POST-TRAUMATIC STRESS DISORDER
Comorbidity and Treatment

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Pre-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

True or False:

- Propranolol is an effective treatment for PTSD.

Question 4

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 5

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

A. EDMR
B. CBT
C. Breathing relaxation
D. Exposure
E. Thought-stopping

Post-Traumatic Stress Disorder (PTSD)

Lifetime prevalence in community of 1% to 14%

One of the least well-studied anxiety disorders

Combat-related PTSD is best studied

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

American Psychiatric Association, 1994.

POST-TRAUMATIC STRESS DISORDER

A characteristic set of symptoms following exposure to extreme traumatic stress

5. experience, witness, or confronted with actual or threatened death or injury
6. Response involves intense fear, helplessness, or horror

Duration more than one month

Significant functional impairment

POST-TRAUMATIC STRESS DISORDER

Experiencing symptoms (1 necessary)

5. intrusive recollections
6. recurrent dreams
7. flashbacks
8. psychological distress with reminders
9. physiologic reactivity with reminders

POST-TRAUMATIC STRESS DISORDER

Avoidance symptoms (3 necessary)

5. avoid thoughts/feelings/conversations
6. avoid activities, places, people
7. inability to remember
8. diminished interest
9. feelings of detachment
10. restricted affect
11. foreshortened future

POST-TRAUMATIC STRESS DISORDER

Arousal symptoms (2 necessary)

5. sleep difficulty
6. irritability
7. concentration
8. hypervigilance
9. exaggerated startle

PTSD

DSM-IV Criteria

Exposure to traumatic event with

5. **Actual or threatened death or serious injury**

and

5. **Response involving intense fear, helplessness, or horror**

American Psychiatric Association. *DSM-IV.* 1994.

PTSD

DSM-IV Criteria (cont.)

5. Re-experiencing the traumatic event
6. Persistent avoidance of stimuli associated with event
7. Numbing of general responsiveness
8. Symptoms of increased arousal
9. At least 1 month's duration (otherwise can diagnose Acute Stress Disorder)
10. Significant distress or impairment in social, occupational, or other functioning

American Psychiatric Association. *DSM-IV.* 1994.

PTSD

Associated Features

5. Alcohol/drug problems
6. Aggression/violence
7. Suicidal ideation, intent, attempts
8. Dissociation
9. Distancing
10. Problems at work
11. Marital problems
12. Homelessness

PTSD

Sleep Disturbances

Subjective

5. Trauma-related nightmares
6. Insomnia/non-restorative sleep

Objective (EEG findings)

5. Increased REM density/impaired REM sleep maintenance
6. Increased motor activity

Ross RJ et al. *Sleep*. 1994;17:723–732.
Mellman TA et al. *Sleep*. 1997;20:46–51.

PTSD

Clinical Implications of Sleep Disturbances

5. Irritability
6. Vigilance
7. Impaired concentration
8. Increased risk for subsequent mood and anxiety disorders

Overview of PTSD

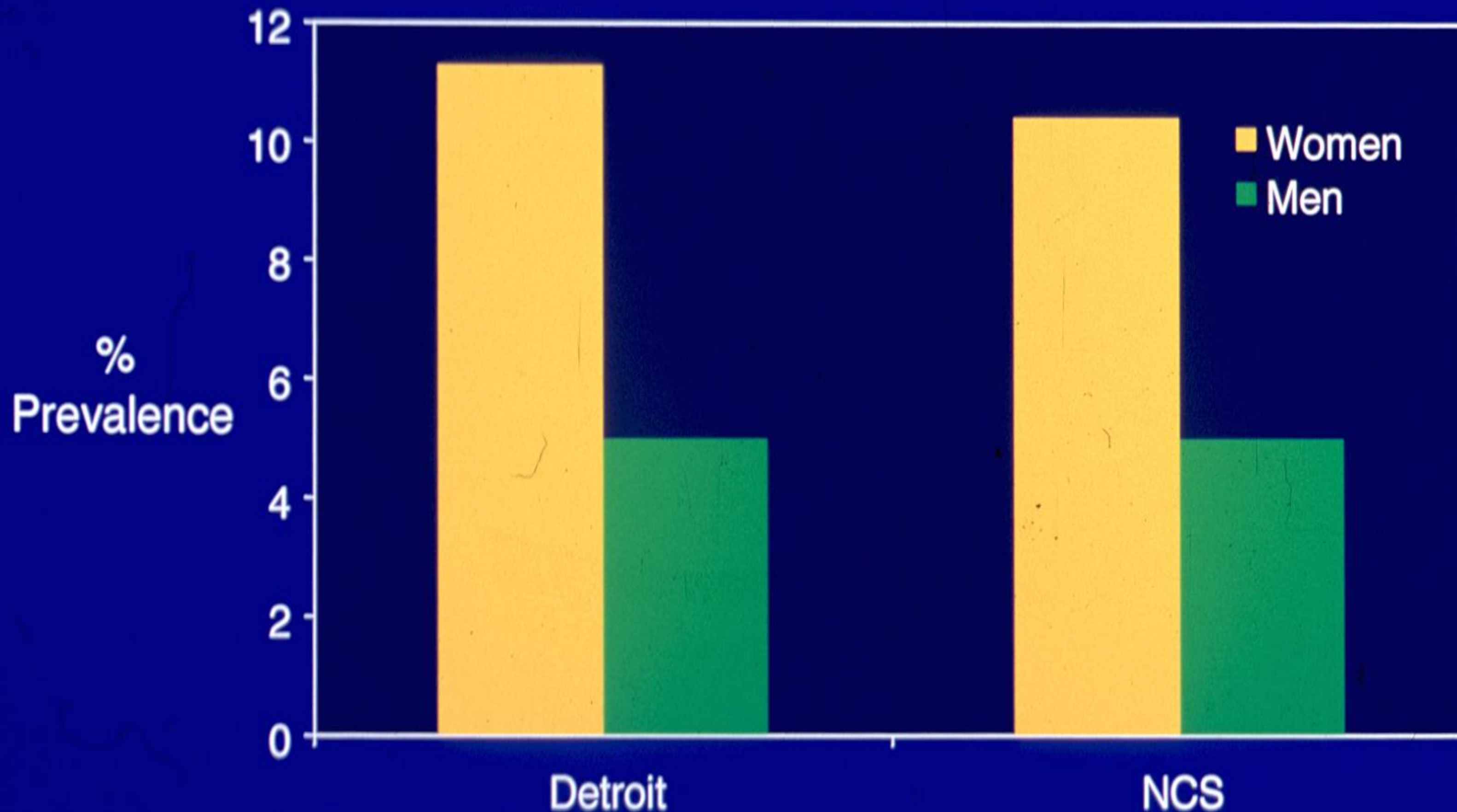
5. Epidemiology
6. Diagnosis
7. Psychiatric Comorbidity
8. Treatment

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.

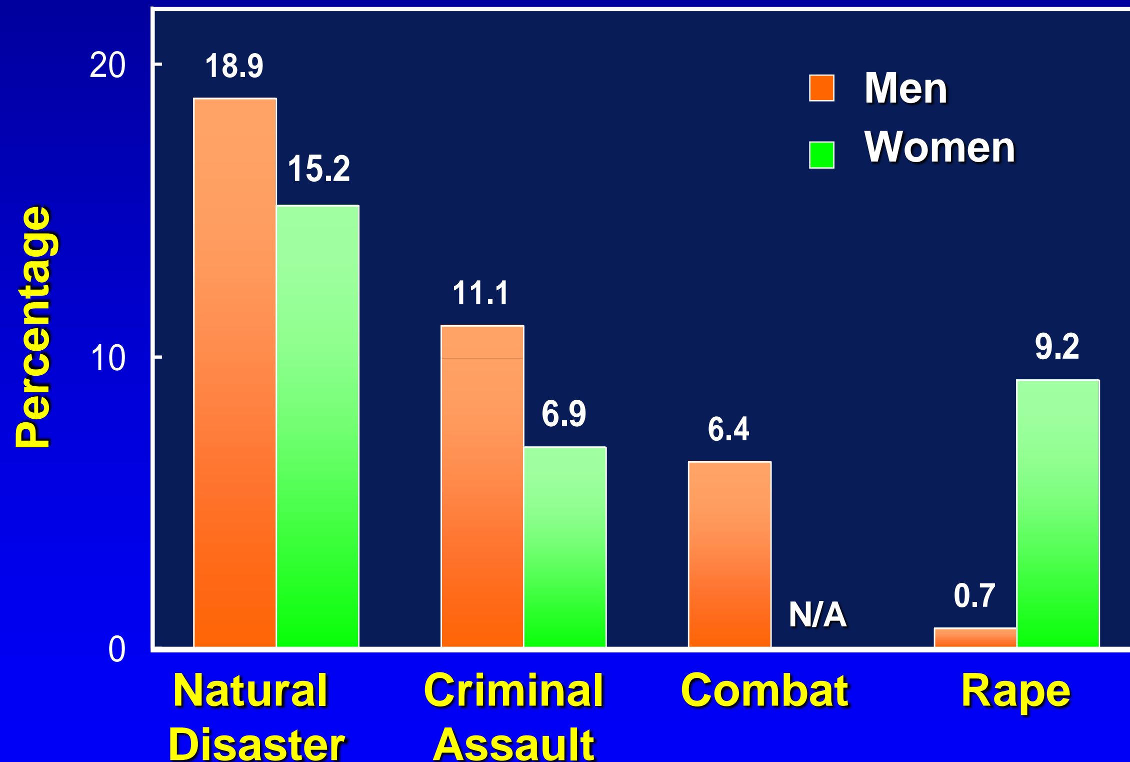
Lifetime Prevalence of PTSD



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

5. Severity of trauma (ie, threat, duration, injury, loss)
6. Prior trauma
7. Gender
8. Prior mood and/or anxiety disorders
9. Family history of mood or anxiety disorders
10. Education

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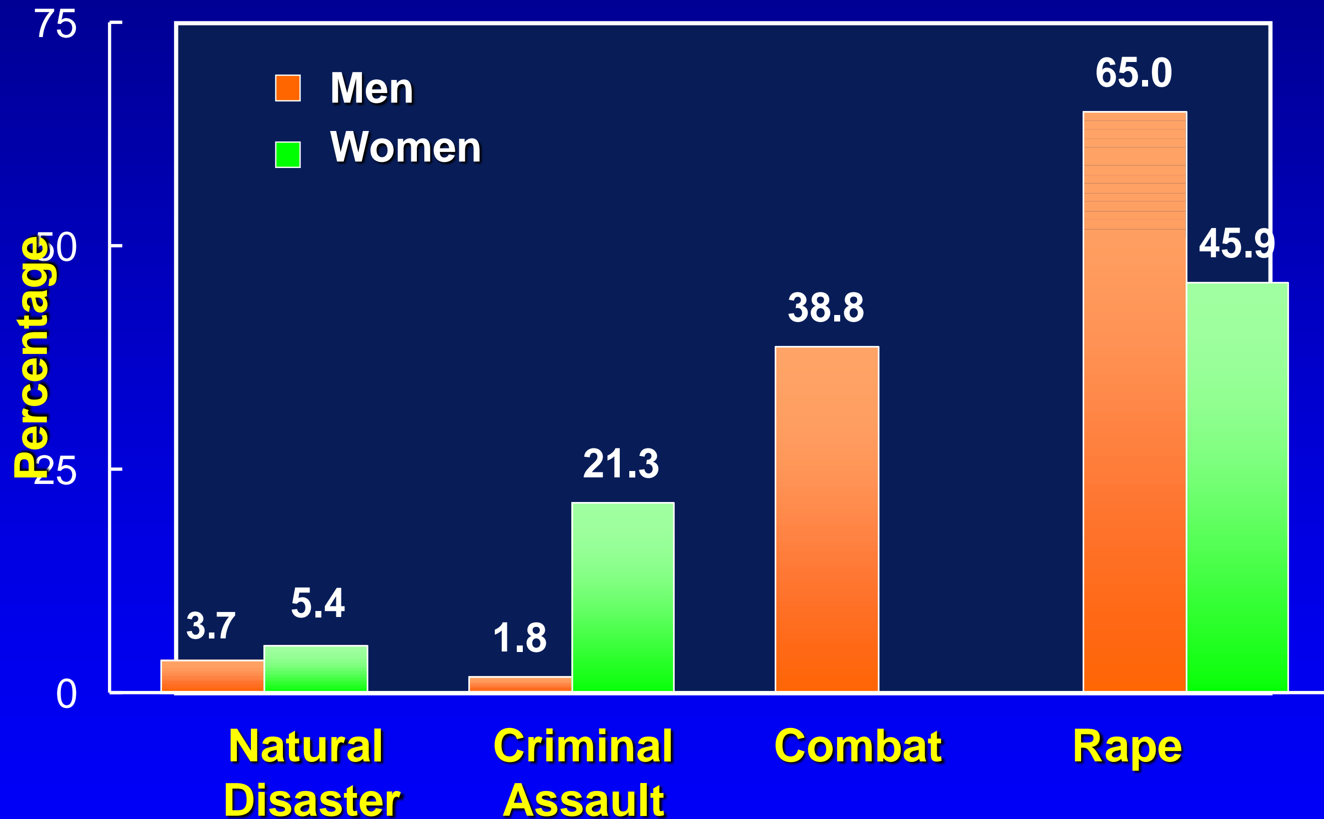
Rates Related to Specific Traumas



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

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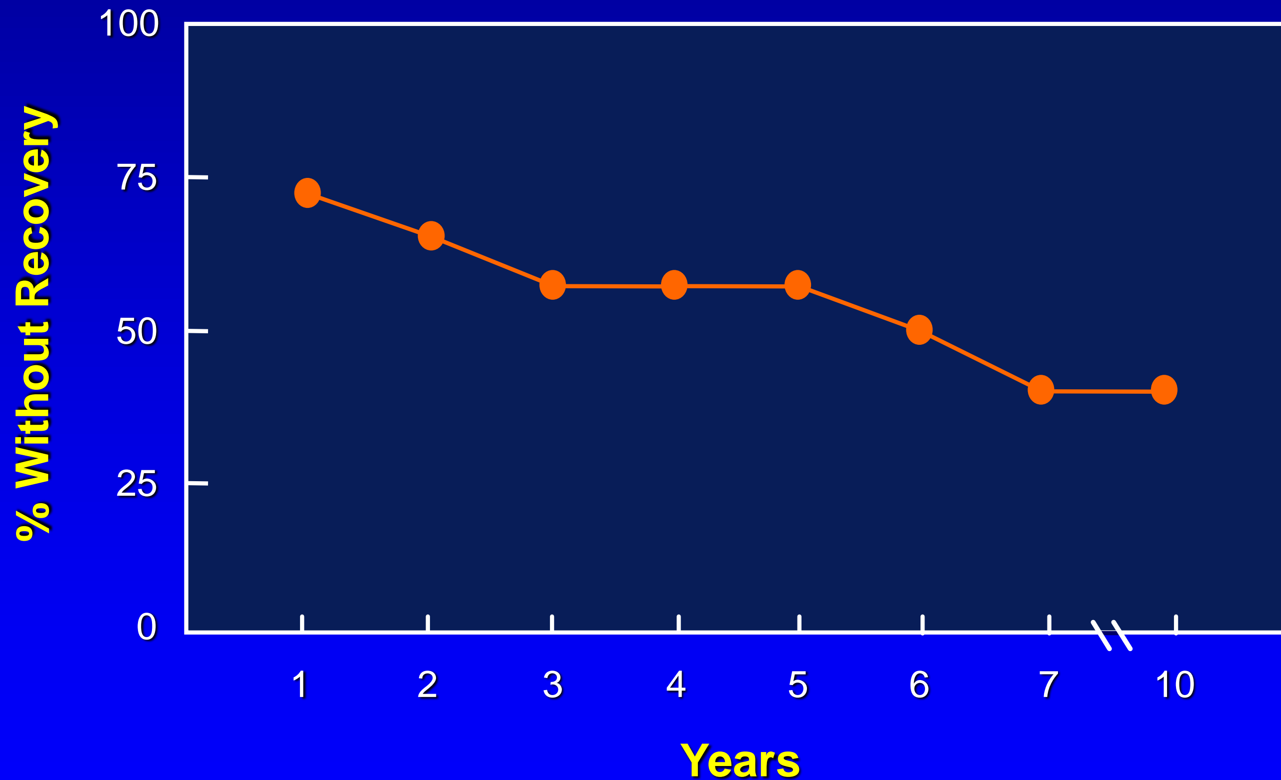
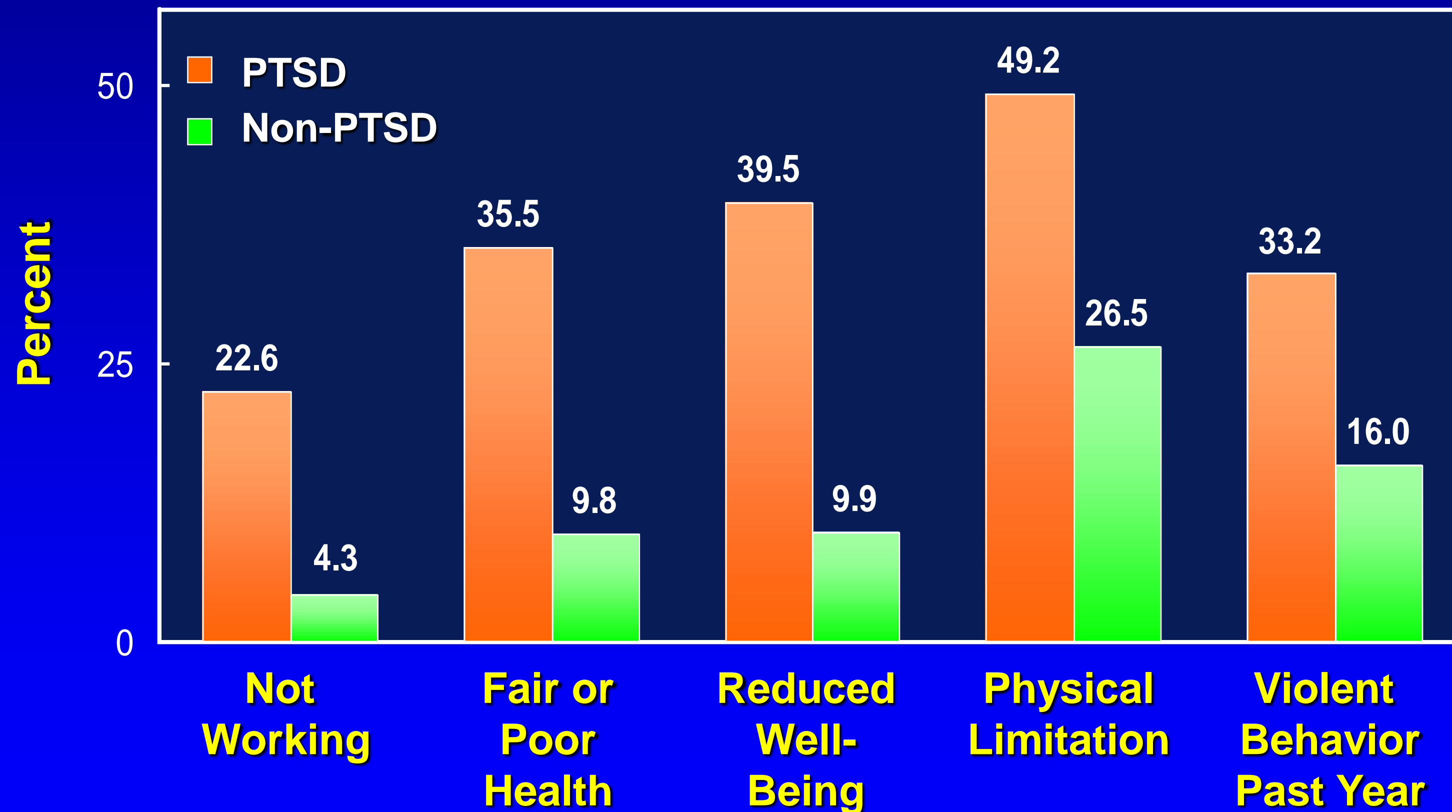
Persistence Over Time



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

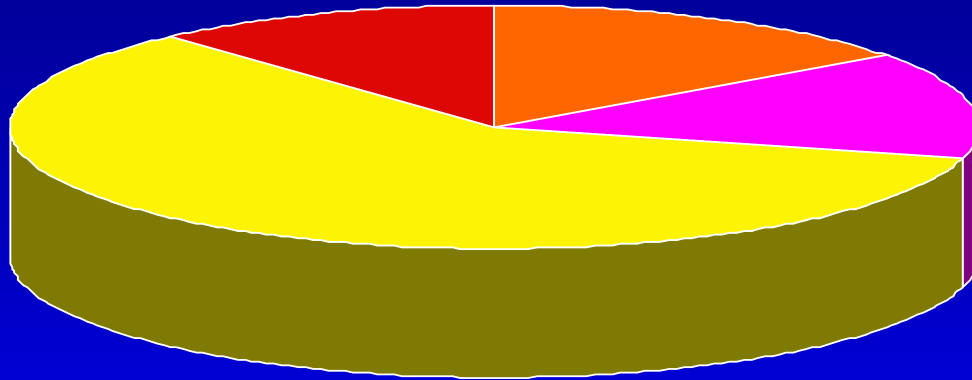
Psychiatric Comorbidity

	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.

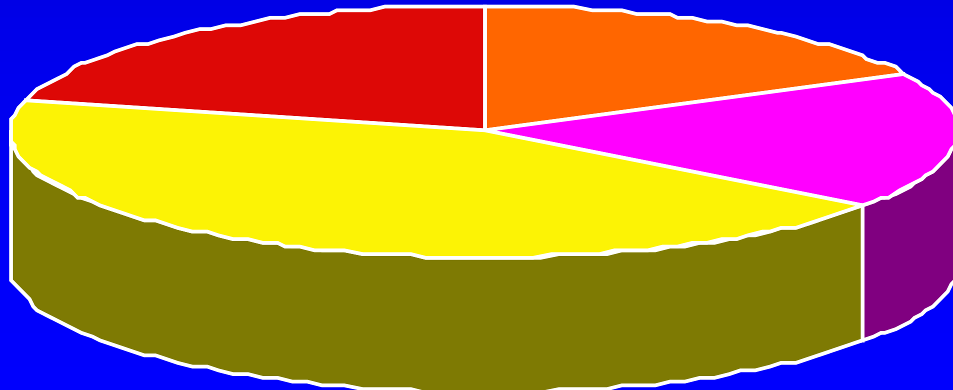
Comorbidity in PTSD
National Comorbidity Study

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

COMORBIDITY IN PTSD

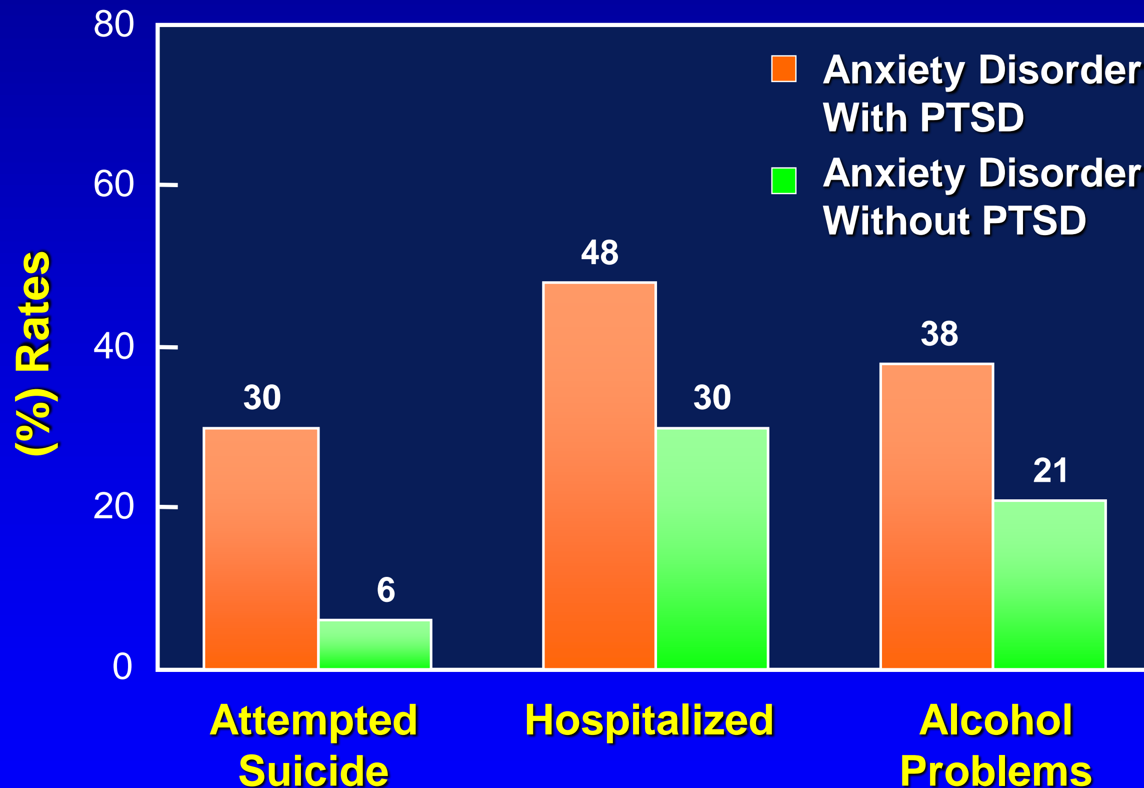
Variability in individual response to stress

Heterogeneous disorder

Symptom overlap

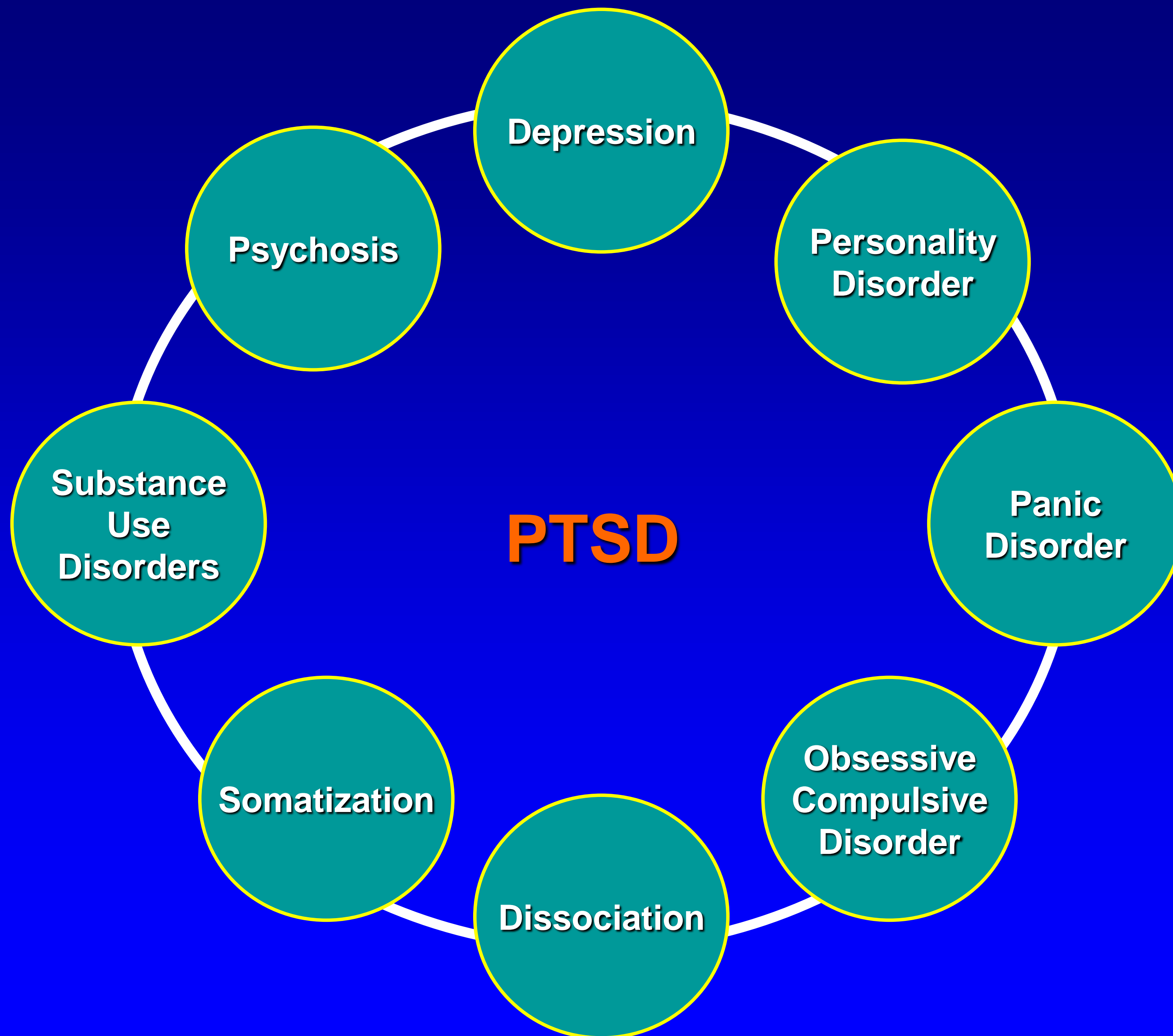
PTSD

Impact of Comorbid PTSD in Subjects With Other Anxiety Disorders



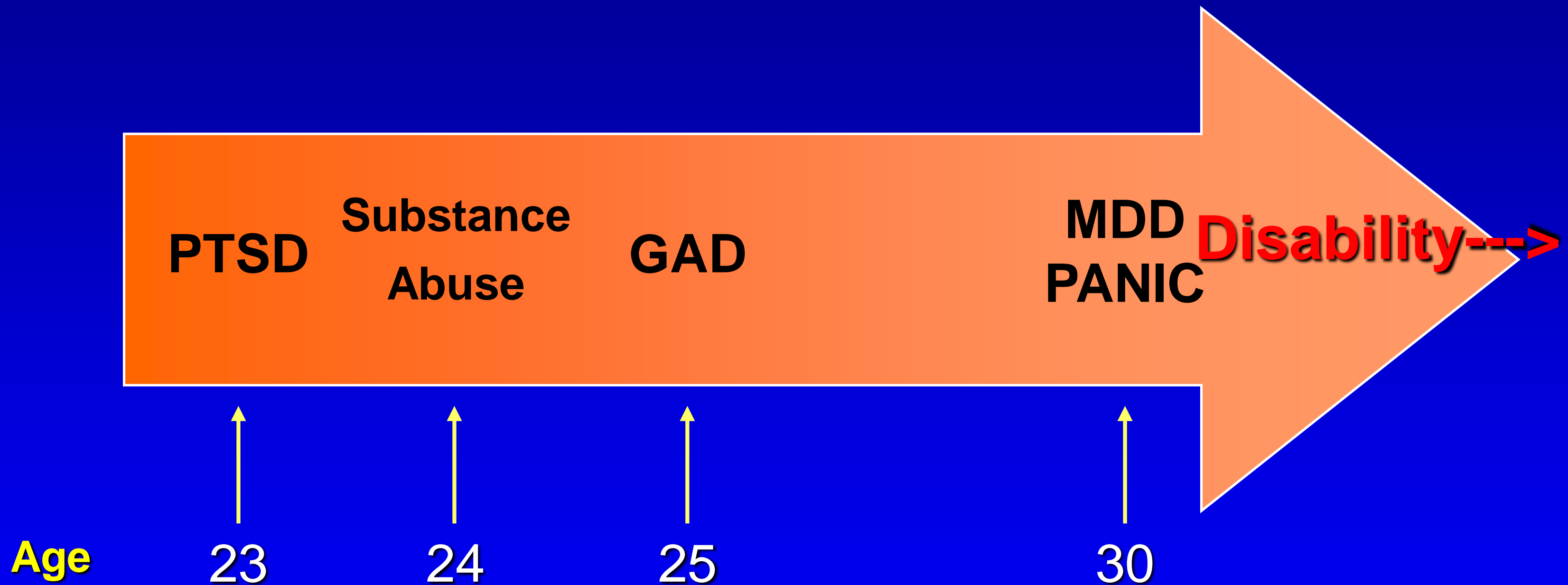
Warshaw MG et al. *Am J Psychiatry*. 1993;150:1512–1516.

DIAGNOSTIC SPECTRUMS



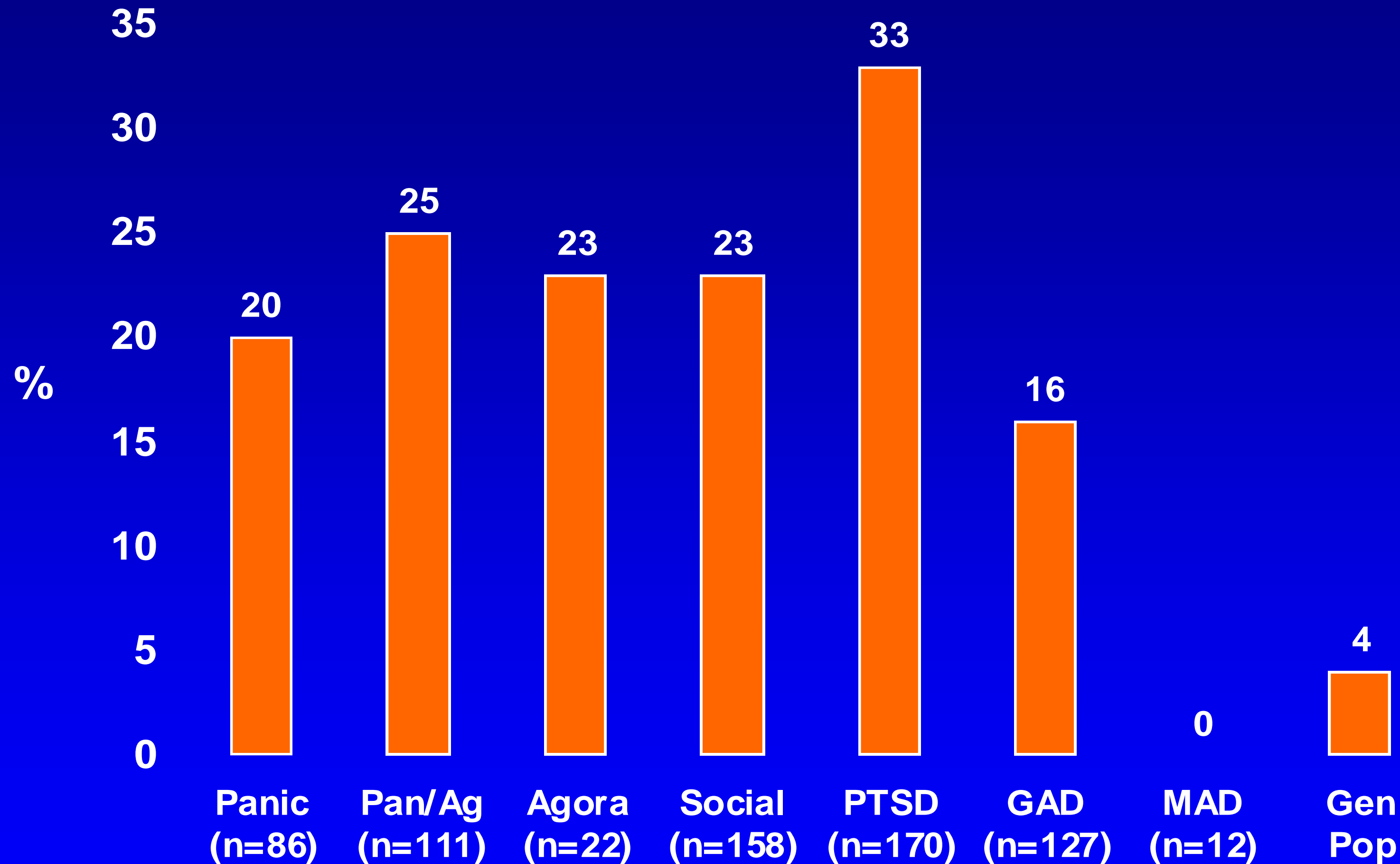
PTSD

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.

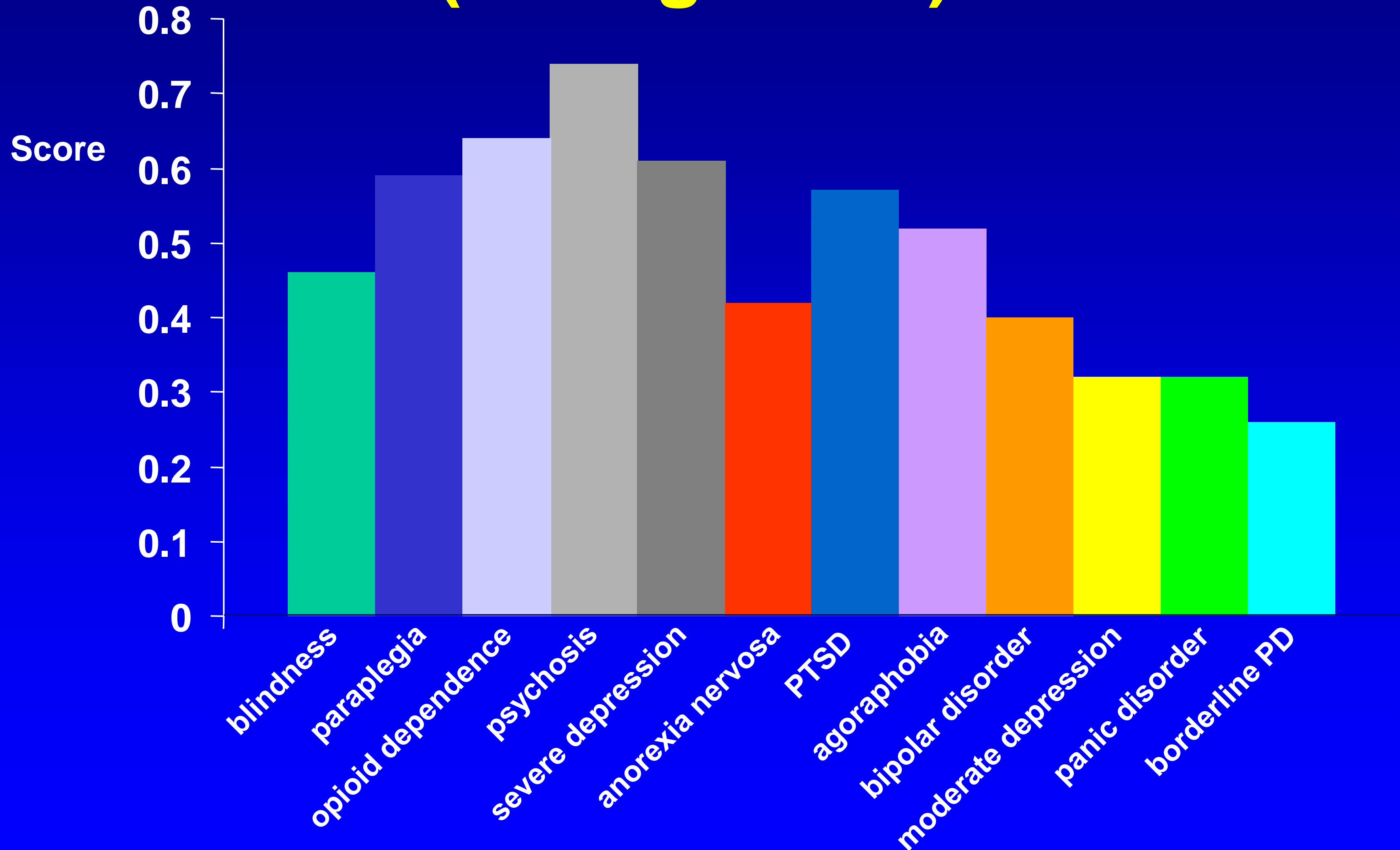
Lifetime History of Suicidal Attempts by Anxiety Disorder



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

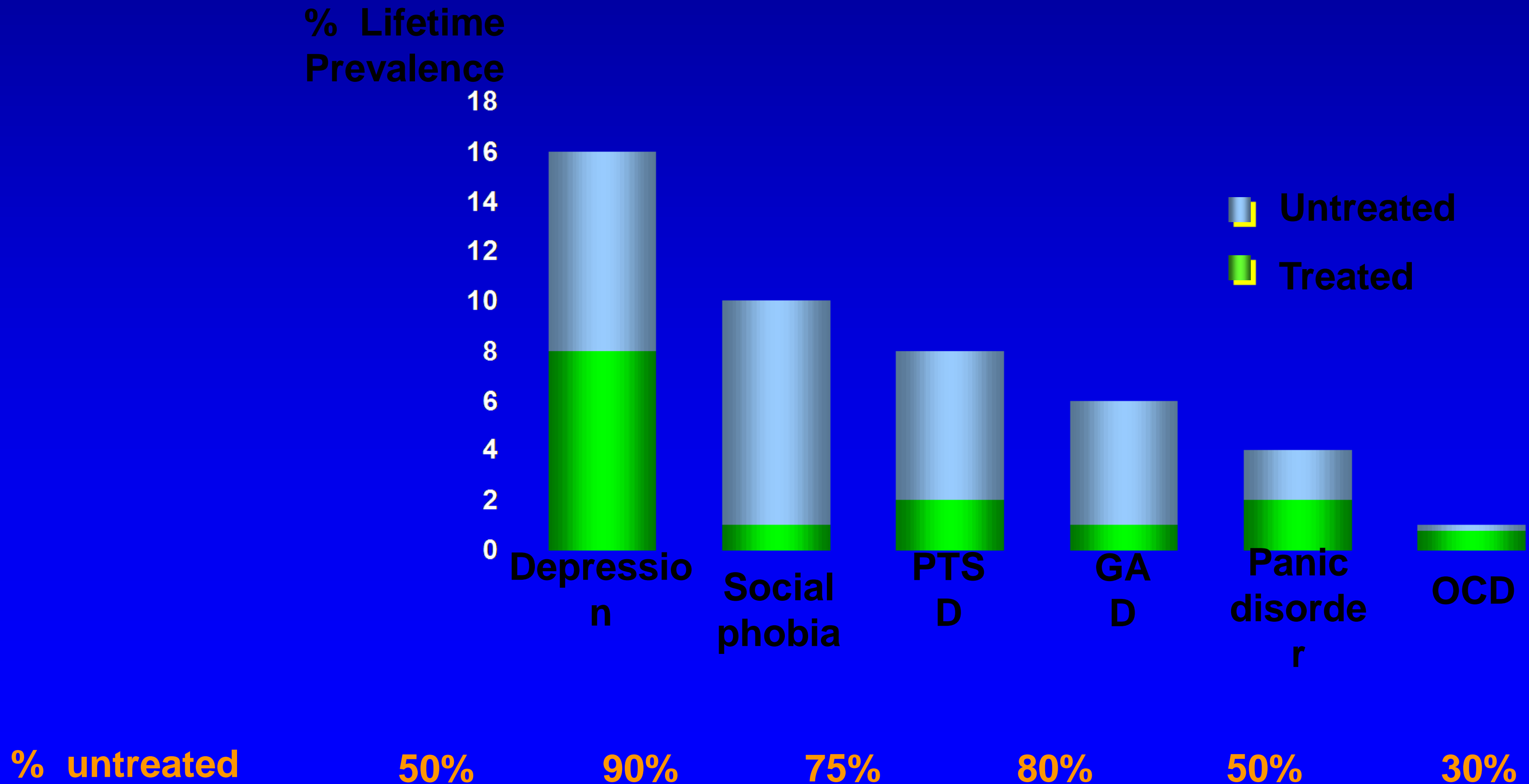
Disability Weights (Rating Scale)



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

PTSD: Unmet Medical Need

Few Are Treated



Psychosocial

- Exposure therapy
- Cognitive therapy
- Anxiety management
- Desensitization
- EMDR
- Hypnotherapy

Pharmacologic

- SSRIs
- TCAs
- MAOIs
- Mood stabilizers
- Antianxiety agents

EMDR = eye movement desensitization and reprocessing.

PTSD

Treatment Options

5. Psychotherapy
6. Pharmacotherapy
7. Multimodal treatment

WHO RESPONDS?

Gender

Trauma

Country

Comorbidity

WHAT RESPONDS

Intrusive, avoidant, numbing, hyperarousal Sx

Individual symptoms

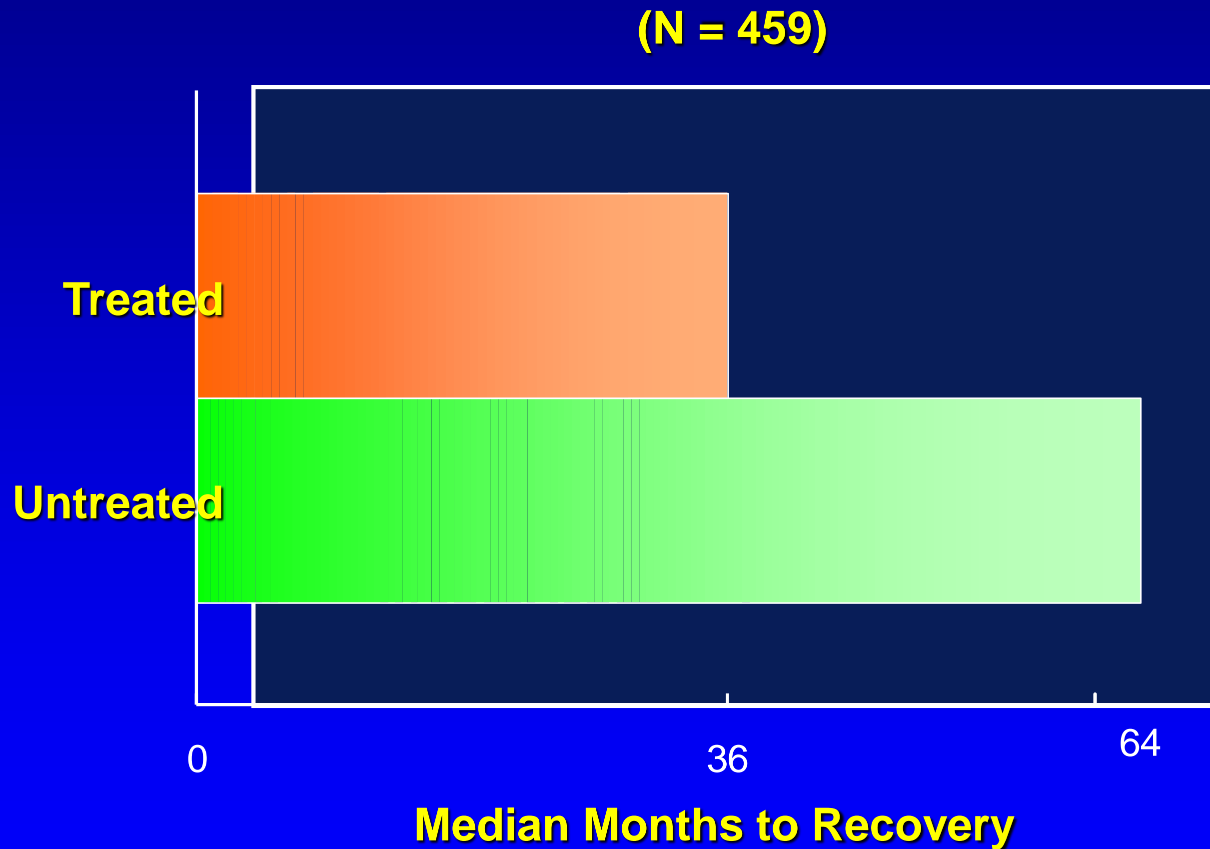
Diagnosis

Disability

Stress vulnerability

PTSD

Impact of Treatment on Recovery



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

PTSD

Considerations for Psychotherapy

5. Capacity to tolerate distress with exposure
6. Motivation/preference
7. Ability to participate and follow structure
8. 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

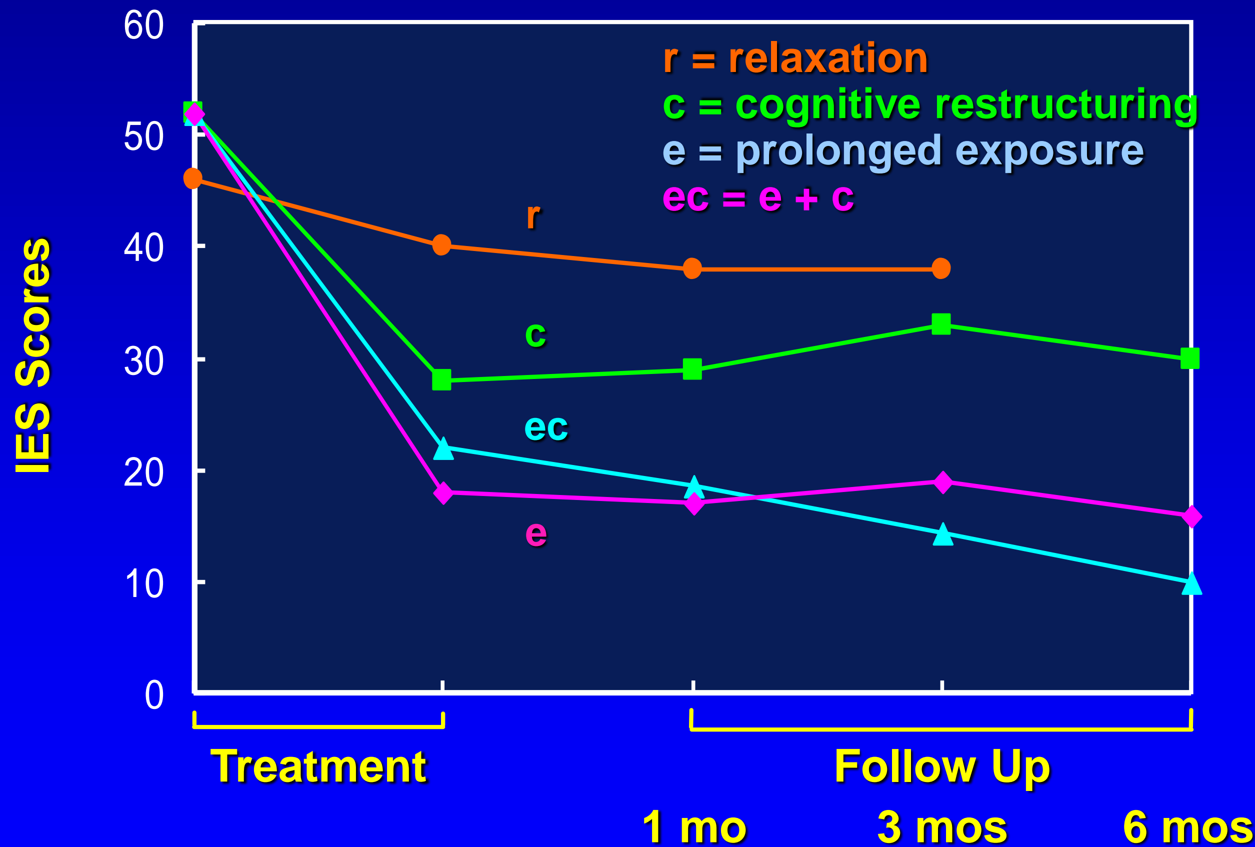
EXPOSURE STUDIES

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

5. PTSD
6. related pathology

Who responds

5. Type of trauma
6. comorbidity
7. gender
8. culture

AIMS OF PHARMACOTHERAPY

Reduce core symptoms

Reduce associated symptoms

Facilitate other therapy

RELEVANCE OF INDOLAMINES TO PTSD

Animal models

5. conditioned avoidance, stress resilience

mCPP effects

Reduced MAO activity

Paroxetine binding

Symptoms of PTSD

PLACEBO-CONTROLLED TRIALS

Study	Drug	N	Population	Results
Davidson et al.	Amitriptyline	62	Combat	Superior to PBO
Kosten et al.	Imipramine Phenelzine	61	Combat	Both superior to PBO
Katz et al.	Brofaromine	45	Mixed	Superior to PBO
Baker et al.	Brofaromine	113	Mixed	Superior to PBO
van der Kolk	Fluoxetine	47	Mixed	Superior to PBO in civilians only
Davidson et al.	Fluoxetine	64	Civilian	Superior to PBO
Davidson et al.	Sertraline	109	Civilian	Superior to PBO
Brady et al.	Sertraline	187	Civilian	Superior to PBO

PTSD

Medications Studied

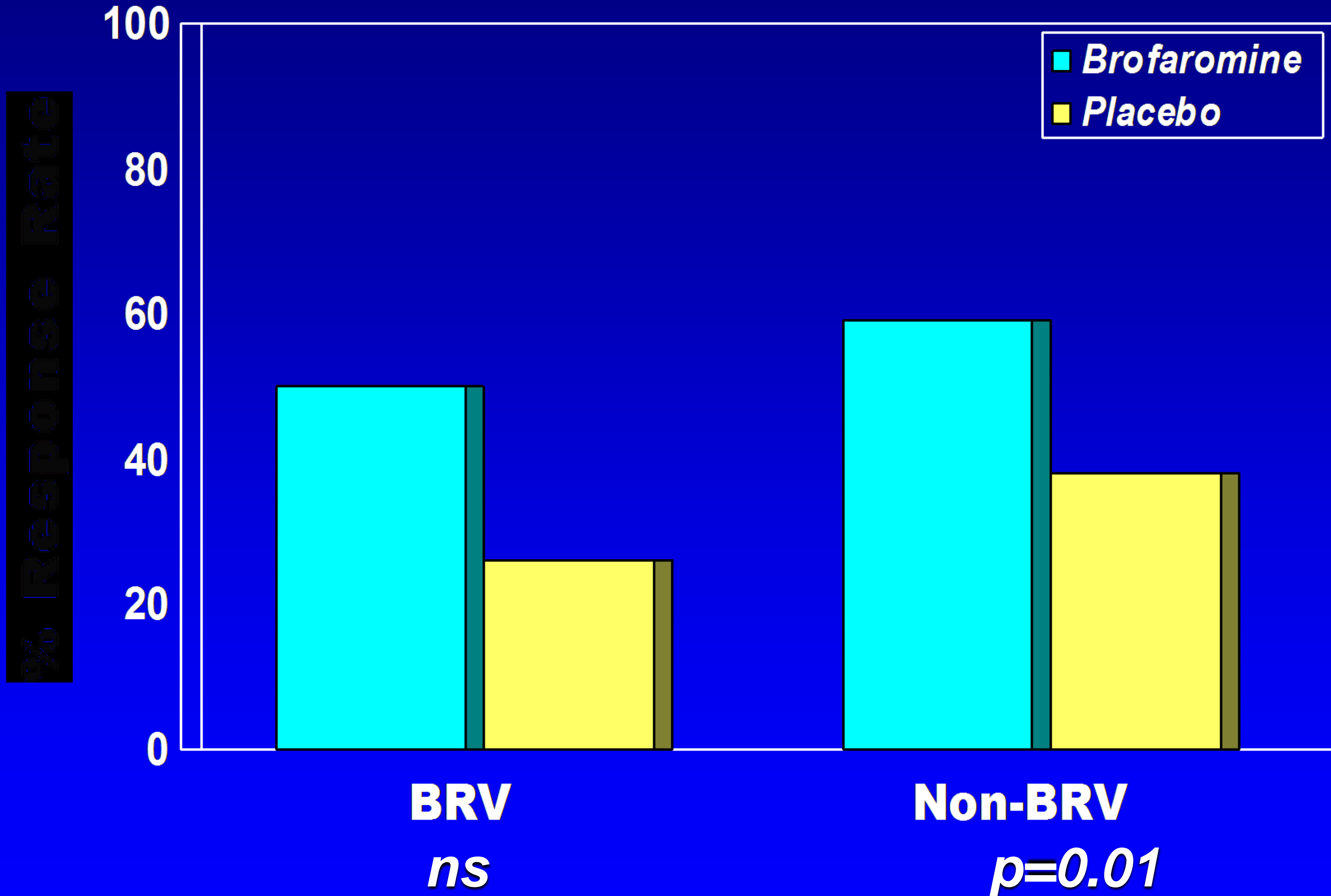
5. Benzodiazepines
6. Antidepressants
   - TCAs
   - MAOIs
   - SSRIs
   - $5\text{-}HT_2$ antagonists
7. Anticonvulsants
8. Noradrenergic agents: clonidine, propranolol

TYPE OF TRAUMA AND RESPONSE TO TREATMENT

BROFAROMINE SAMPLE

Sample	N = 182
Sites	USA, England, Ireland, France, Norway
Duration of Treatment	12-14 weeks
Men:Women	74:26
Age (years)	41.9

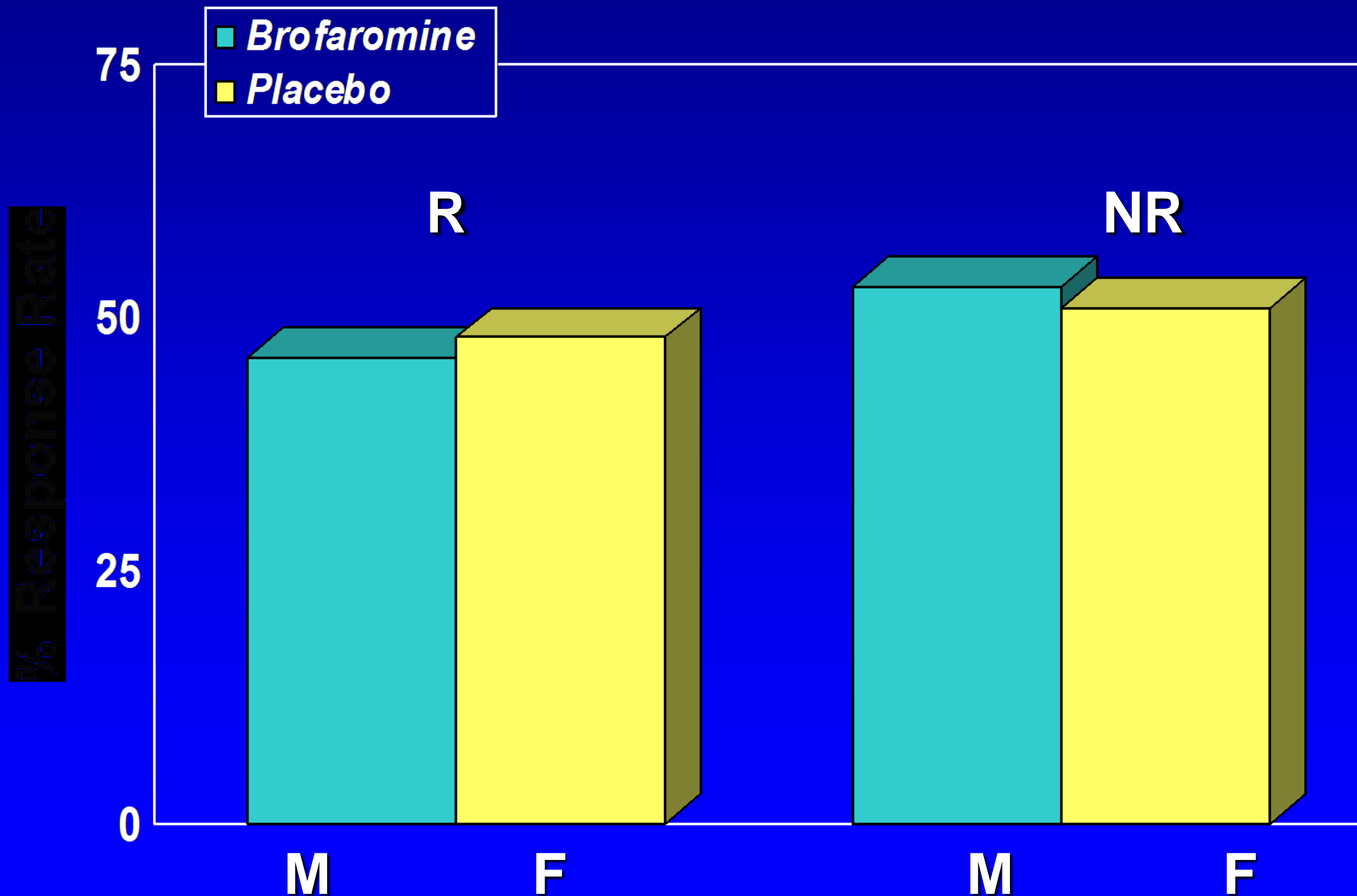
BEREAVEMENT-RELATED PTSD



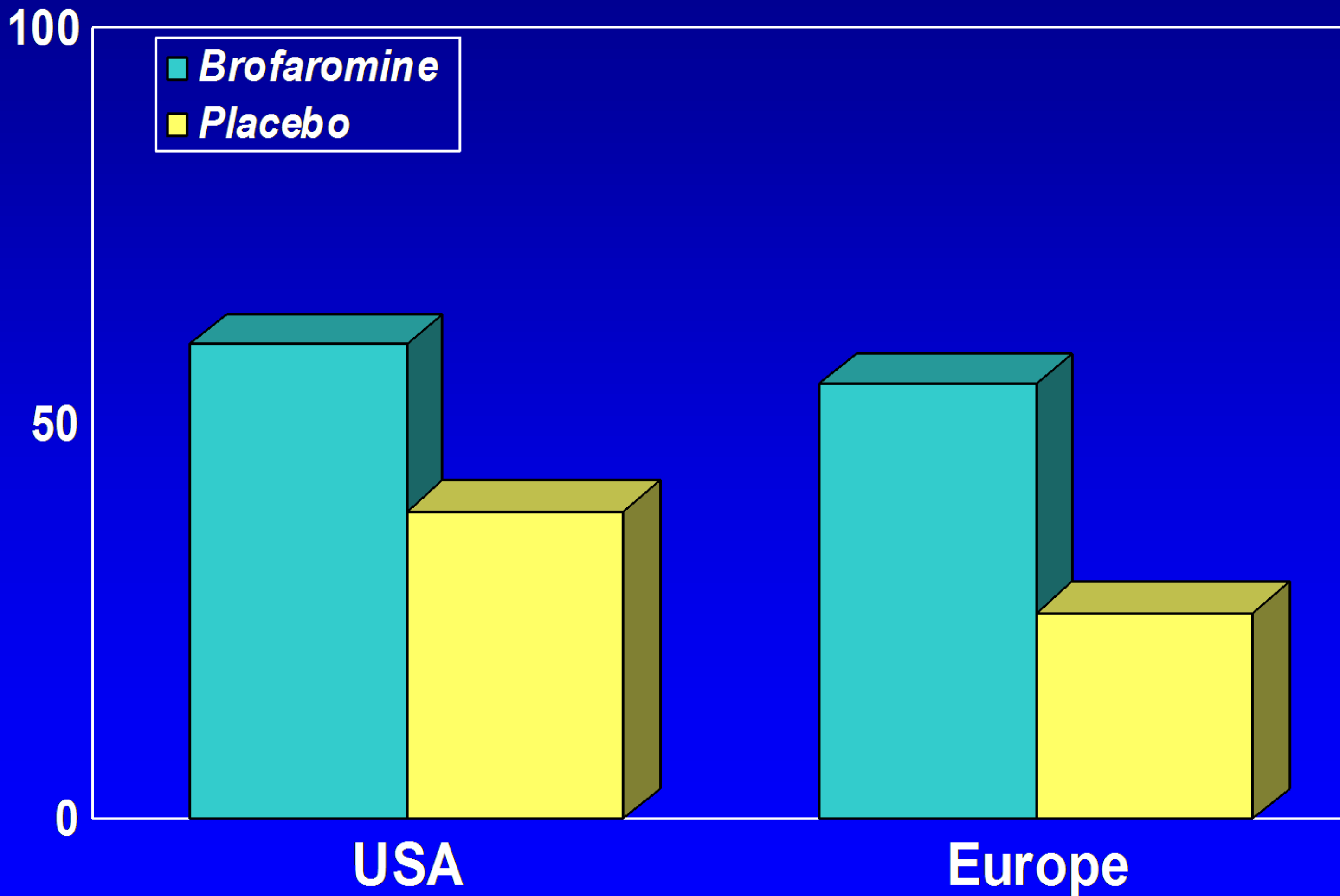
DIFFERENCES IN BEREAVEMENT-RELATED PTSD vs NON-BEREAVEMENT RELATED PTSD

Demographic	Older, Male
Trauma	Earlier; more; longer-lasting PTSD
Symptoms	Less intrusive Less startle More hypervigilanceanhedonia/numbing
Treatment	Poorer overall response

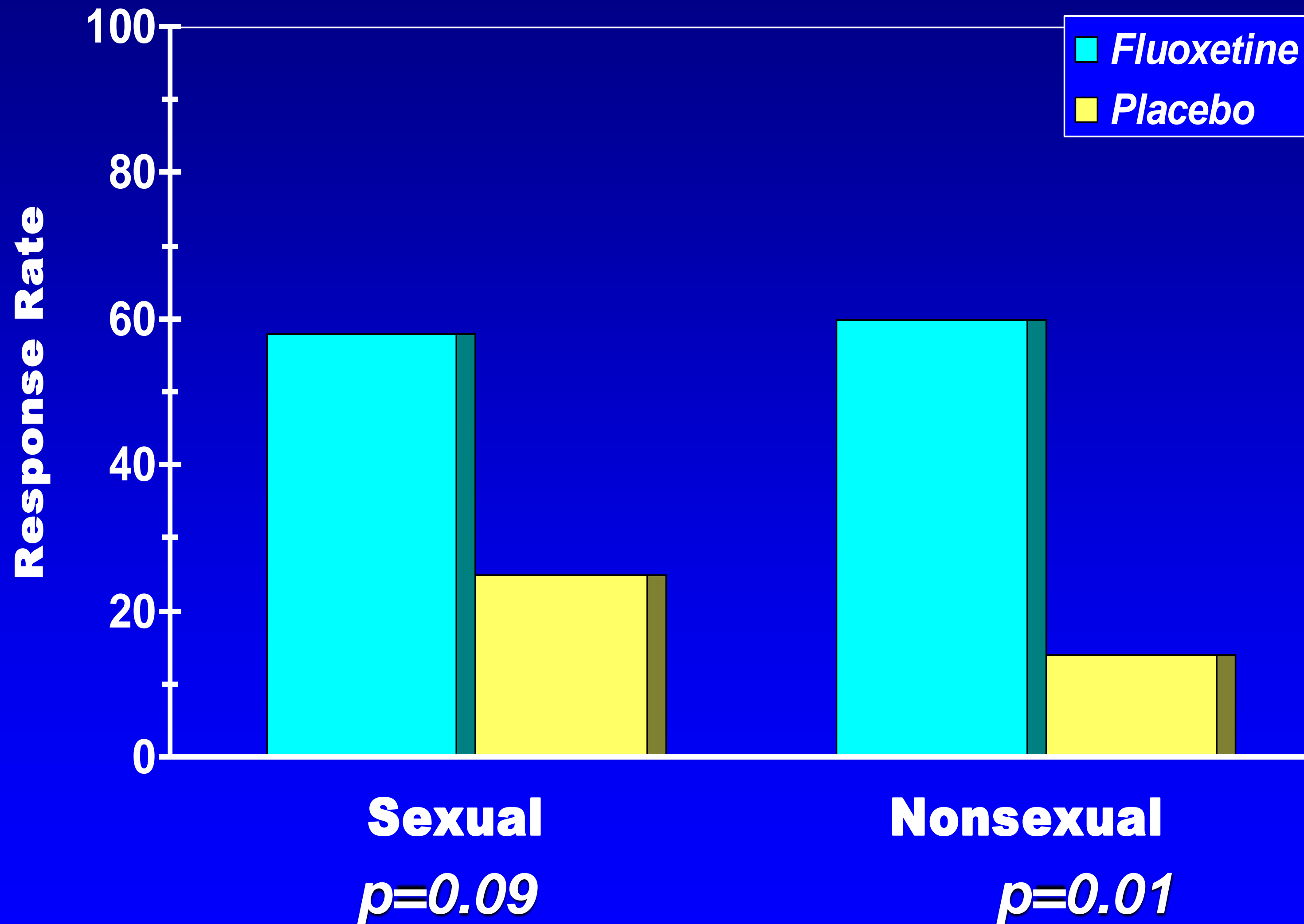
OVERALL RESPONSE RATES
Brofaromine and Placebo



RESPONSE TO TREATMENT IN DIFFERENT COUNTRIES

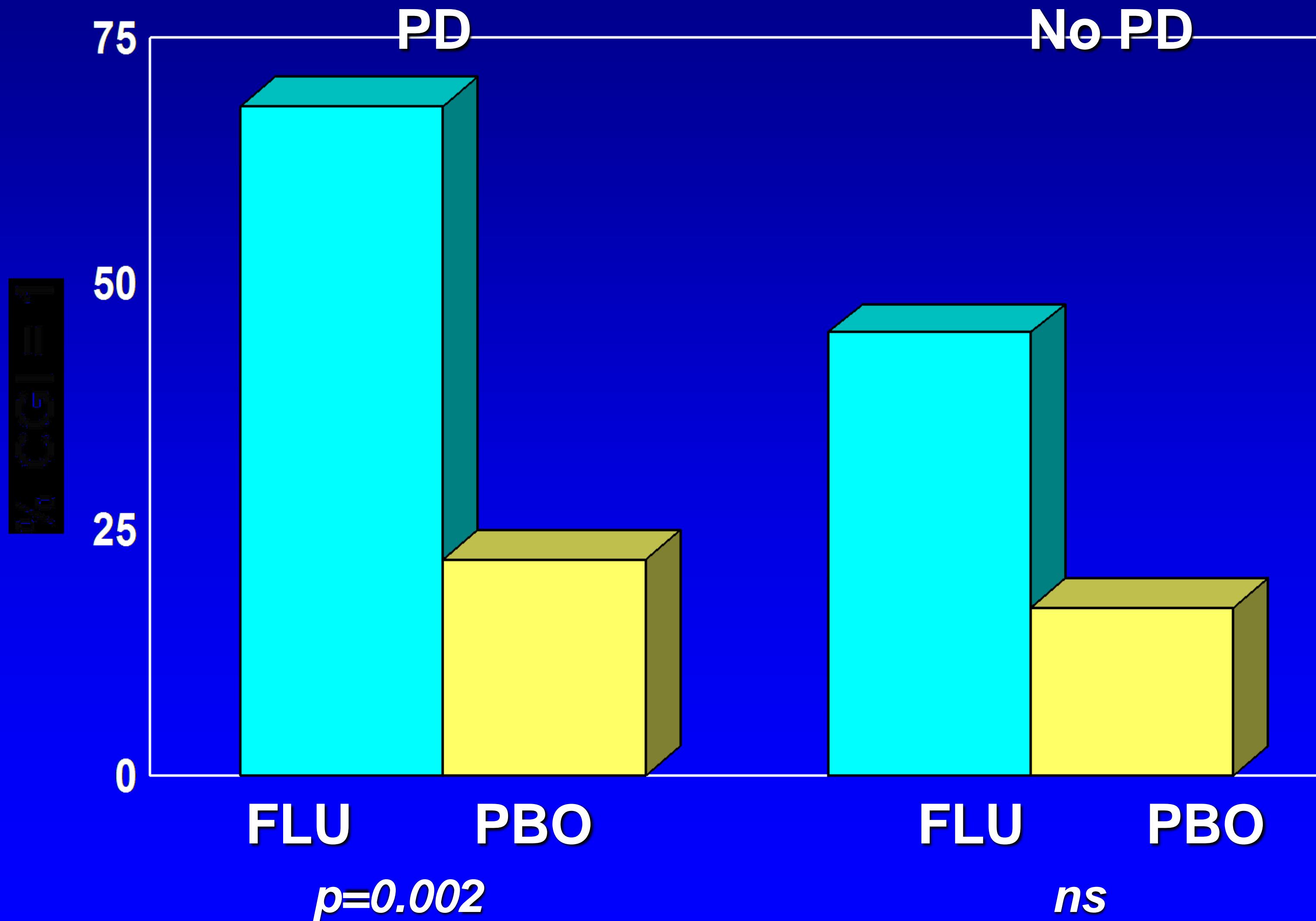


SEXUAL TRAUMA-RELATED PTSD

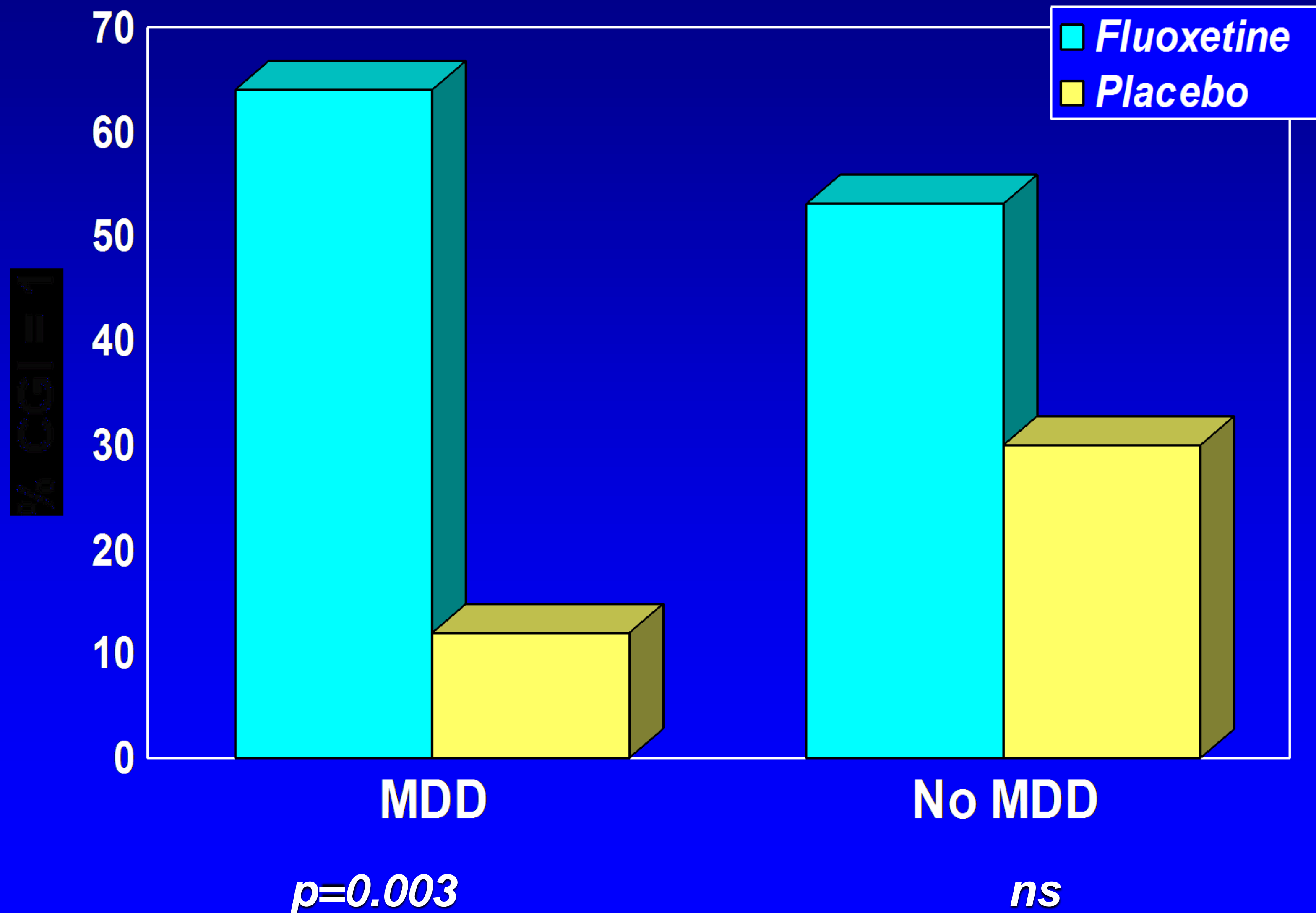


Davidson et al., 1997

DOES COMORBID PERSONALITY DISORDER AFFECT THE RESPONSE TO AN SSRI?

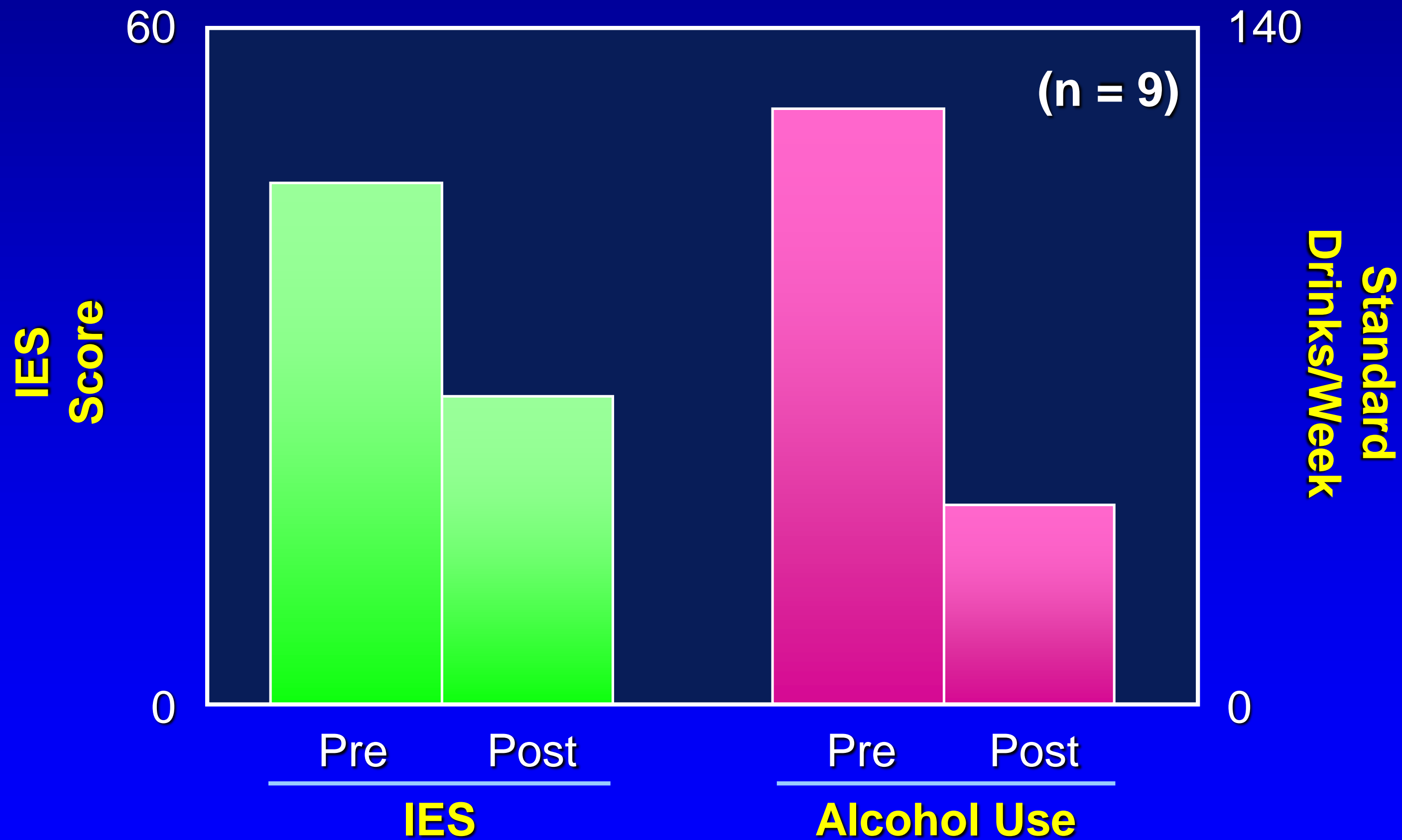


DOES COMORBID DEPRESSION AFFECT THE RESPONSE TO AN SSRI?



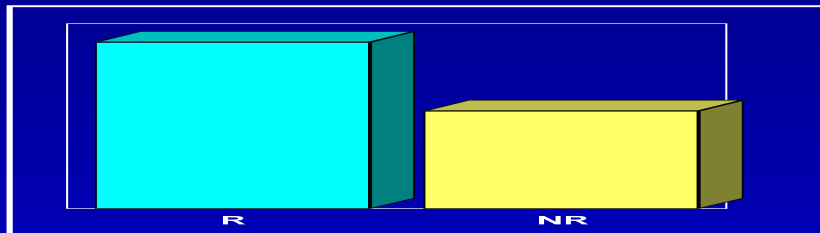
PTSD Treatment With SSRIs

Open-Label Sertraline in Comorbid PTSD and Alcoholism



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

RESPONSE TO SERTRALINE IN 19 COMBAT VETERANS WITH PTSD AND MDD



N=19

At least 12 weeks of treatment

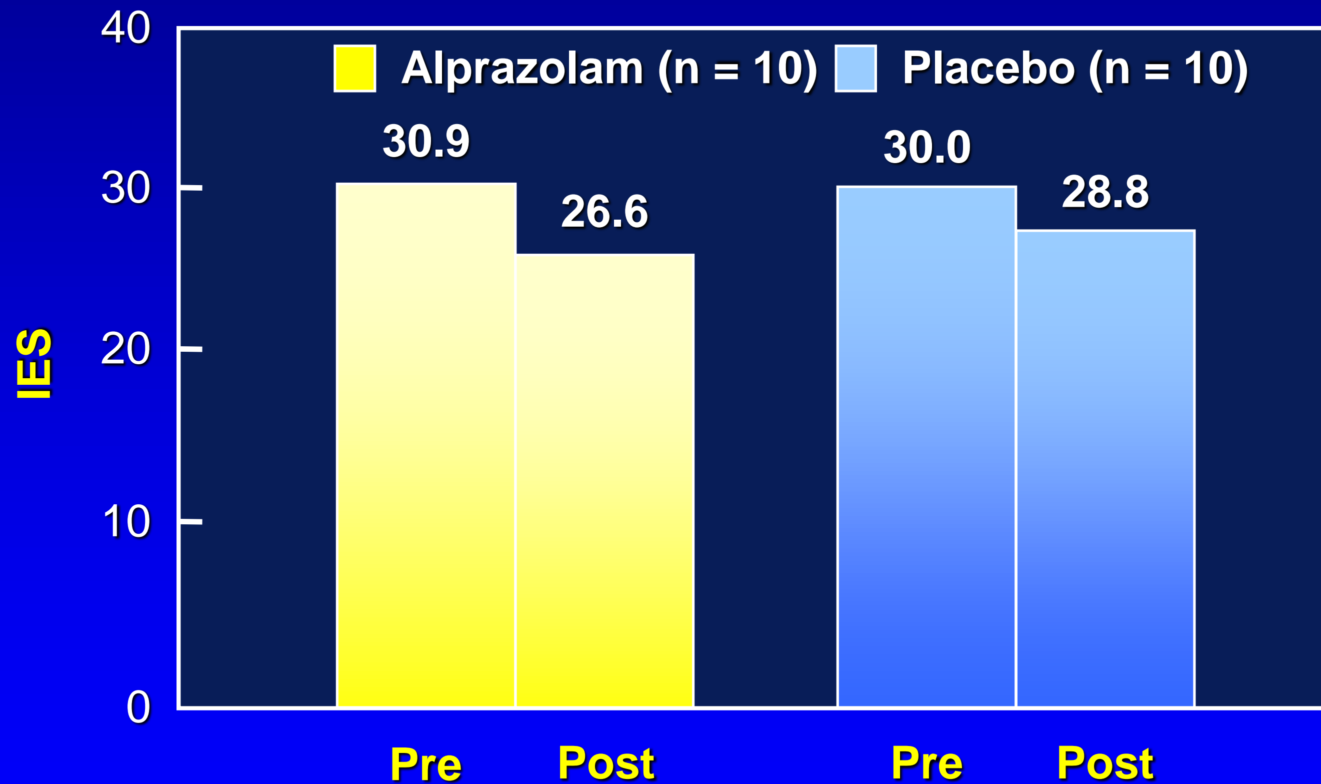
Failure of other antidepressants

(N=12) ***(N=7)***

Kline et al., Am J Psychiatry 1994;151:621

PTSD

Treatment With Benzodiazepines



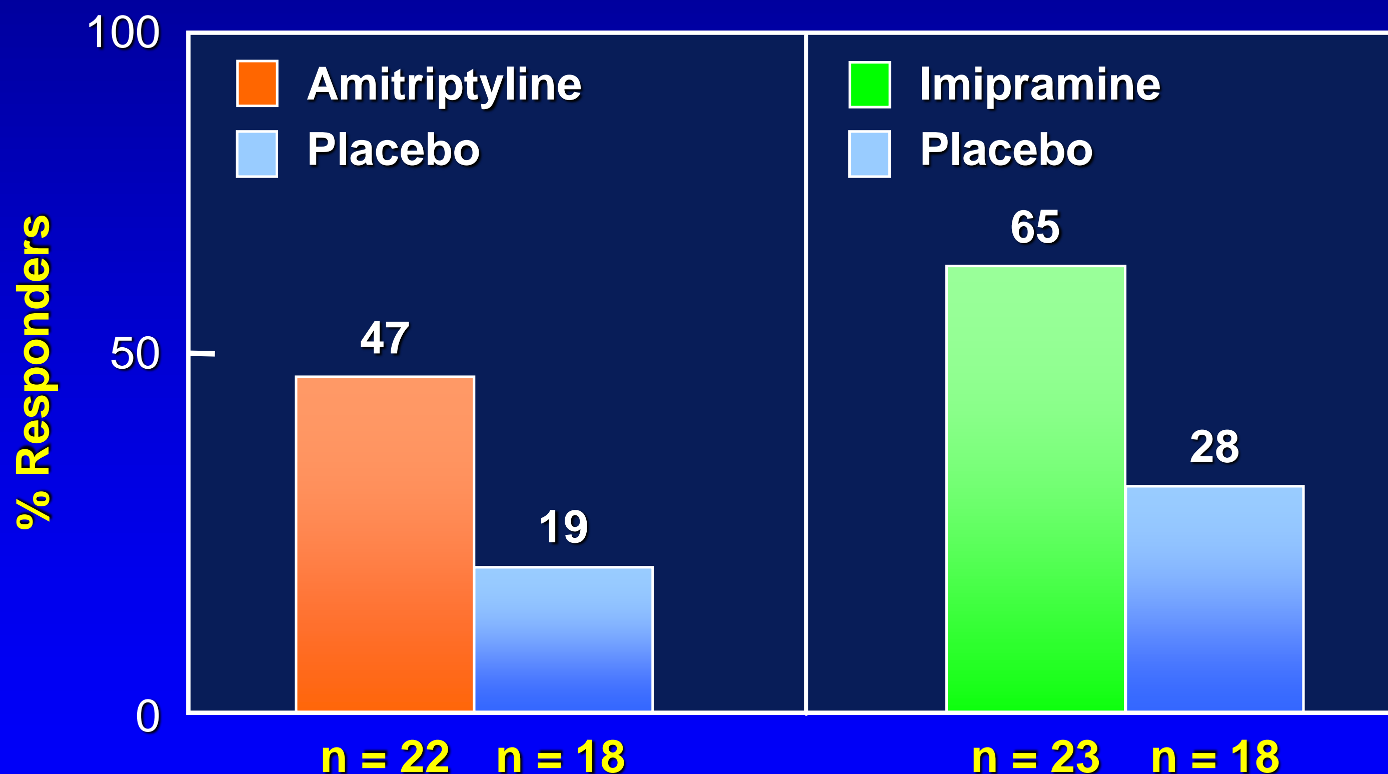
Braun P et al. *J Clin Psychiatry*. 1990;51:236–238.

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 Tricyclics



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

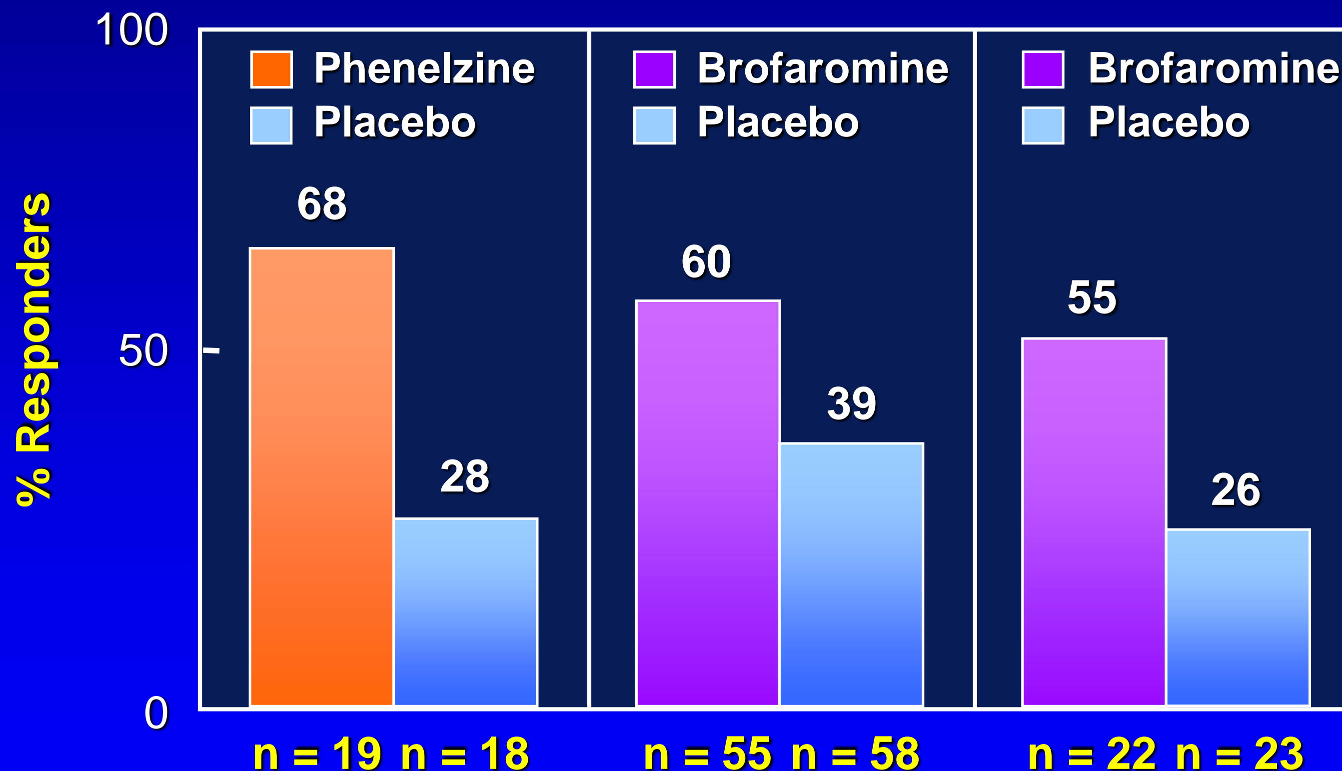
Kosten TR et al. *J Nerv Ment Dis.* 1991;179:366–370.

ADVANTAGES AND DISADVANTAGES OF MAOIs

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

PTSD

Treatment With MAOIs



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

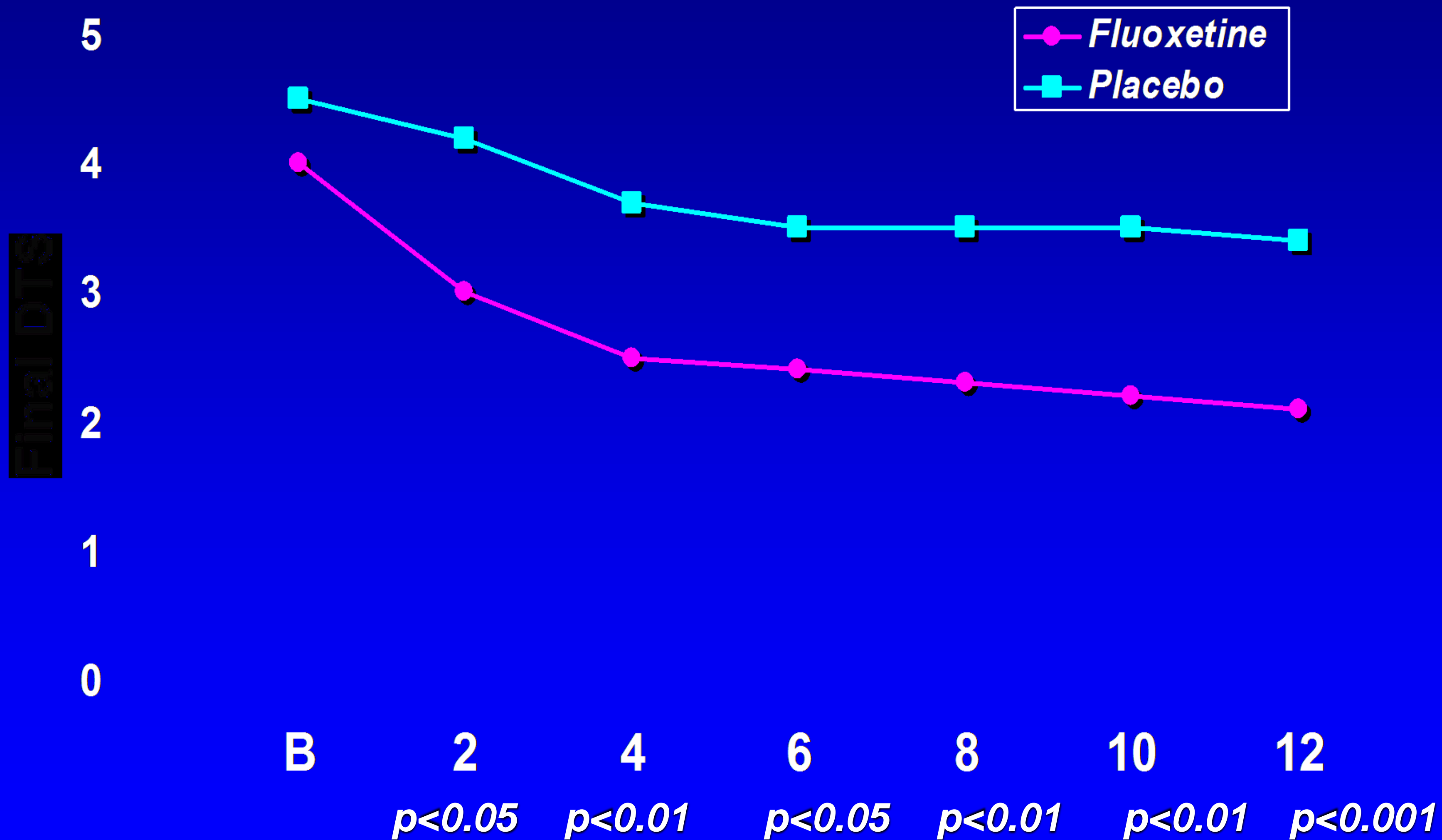
Baker DG et al. *Psychopharmacology*. 1995;122:386–389.

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

ADVANTAGES AND DISADVANTAGES OF 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

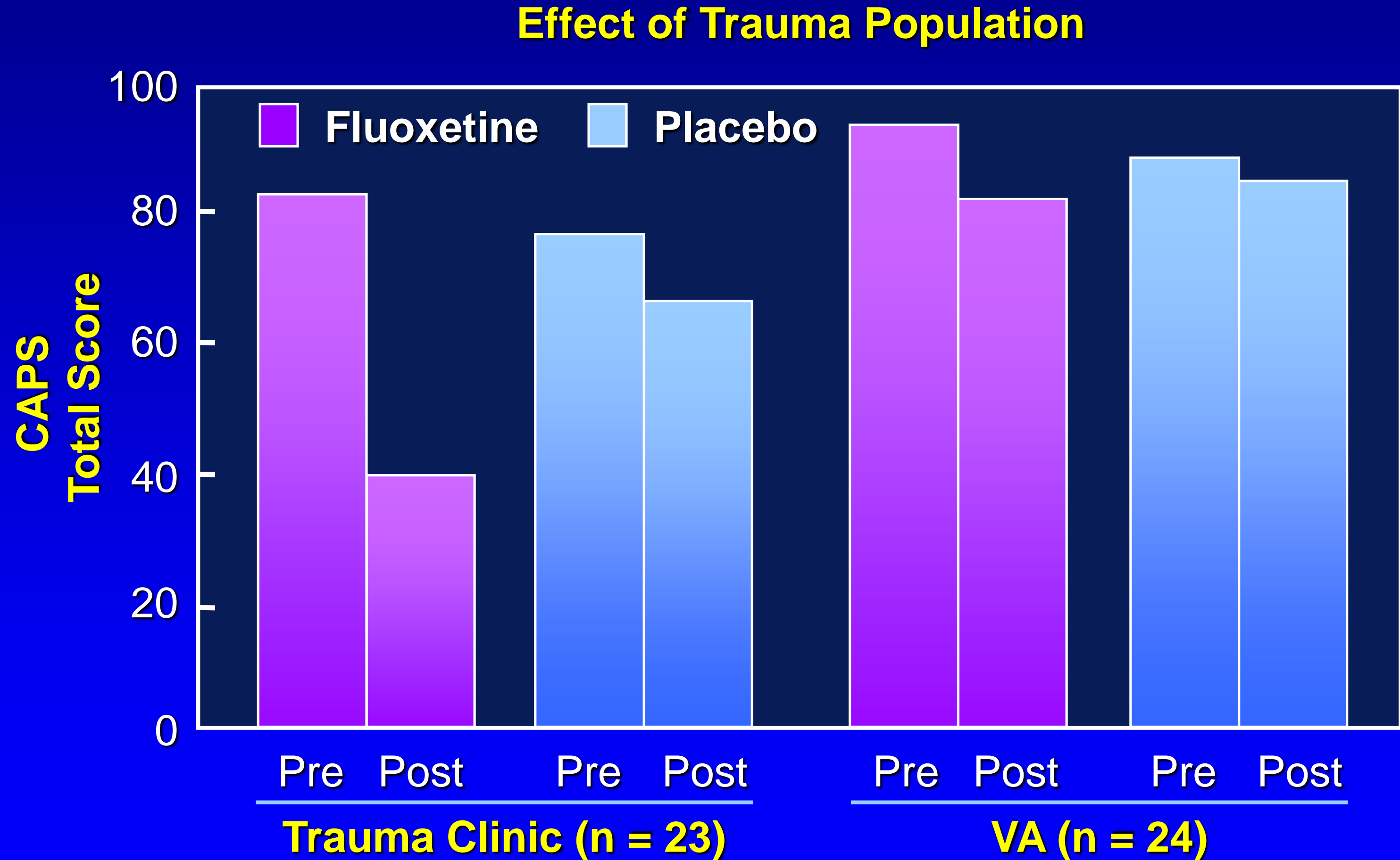
GLOBAL SEVERITY OF PTSD
Fluoxetine vs Placebo



Davidson et al., 1997

PTSD Treatment With SSRIs

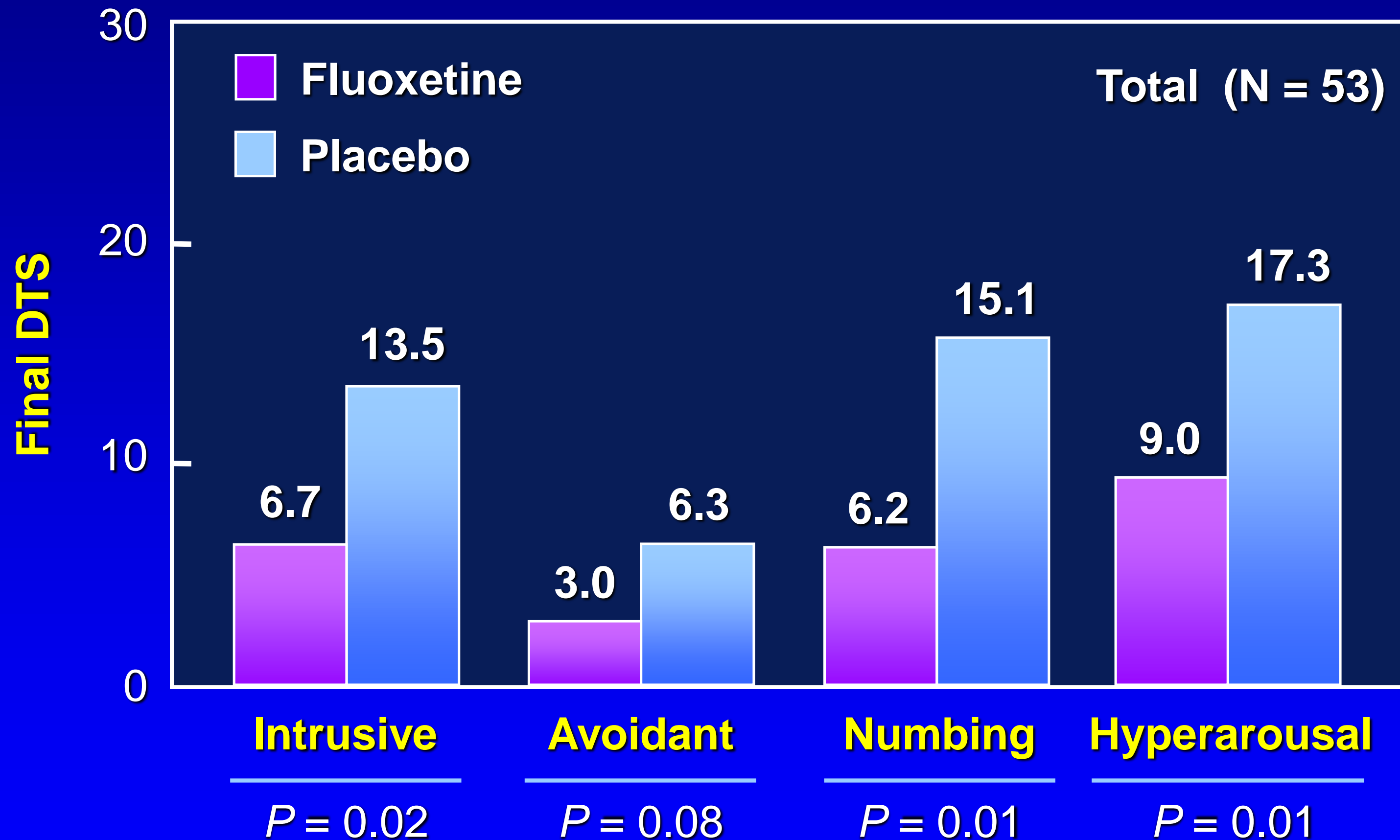
Effect of Fluoxetine



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

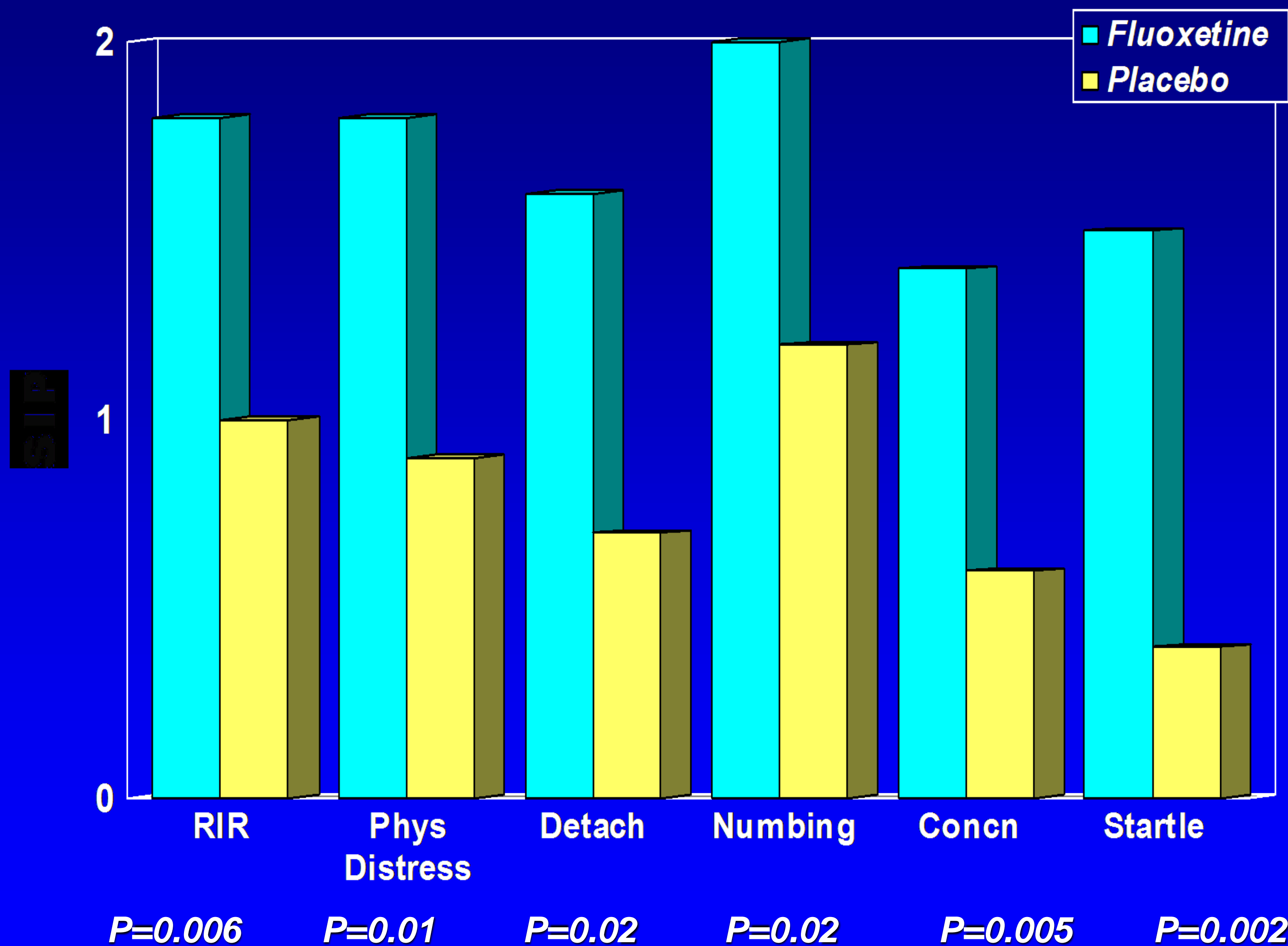
PTSD Treatment With SSRIs

Effect of Fluoxetine in Symptom Clusters



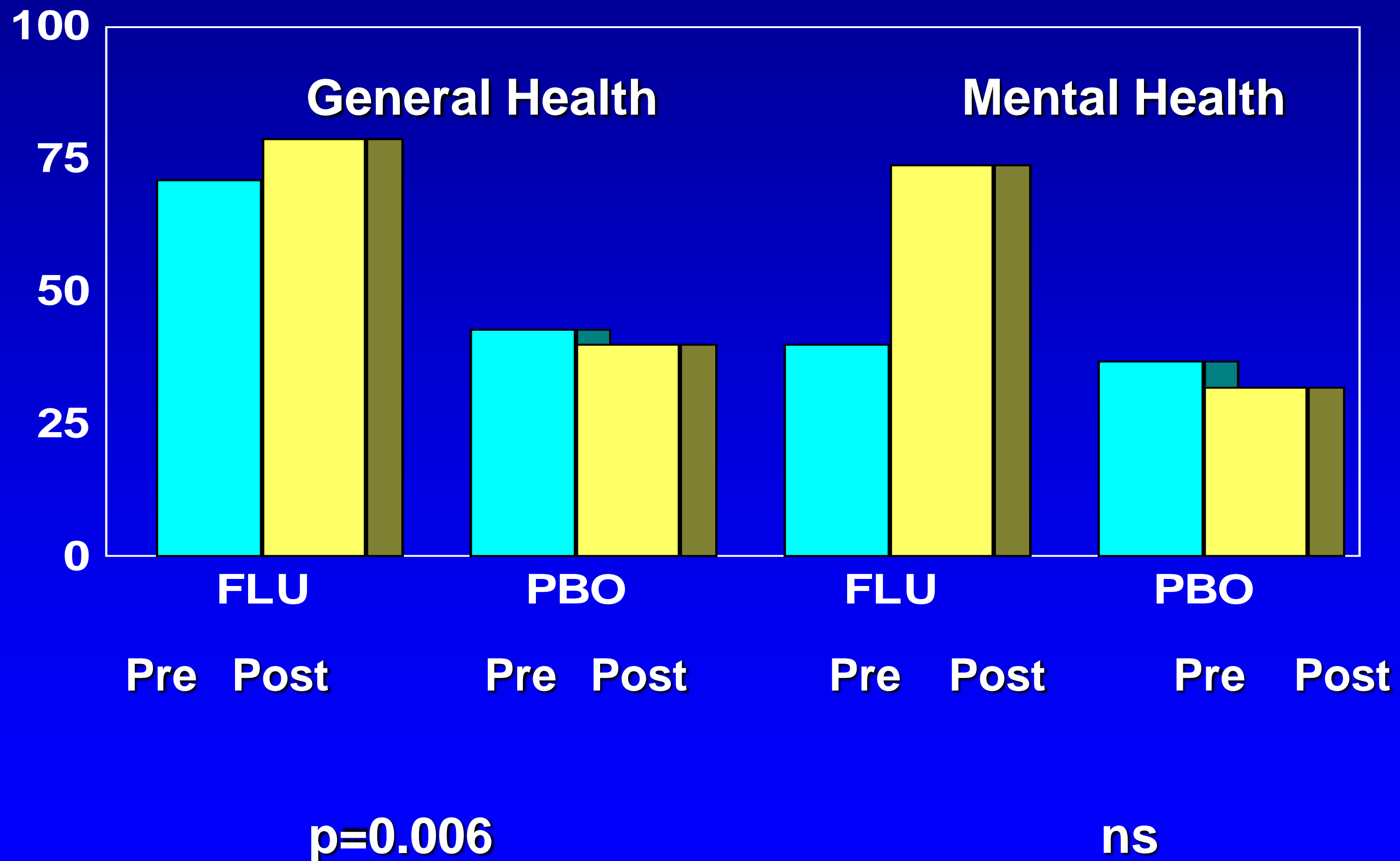
Davidson JR et al. *Int Clin Psychopharmacol*. 1997;12:291–296.

WHICH SYMPTOMS RESPOND TO AN SSRI?



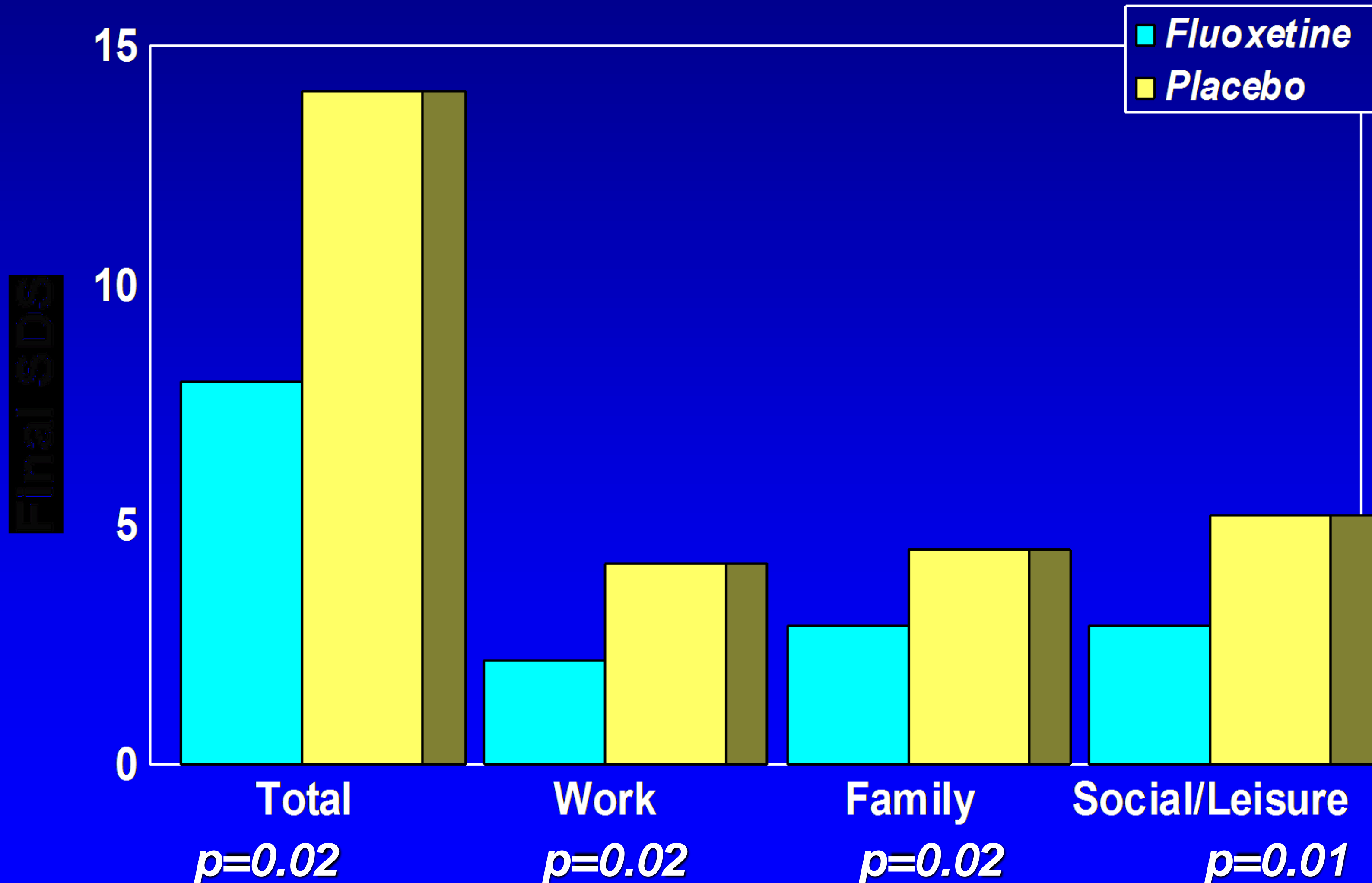
Davidson et al., 1997

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



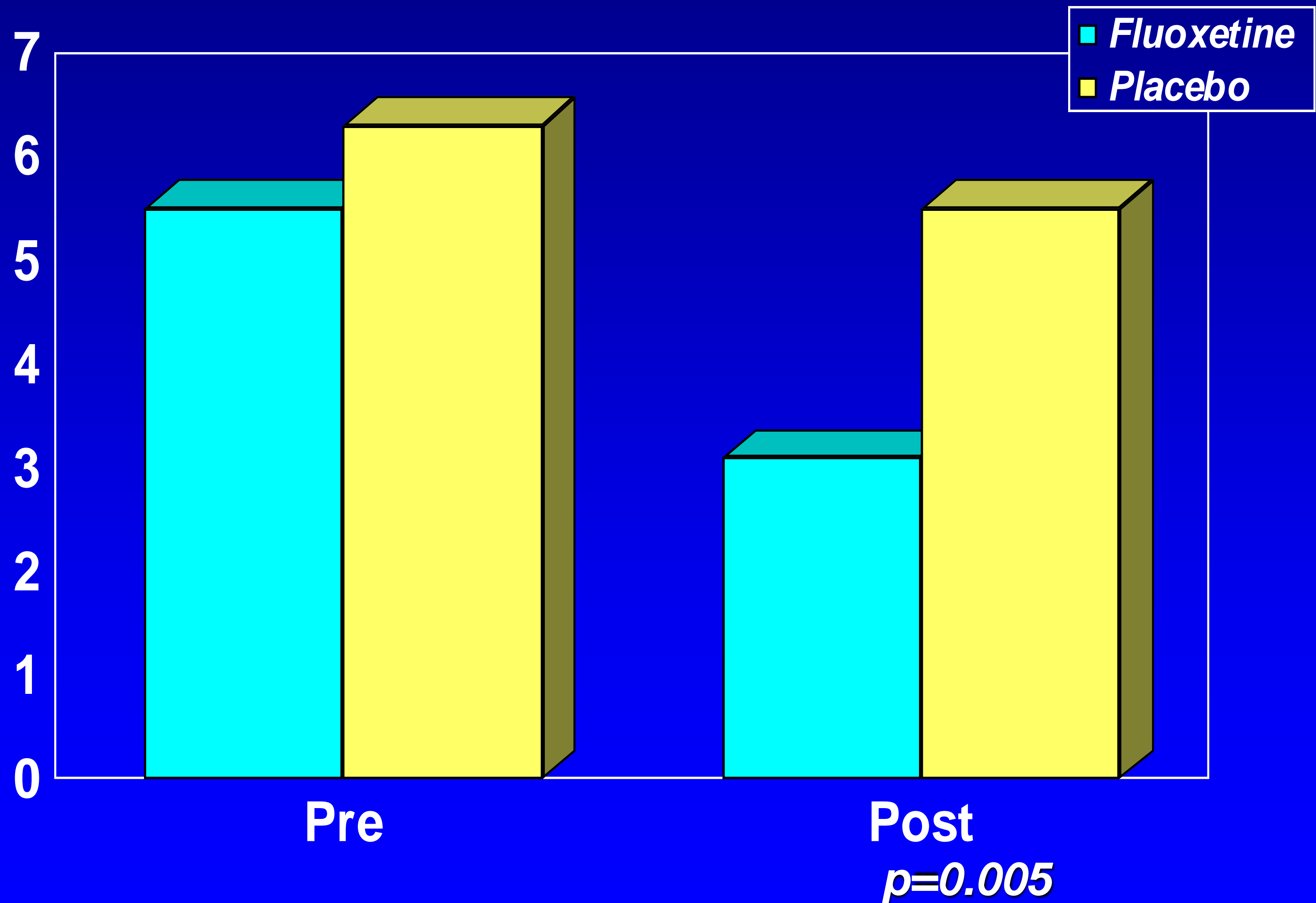
Davidson et al., 1997

IMPROVEMENT IN DISABILITY: Fluoxetine vs Placebo



Davidson et al., 1997

IMPROVEMENT IN STRESS VULNERABILITY: Fluoxetine vs Placebo



Davidson et al., 1997

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

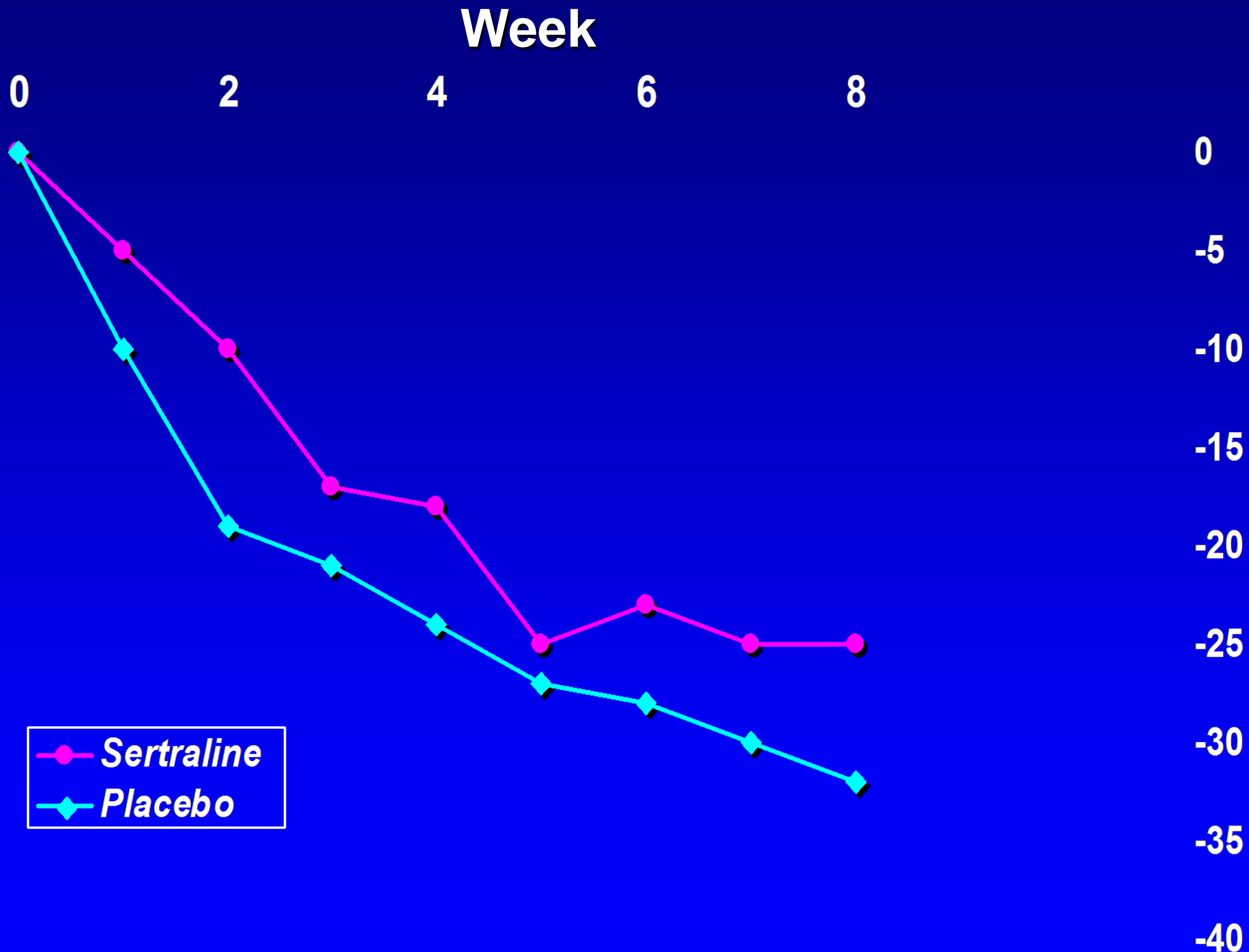
Davidson et al., 1997

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

Sertraline vs Placebo in Non-Combat-related PTSD

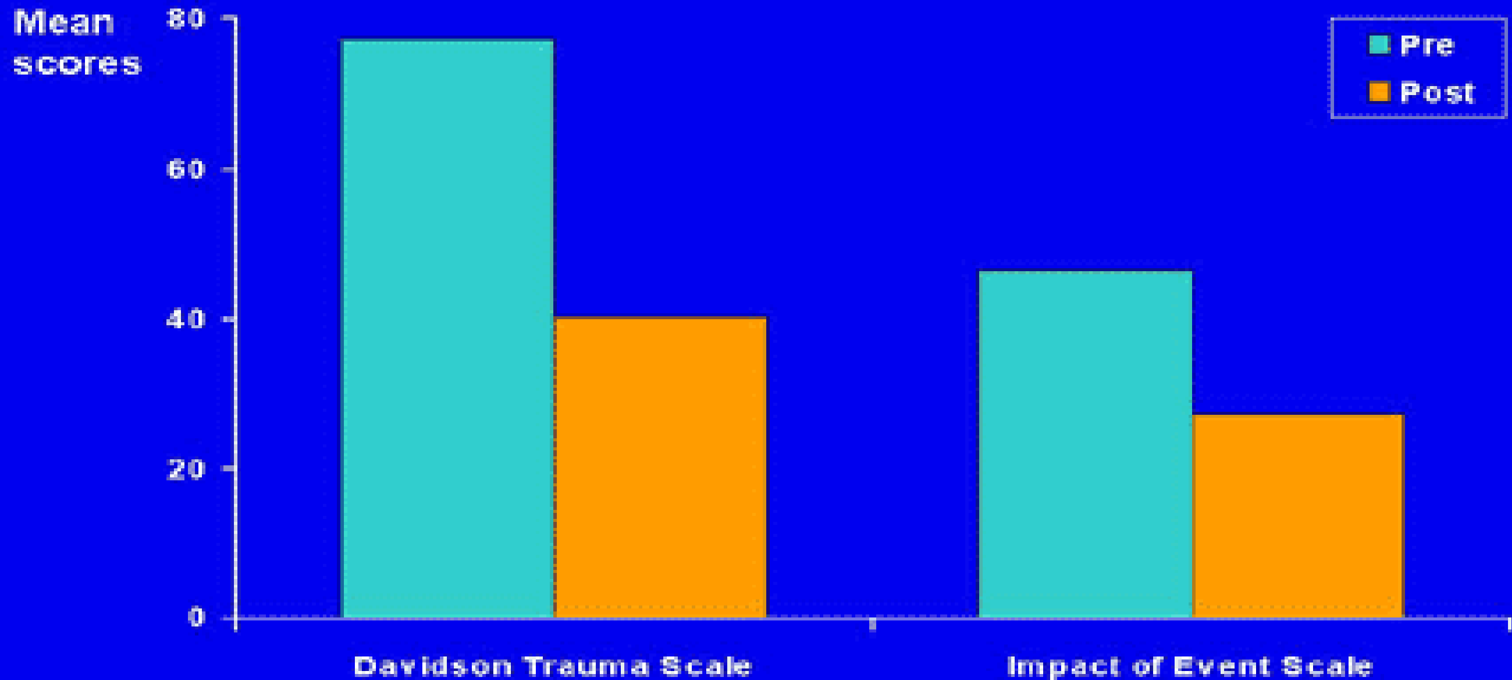


Brady et al.. JAMA 2000, in press

RESPONSE TO SERTRALINE IN 5 RAPE VICTIMS WITH PTSD

Rothbaum et al. J Trauma Stress 1996;9:865-871

Paroxetine in PTSD



PTSD

Treatment With Nefazodone

Open-Label Clinical Trials

Investigator	Population	N	Duration (Weeks)	Mean Endpoint Dosage (mg/day)
Weisler, Davidson et al	Multiple etiology	386	17	12
Hertzberg et al	Combat	10	12	490
Mellman et al	Combat, Holocaust	11	6	272
Petty et al	Combat, Sexual trauma	36	8	583
Tucker et al	Multiple etiology	10	10	*
Zisook et al	Combat	21	12	400
Overall	Mixed trauma (23% females, 77% male)	105	6–12	272–583

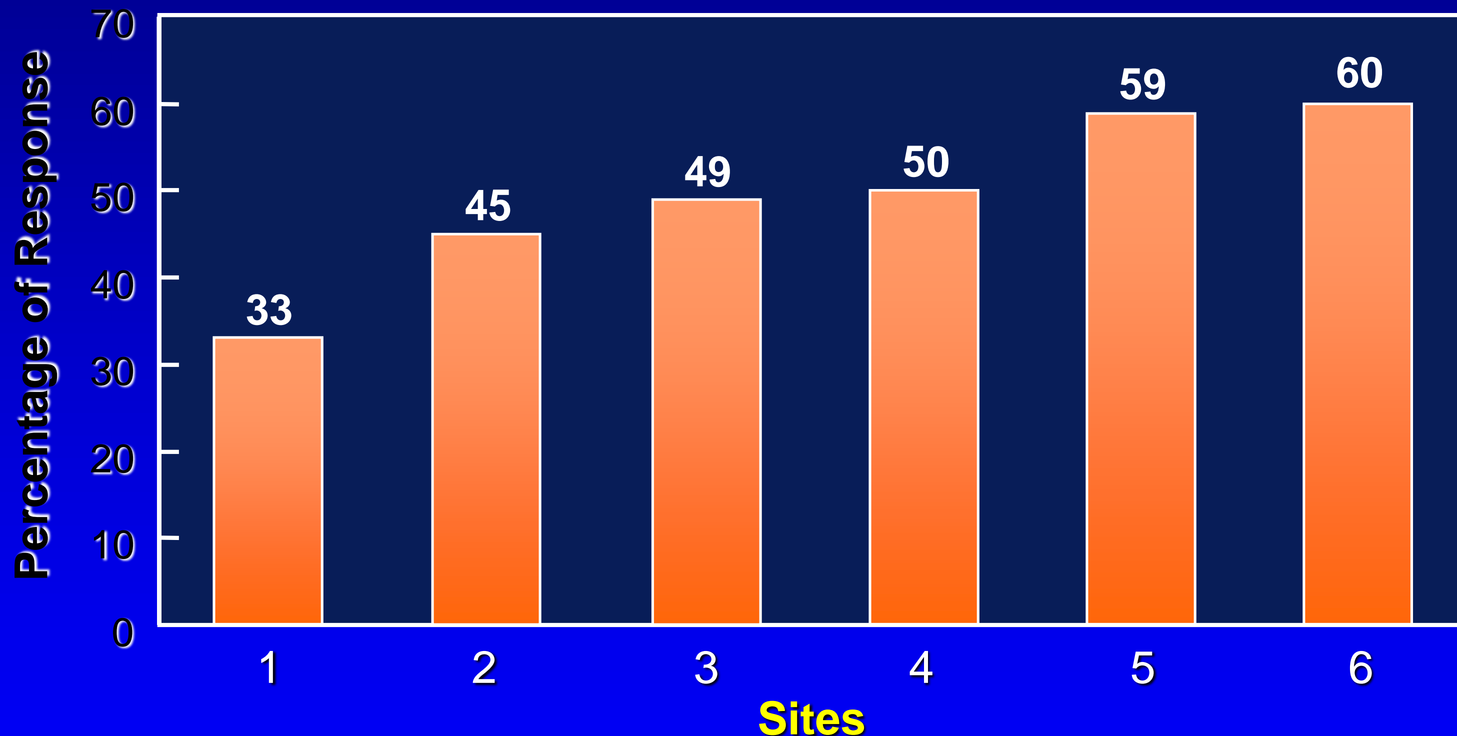
*Dosage range 100–600 mg/day.

Hidalgo R. Int Clin Psychopharmacol. 1999;14:61–68.

PTSD

Open-Label Treatment With Nefazodone

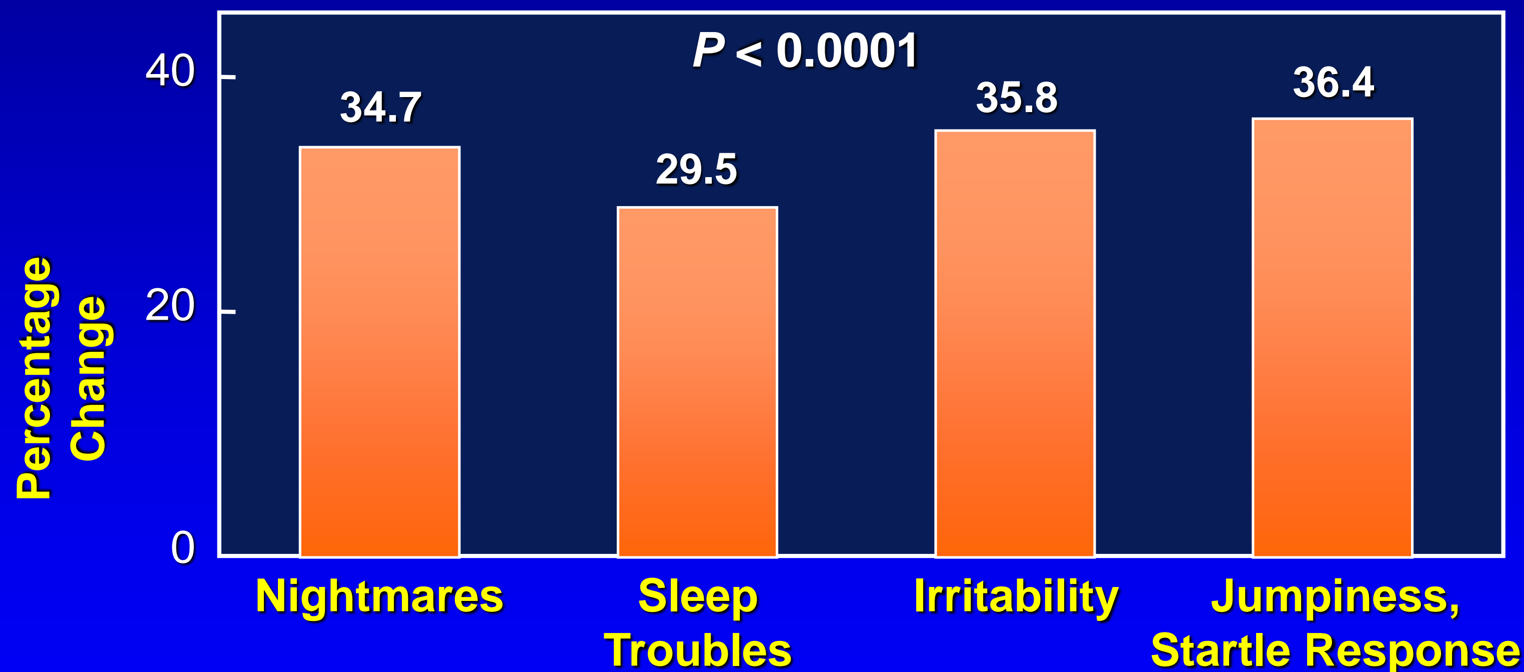
Efficacy (% Responders) Based on PTSD Main Scales*



Sites: 1: Petty et al, Dallas VAMC; 2: Mellman et al, Miami VAMC (1997);
3: Zisook et al, San Diego VAMC (1998); 4: Hertzberg et al, Durham VAMC (1998);
5: Davidson et al, DUMC and Raleigh (1998); 6: Tucker et al, Oklahoma University (1998).
*Responder is defined as decrease ≥30% from baseline.
Hildalgo R. *Int Clin Psychopharmacol*. 1999;14:61–68.

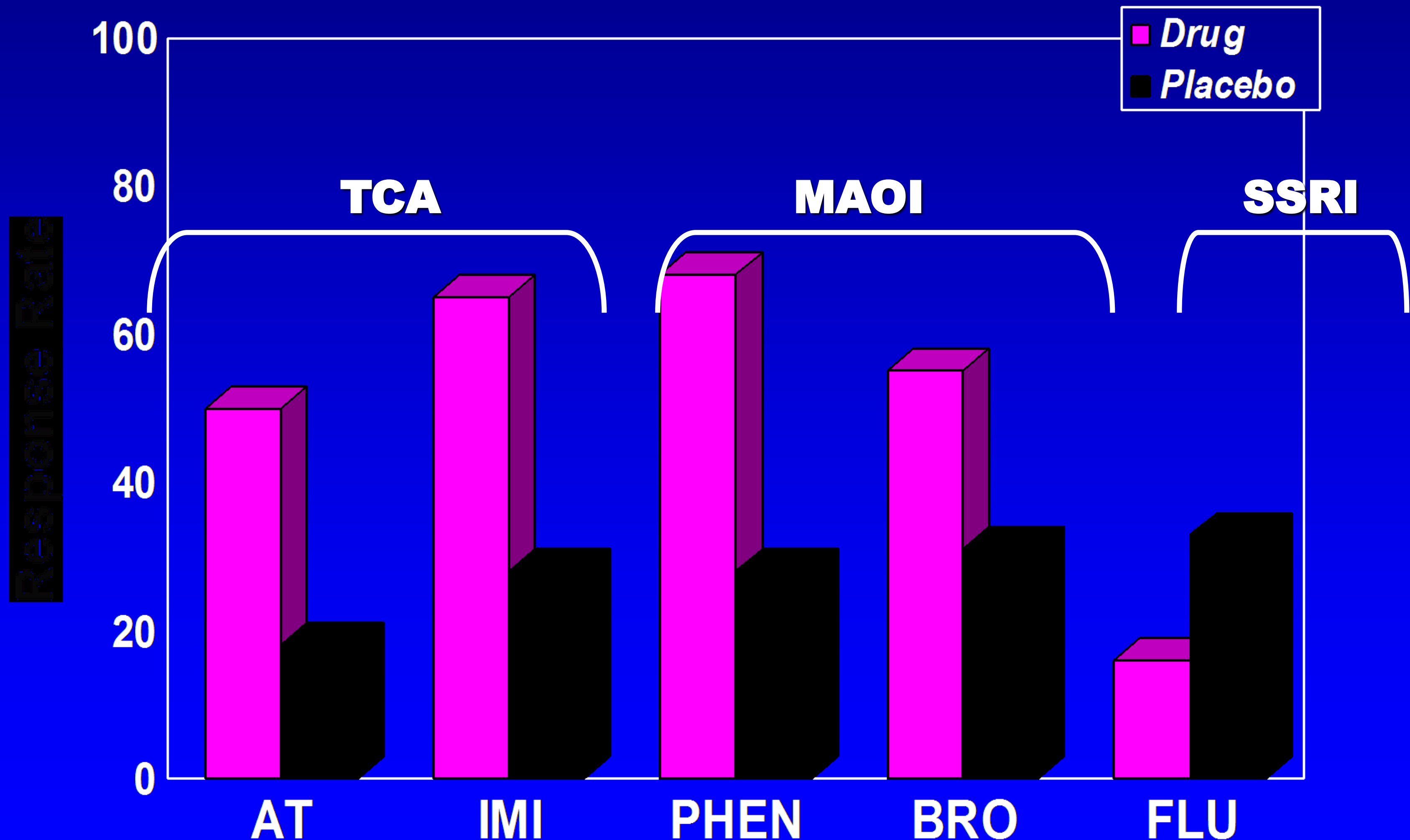
PTSD

Mean Percentage Change In Individual Symptoms After Treatment With Nefazodone



Hildalgo R. *Int Clin Psychopharmacol*. 1999;14:61–68.

COMBAT-RELATED PTSD RESPONDS TO TCA & MAOI, BUT NOT SSRI



PTSD

Summary

5. PTSD is common
   - Usually chronic
   - Presentations vary
   - Comorbidity is the rule
6. Comprehensive assessment of patients is critical to develop an individualized treatment plan
7. Treatment often involves multiple modalities

CONCLUSIONS

PTSD prevalent and *treatable* disorder

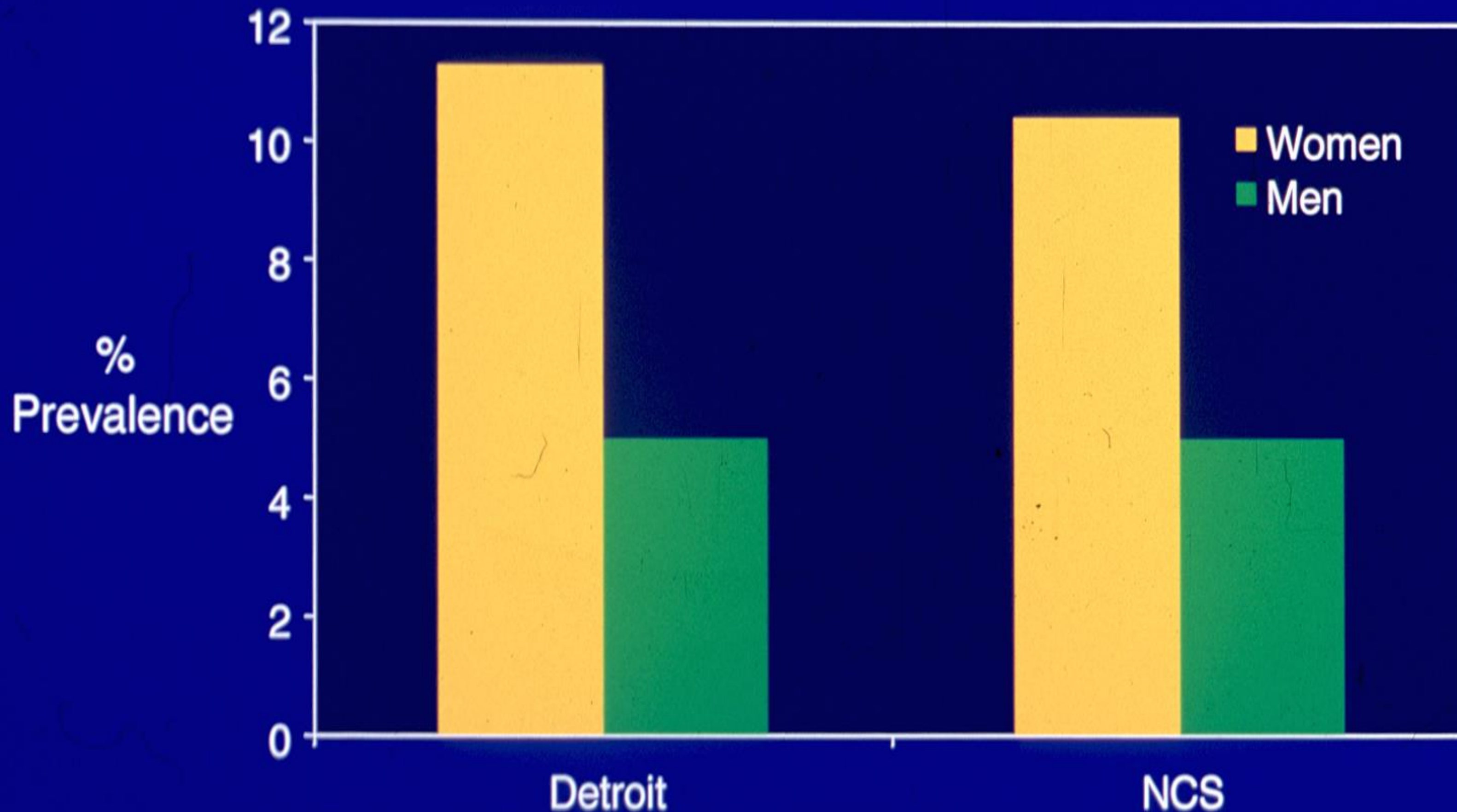
CBT effective

Antidepressant agents effective

5. **SSRI, MAOI, TCA, RIMA**

Combined CBT & pharmacotherapy trial needed

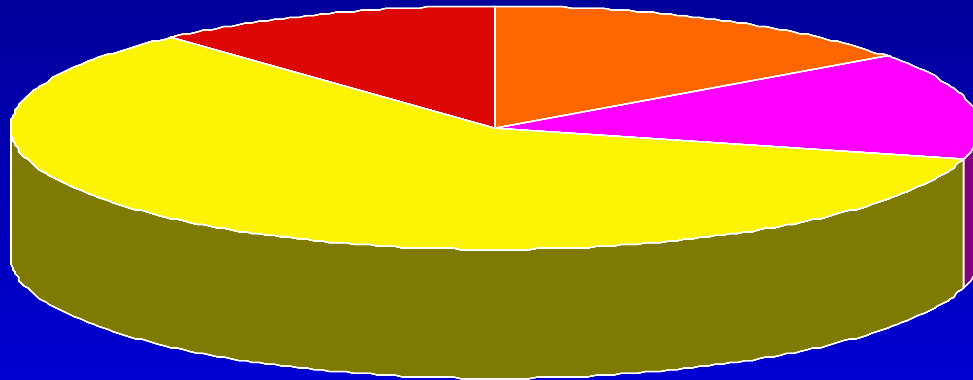
Lifetime Prevalence of PTSD



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

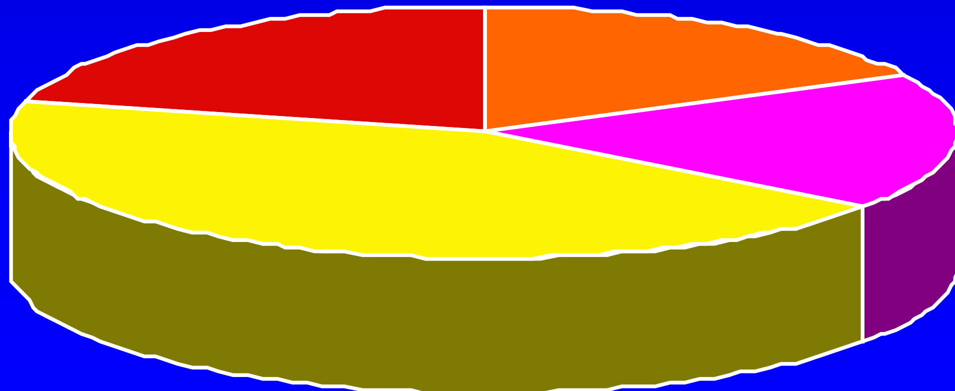
Comorbidity in PTSD
National Comorbidity Study

MEN



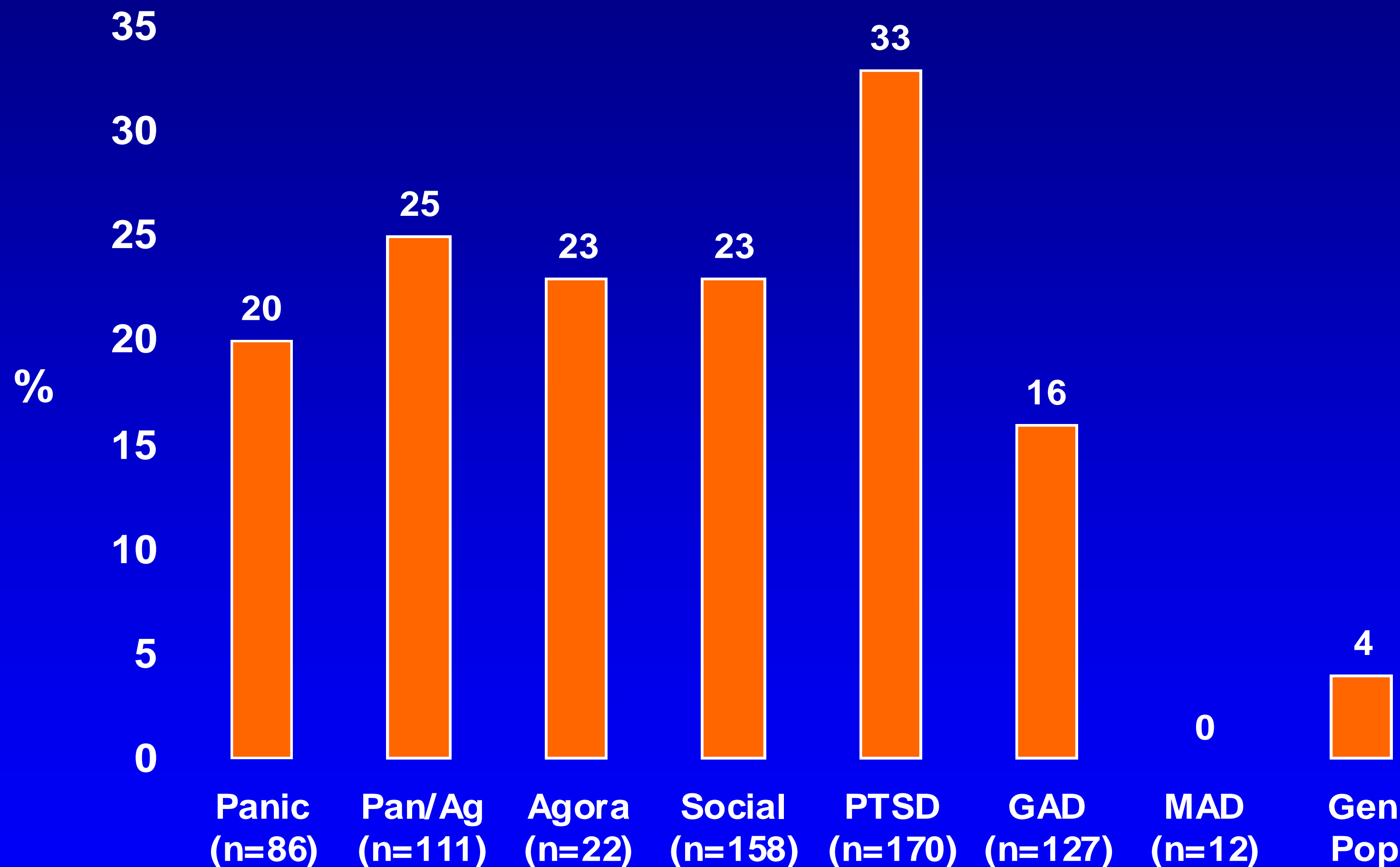
- 1 Other Diagnoses
- 2 Other Diagnoses
- 3 Other Diagnoses
- No Other Diagnosis

WOMEN



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

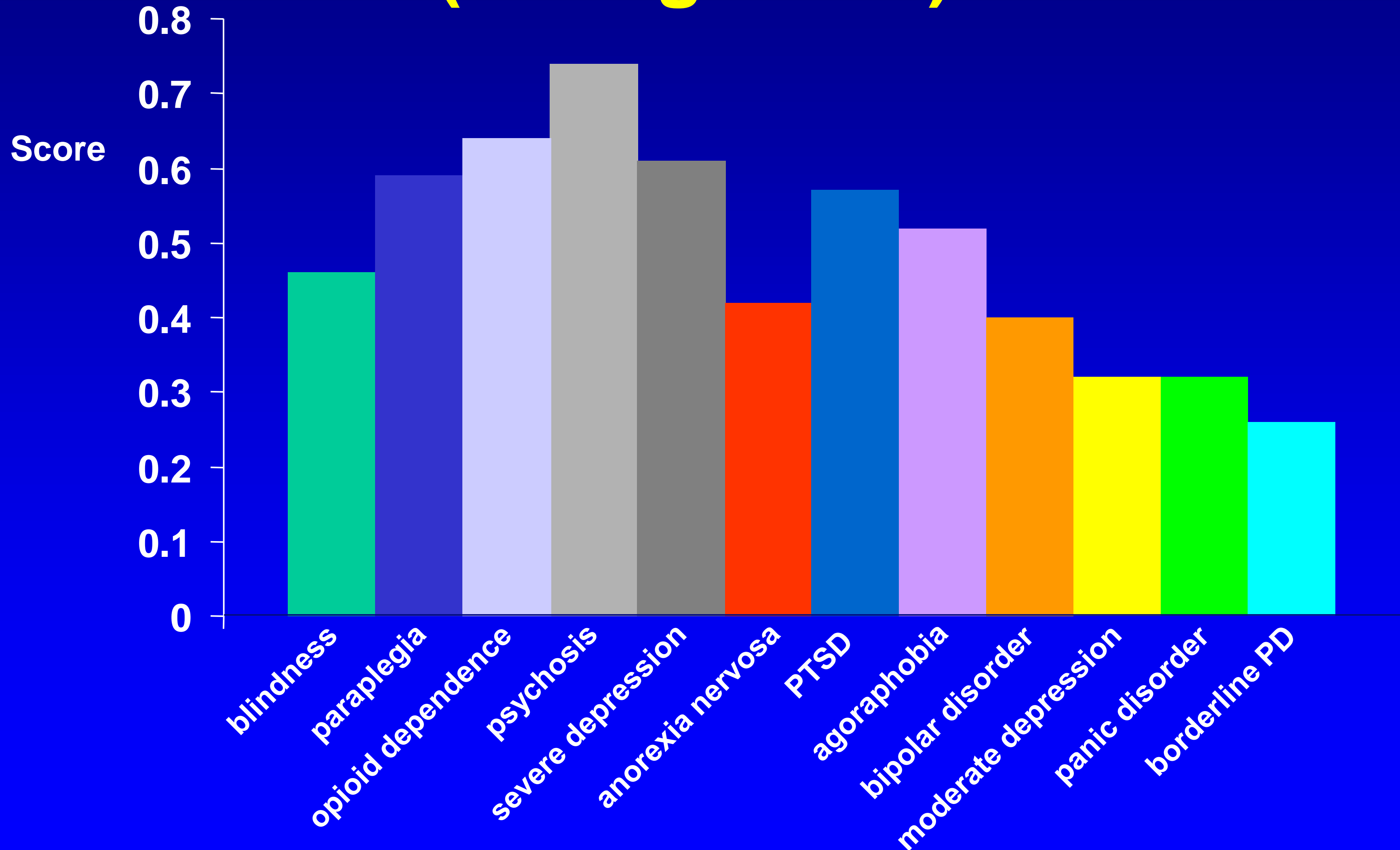
Lifetime History of Suicidal Attempts by Anxiety Disorder



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

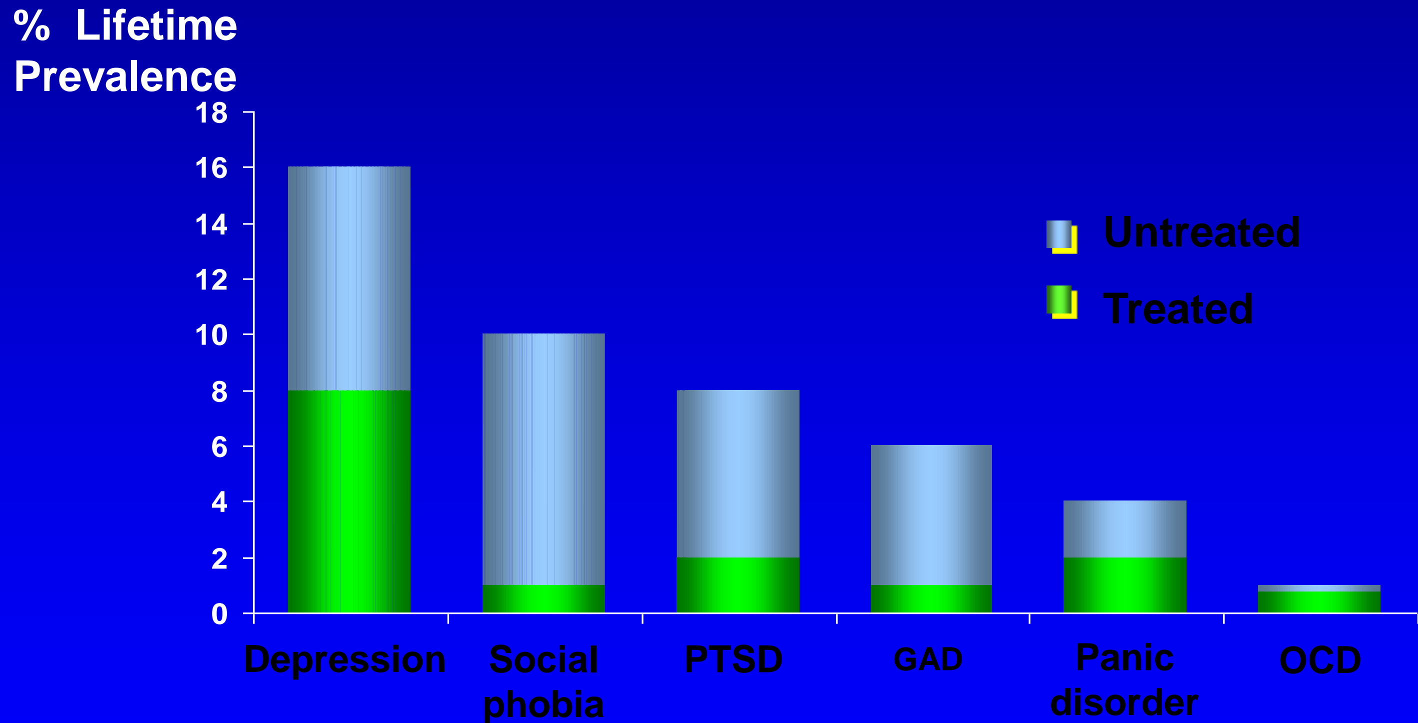
Disability Weights (Rating Scale)



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%

Psychosocial

Exposure therapy
Cognitive therapy
Anxiety management
Desensitization
EMDR
Hypnotherapy

Pharmacologic

TCAs
MAOIs
SSRIs
Mood stabilizers
Antianxiety agents

EMDR = eye movement desensitization and reprocessing.

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

True or False:

- Propranolol is an effective treatment for PTSD.

Question 4

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 5

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

A. EDMR
B. CBT
C. Breathing relaxation
D. Exposure
E. Thought-stopping

Answers to Pre & Post Competency Exams

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