DEPRESSION AFFECT THE RESPONSE TO AN SSRI?



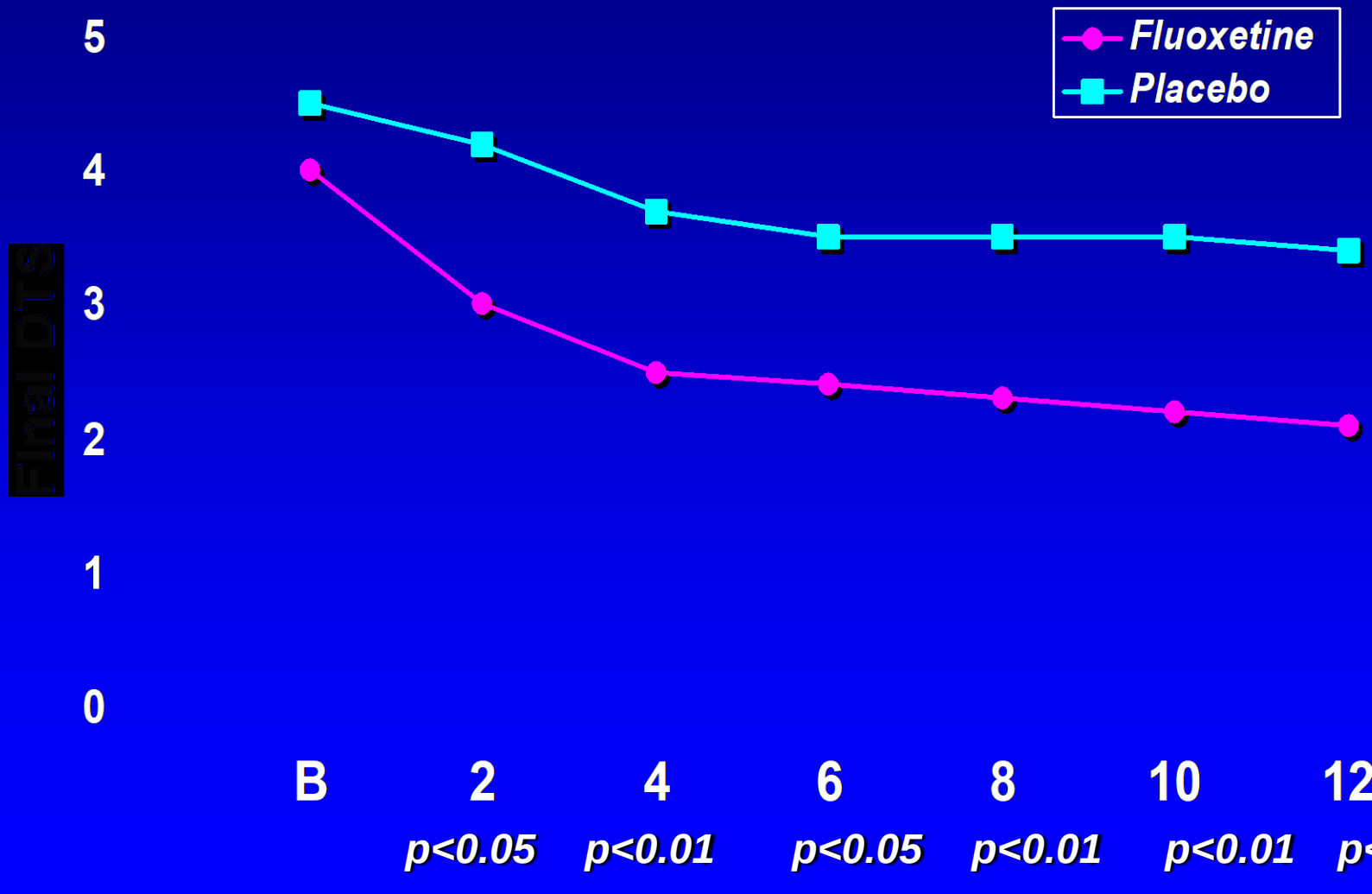
PTSD Treatment With SSRIs

Open-Label Sertraline in Comorbid PTSD and Alcoholism



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

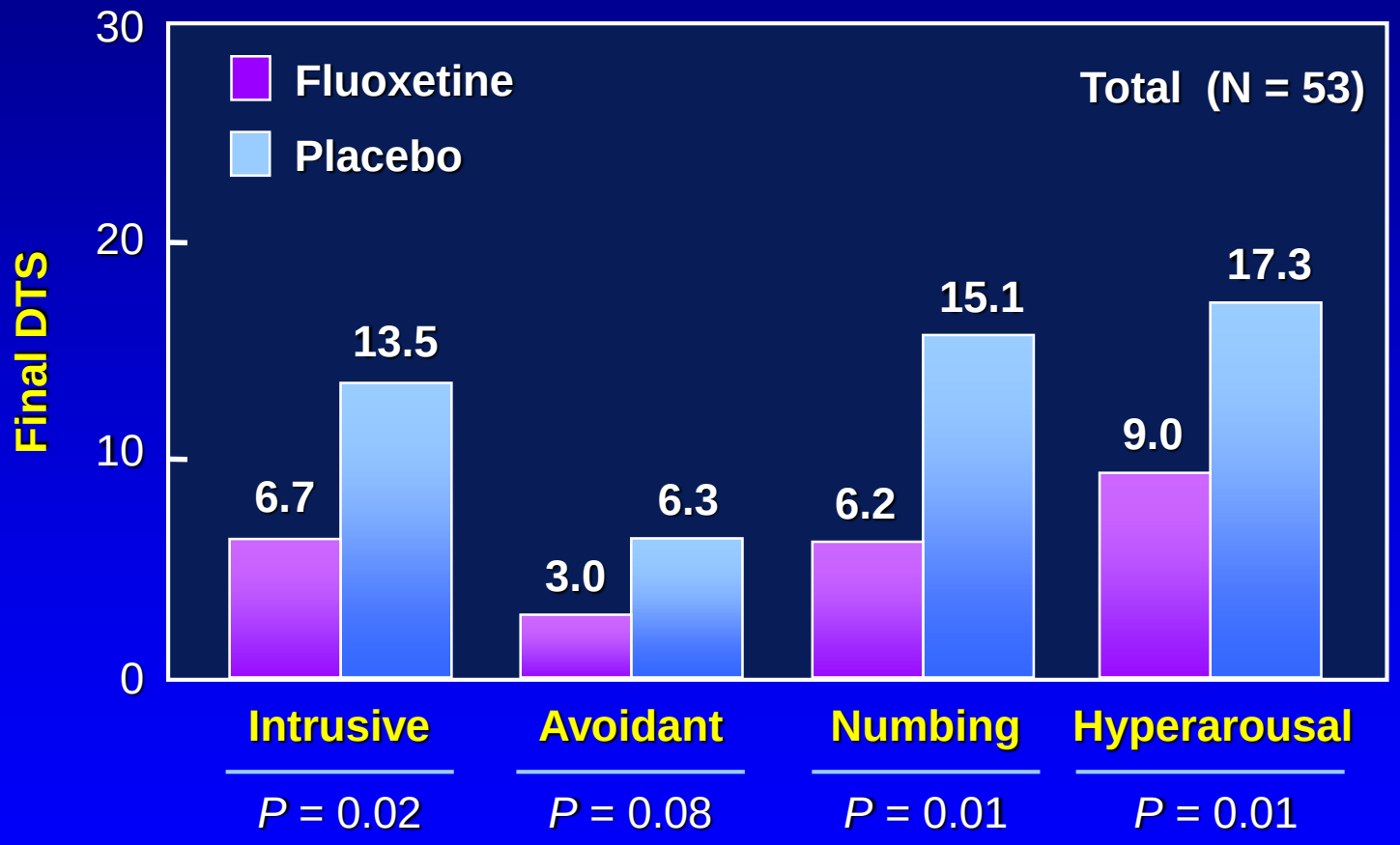
GLOBAL SEVERITY OF PTSD
Fluoxetine vs Placebo



Davidson et al., 1997

PTSD Treatment With SSRIs

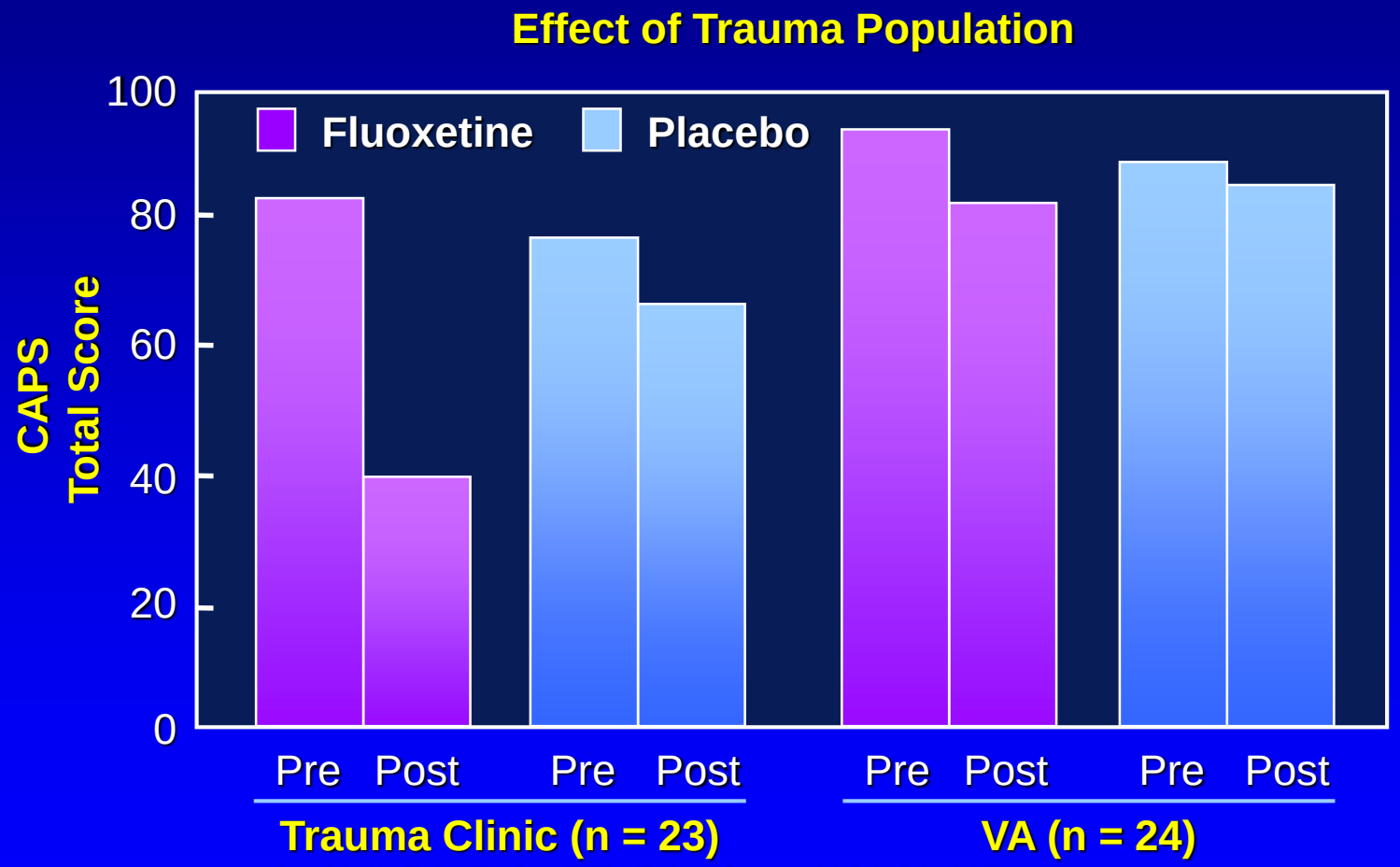
Effect of Fluoxetine in Symptom Clusters



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

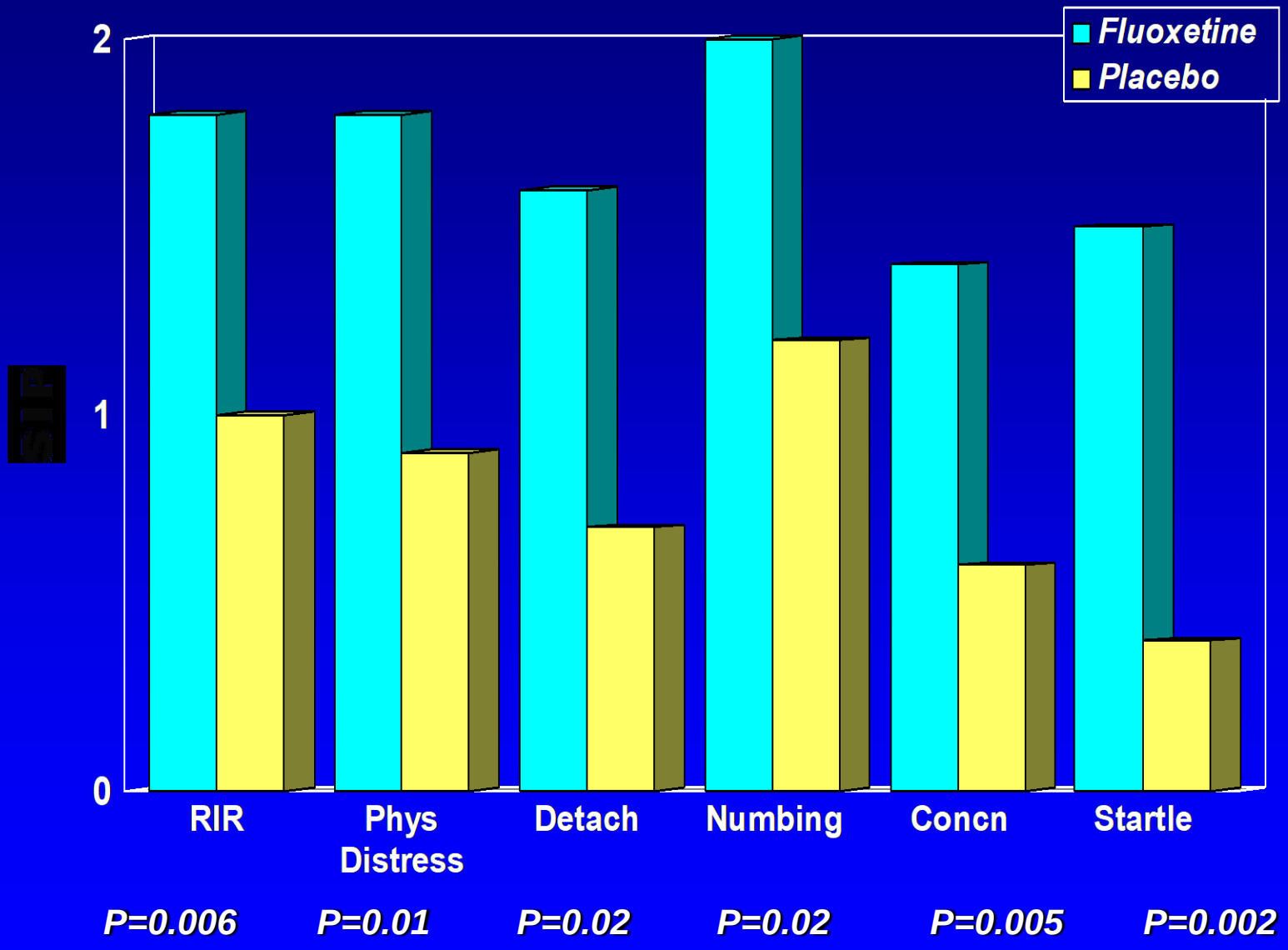
PTSD Treatment With SSRIs

Effect of Fluoxetine



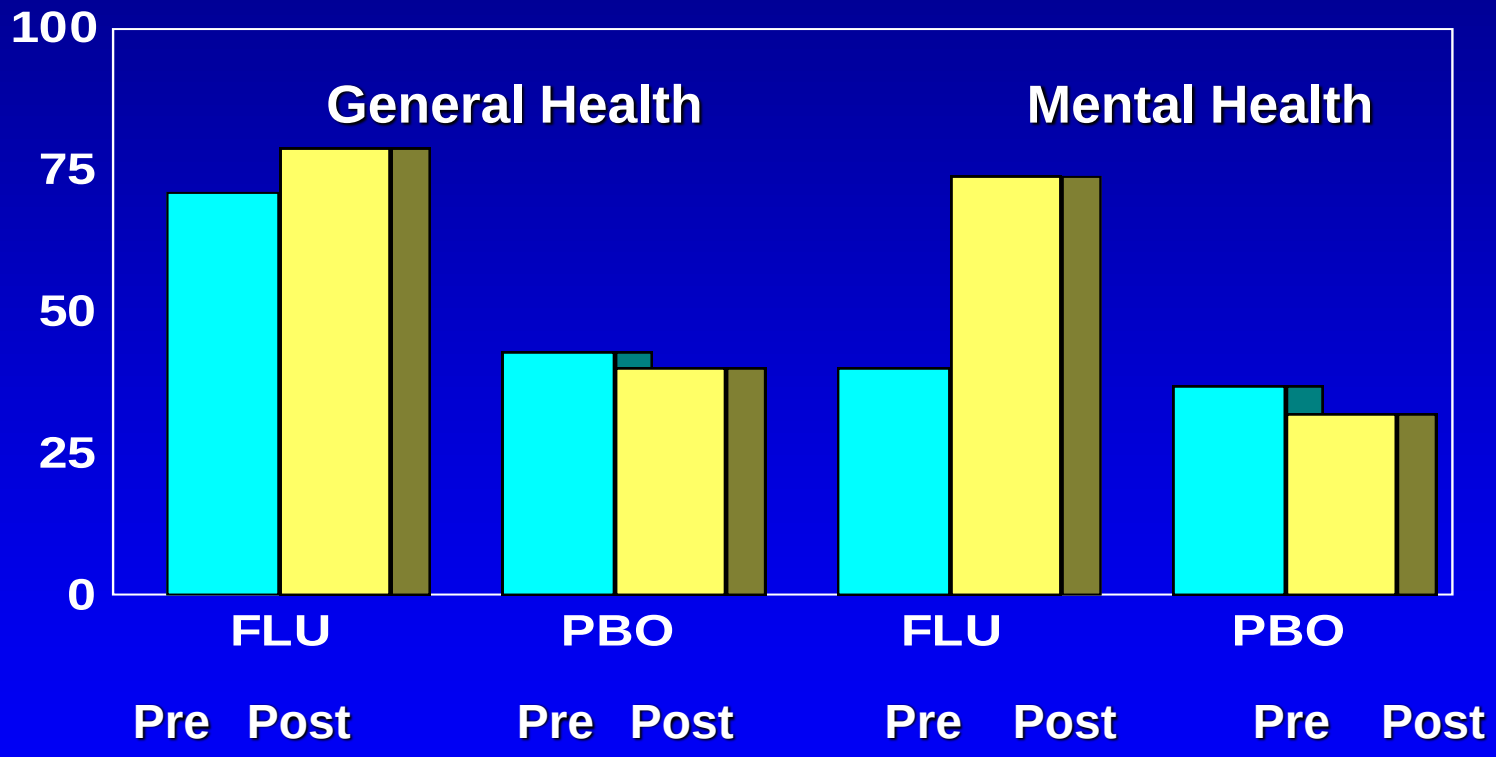
van der Kolk BA, Fisler RE. *Prim Care*. 1993;20:417–432.

WHICH SYMPTOMS RESPOND TO AN SSRI?



Davidson et al., 1997

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

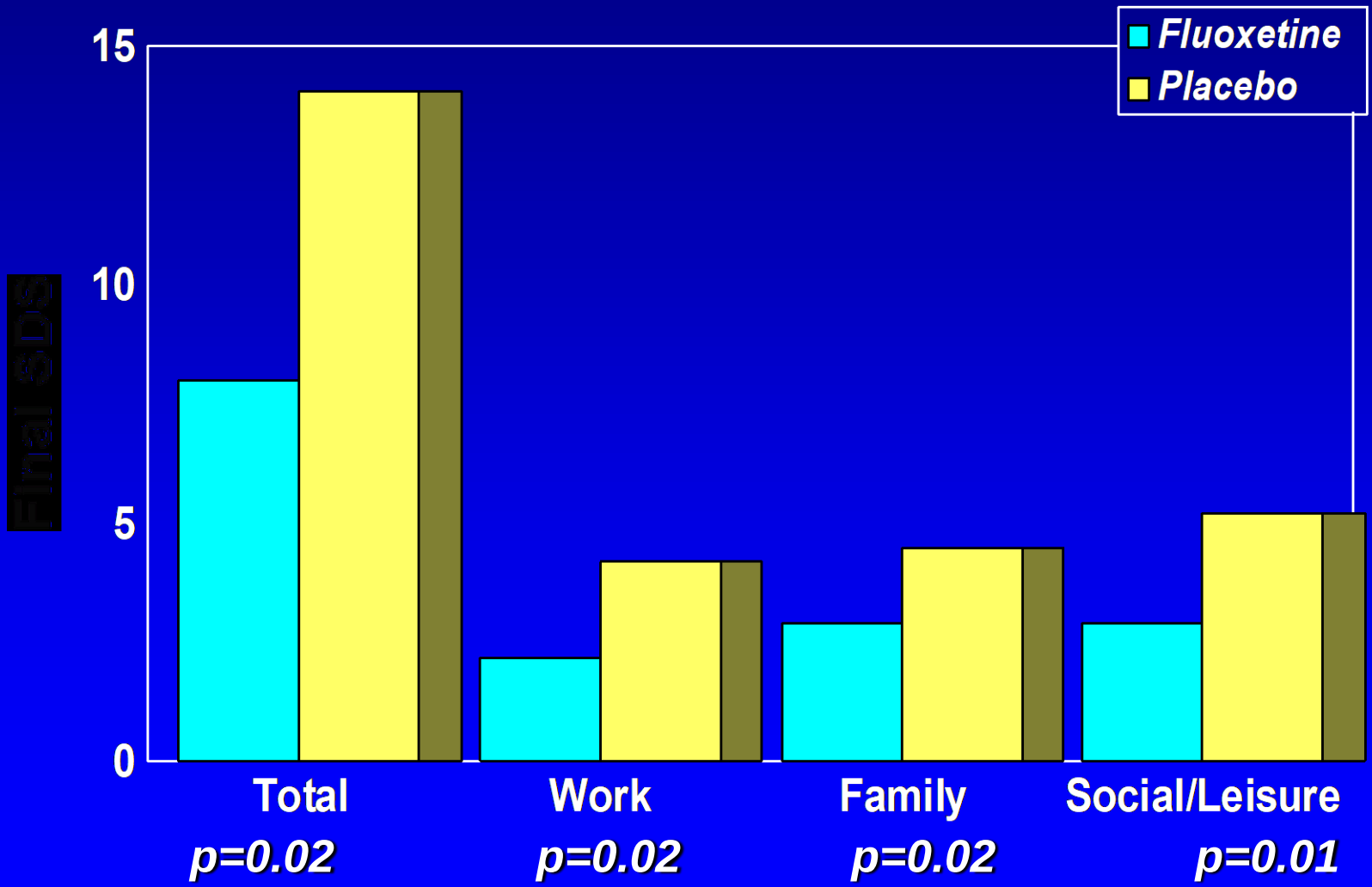


p=0.006

ns

Davidson et al., 1997

IMPROVEMENT IN DISABILITY: Fluoxetine vs Placebo



Davidson et al., 1997

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

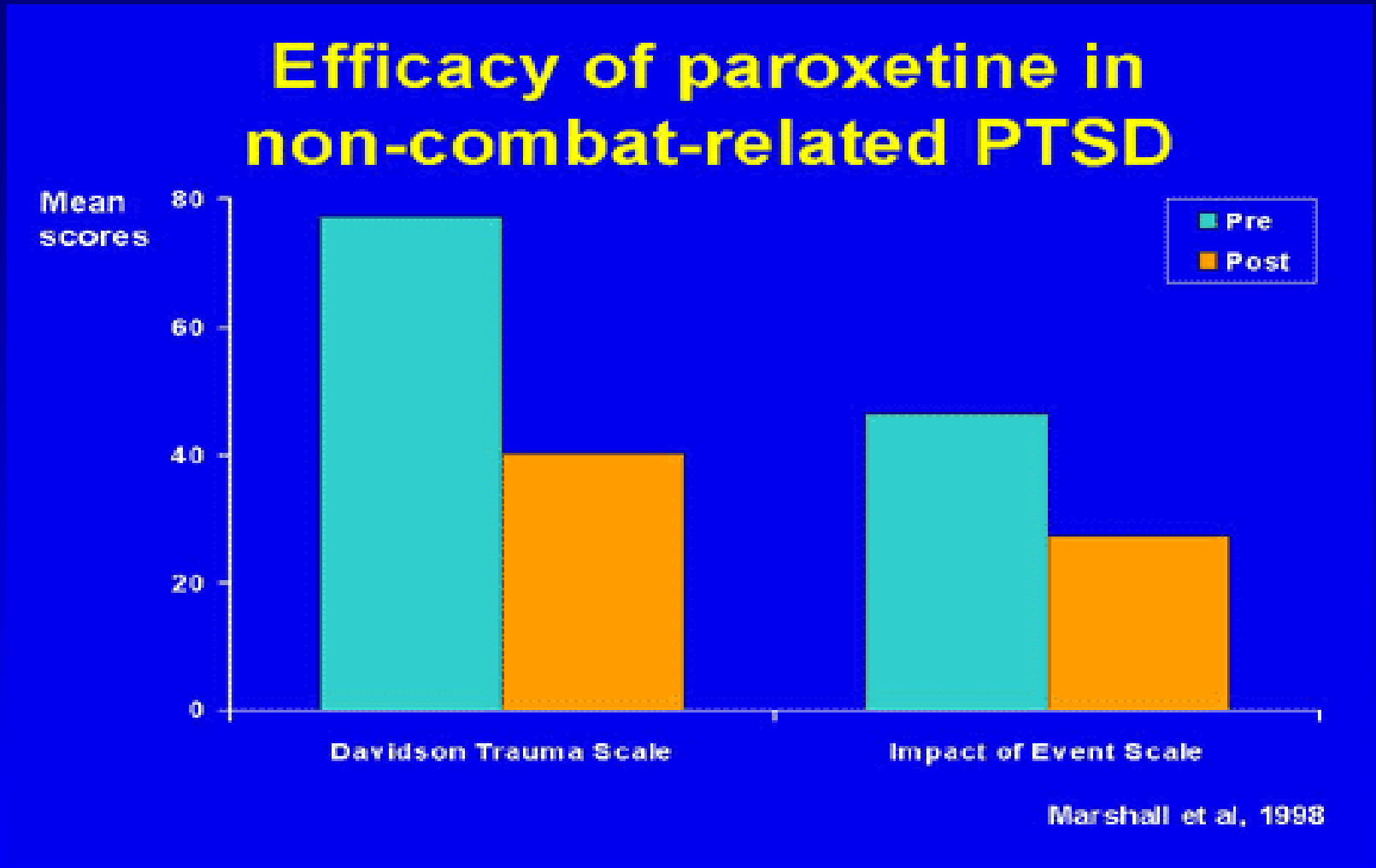
SEQUENCE OF SYMPTOM IMPROVEMENT WITH FLUOXETINE (DTS)

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

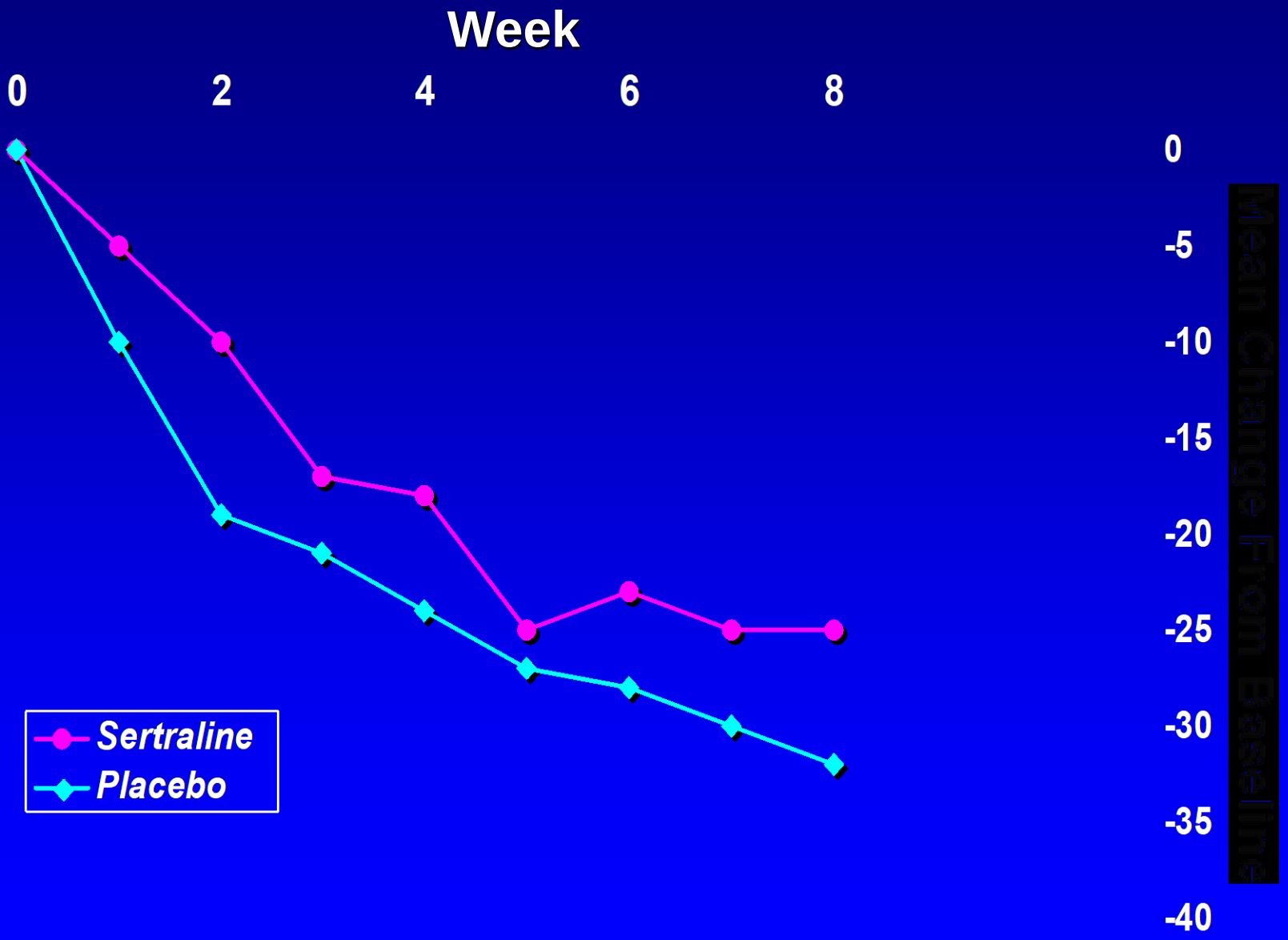
*p<0.05 **p<0.01 ***p<0.001

Davidson et al., 1997

Paroxetine in PTSD



Sertraline vs Placebo in Non-Combat-related PTSD



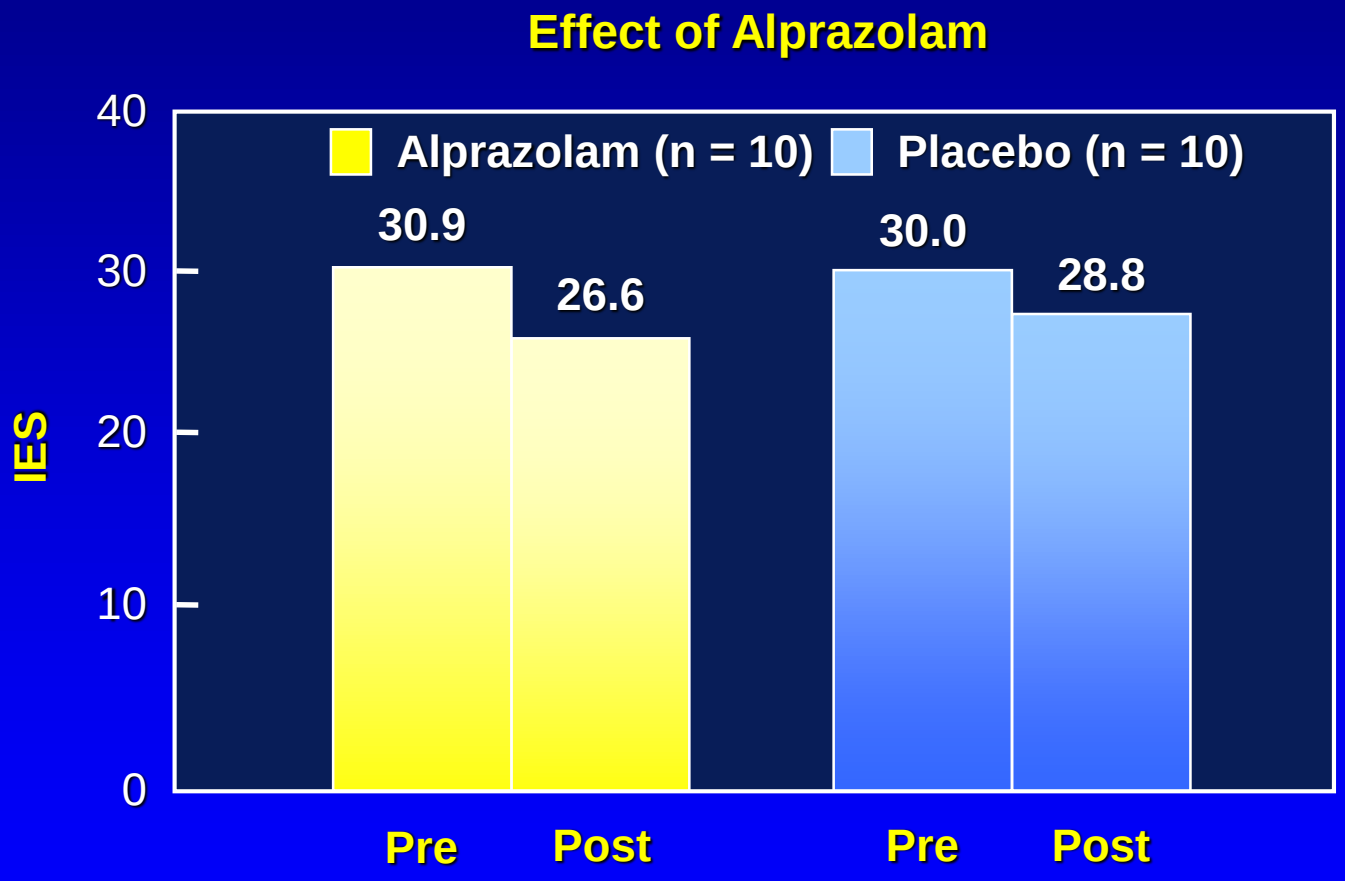
Brady et al.. JAMA 2000

ADVANTAGES AND DISADVANTAGES OF SSRIs

Advantages	Disadvantages
Effective on all PTSD symptoms	Medication interactions
Abuse-free	GI, sexual, activating side effects
Once daily	May be ineffective in some types of PTSD

PTSD

Treatment With Benzodiazepines



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

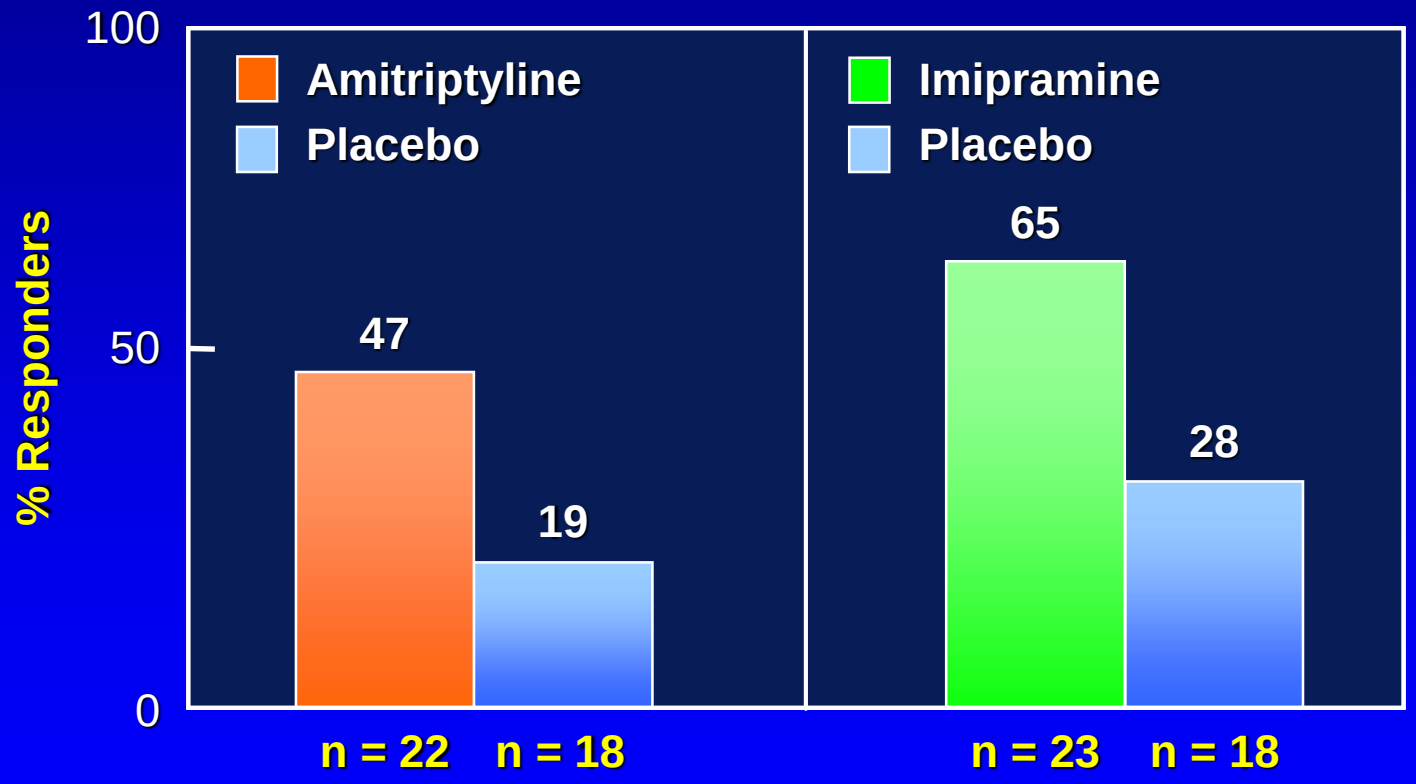
ADVANTAGES AND DISADVANTAGES OF BZDs

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.

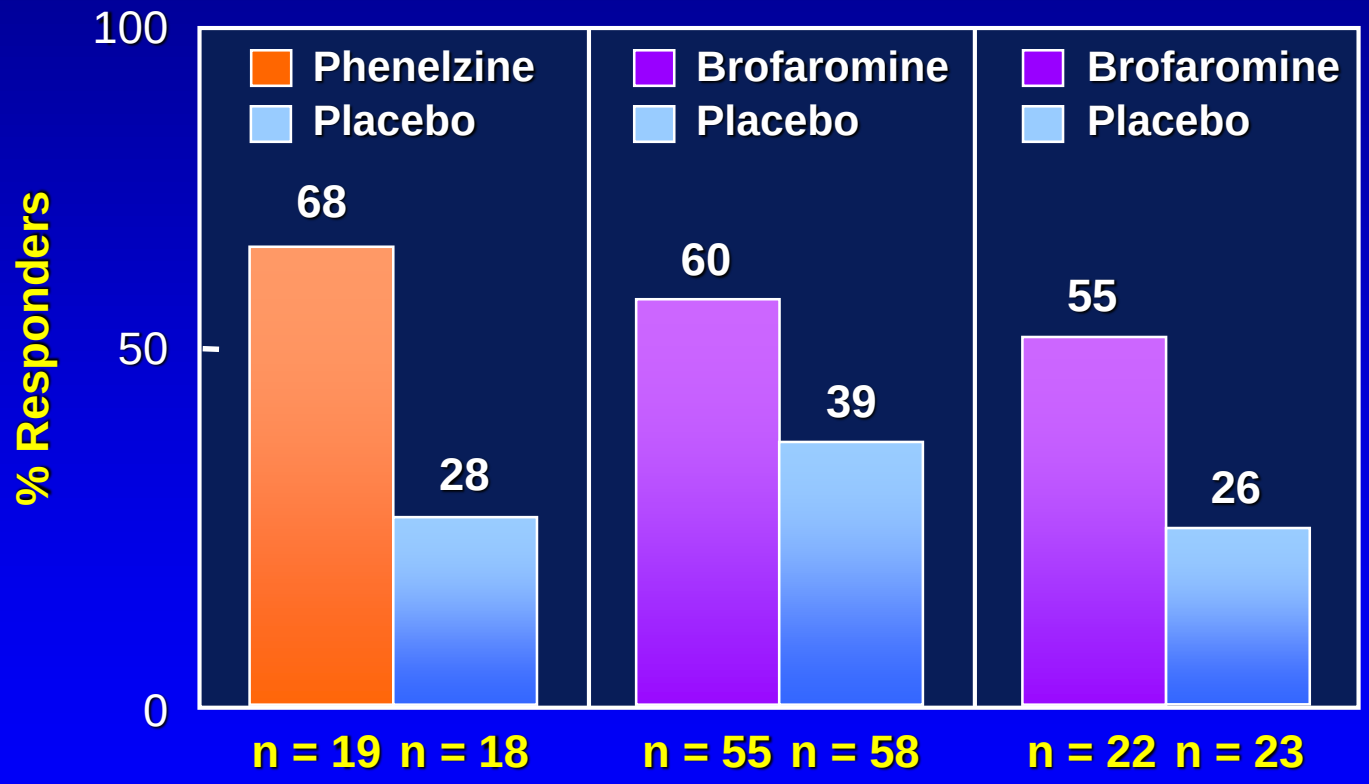
ADVANTAGES AND DISADVANTAGES OF TCAs

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

- **Olanzapine**
  - Adjunct efficacy, ? primarily related to sleep weight gain (Stein et al., AmJ Psych, 2002)
- **Preliminary support also for risperidone as add on Rx** (Leyba ’98 Psych Serv)
- **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)

Medication Treatments for Traumatic Nightmares (None are FDA approved for indication)

Prazosin (controlled trial)[1]

- Cyproheptadine — (positive results, open label; pilot placebo-controlled study,negative)[2,3]
- Trazodone[4]
- Nefazodone — (changes in qualitative features of dream recall)[5]
- Clonidine/guanfacine — (have been used in children)[6,7]
- Novel antipsychotics (adjunct use improves sleep)[8]

1. Raskind MA, et al. A J Psychiatry. 2002;160:371-3.
2. Brophy MH. Mil Med. 1991;156:100-101.
3. Jacobs-Rebhun S, et al. Am J Psych. 2000;157:1525-6
4. Ashford, Miller. 1996.
5. Mellman TA, et al. Depress Anxiety. 1999;9:146-148.
6. Kinzie JD, et al. J Nerv Ment Dis. 1994;182:585-587.
7. Horrigan JP, JAA CAP. 1996;35:975-976.
8. Stein MB et al., Am J Psychiatry. 2002; 159:1777-1779

PTSD

Summary

1. PTSD is common

   Usually chronic

   Presentations vary

   Comorbidity is the rule

2. Comprehensive assessment of patients is critical to develop an individualized treatment plan

3. Treatment often involves multiple modalities

CONCLUSIONS

PTSD prevalent and *treatable* disorder

CBT effective

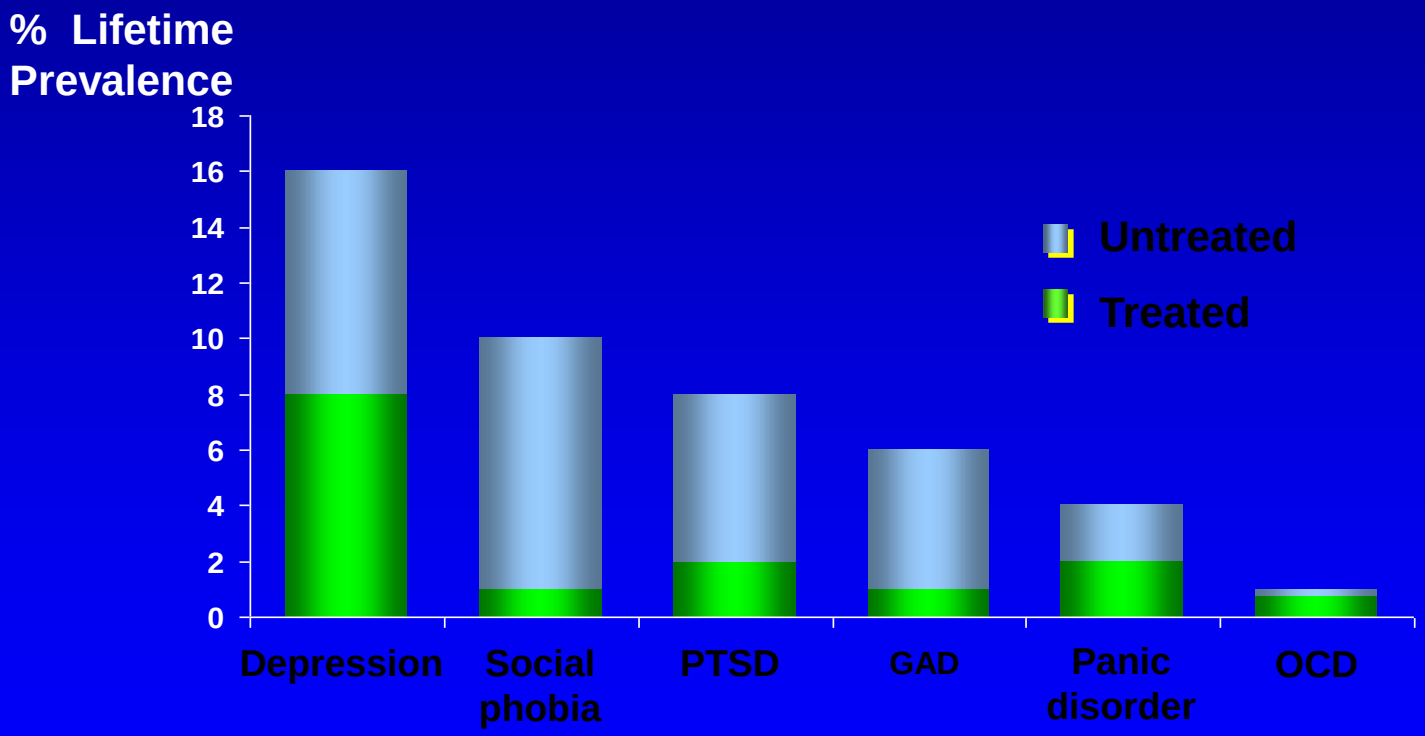
Antidepressant agents effective

SSRI, MAOI, TCA

Combined CBT & pharmacotherapy trial needed

PTSD: Unmet Medical Need

Few Are Treated



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

Post Lecture Exam
Question 1

True or False:

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

Question 2

True or False:

2. Combat-related PTSD is not responsive to treatment.

Question 3

1. **Pharmacological agents with proven efficacy in PTSD include all but which of the following:**

A. SSRI’s

B. TCA’s

C. MAOI’s

D. Benzodiazepines

E. Anticonvulsants

Question 4

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

A. EDMR

B. Breathing relaxation

C. Exposure

D. Thought-stopping

Answers to Pre & Post Competency Exams

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