Generalized Anxiety Disorder

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Generalized Anxiety Disorder (GAD) Presentation OUTLINE

- Questions and Learning Points
  - Illness Characteristics
  - Morbidity and Comorbidity
  - Diagnosis and Assessment
  - Treatment
  - Summary
  - Questions and Answers
  - Future Treatments (Optional)

Question #1

True or False

Women have a HIGHER Lifetime Prevalence of GAD as compared to Men.

Question #2

Which Psychiatric Illness has the HIGHEST LIFETIME PREVALENCE of COMORBIDITY with GAD?

Question #3

What Anxiety Assessment Scale is commonly used to Assess Outcomes in GAD? and…

A decrease of ___% or greater on this scale defines RESPONSE while a score of ___ or less on this scale defines REMISSION.

Question #4

What PHARMACOLOGIC TREATMENTS are Effective in Treating GAD?

Question #5

What Percentage of Patients with GAD Relapse Within the First Year After Stopping Pharmacotherapy?

Teaching Point #1

GAD…

- **Is More Likely to Occur in Women**
- **Has a Modal Age of Onset in the Early 20s**
- **Is Usually Comorbid with Another Psychiatric Illness**

Teaching Point #2

Somatic Symptoms are Prevalent in GAD

HOWEVER,

Medications and Medical Conditions Should be Included in the Differential Diagnosis of a Patient Suspected of Having GAD

Teaching Point #3

Selective Serotonin Reuptake Inhibitors, Serotonin Norepinephrine Reuptake Inhibitors, and Benzodiazepines are Commonly used to Treat GAD

Long Term Treatment May be Required

GAD Diagnostic Criteria

- Excessive anxiety and worry
- More days than not for ≥6 months
- Worry is excessive and difficult to control
- Symptoms impair social,occupational, family role functioning and/or cause significant distress

DSM IV-TR. Washington, DC: American Psychiatric Association. 2000.

Diagnostic Criteria for GAD

- Associated with 3 of the following
  - restlessness/keyed-up
  - easily fatigued
  - difficulty concentrating
  - irritability
  - muscle tension
  - sleep disturbance
- Cannot be confined to another Axis 1 diagnosis or the effects of a substance or medical condition

DSM IV-TR. Washington, DC: American Psychiatric Association. 2000.

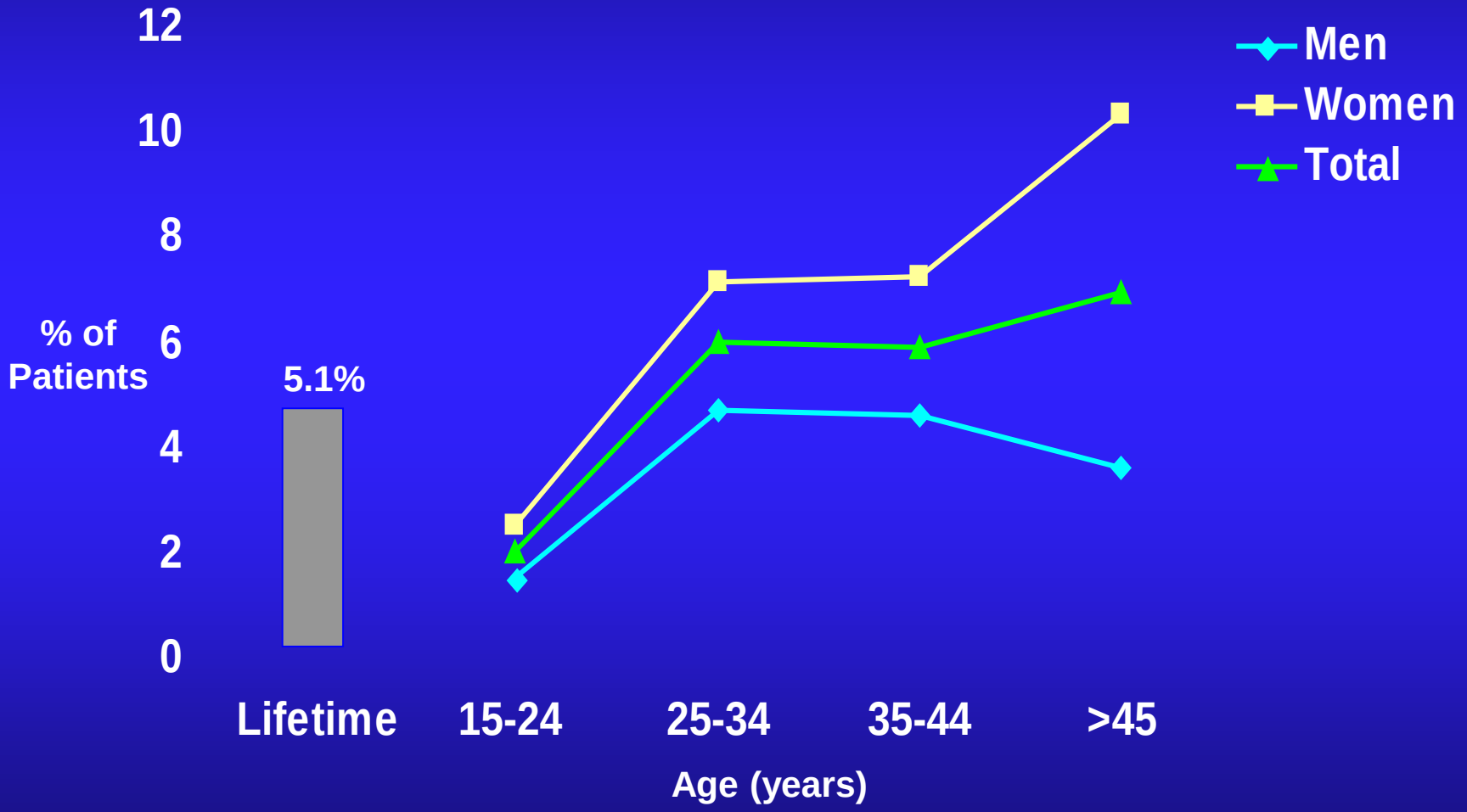
GAD Symptoms

- Psychic symptoms
  - worry
  - “on edge”/unable to relax
  - Impaired concentration-memory
  - *Concern over health*
- Somatic symptoms
  - muscle tension
  - Insomnia
  - Fatigue
  - irritability
  - nausea or diarrhea*
  - Sweating*
  - urinary frequency*
  - Palpitations*
  - Pain*

DSM IV-TR. Washington, DC: American Psychiatric Association. 2000.

Symptoms not diagnostic but often present (Schweizer E et al. J Clin Psychiatry. 1997;58(suppl 3):27-31.)

Lifetime Prevalence of GAD: National Comorbidity Survey



Wittchen H et al. Arch Gen Psychiatry. 1994;51:355-364.

Epidemiology of GAD

- **Lifetime prevalence 5.1 %**
- **Women > men 2:1**
- **Modal age of onset is early 20s**
- **High comorbidity in clinical and community samples. : “Pure” Gad is rare.**

Kessler RC et al. Arch Gen Psychiatry. 1994;51:8
DSM-IV. Washington, DC: American Psychiatric Association, 1994

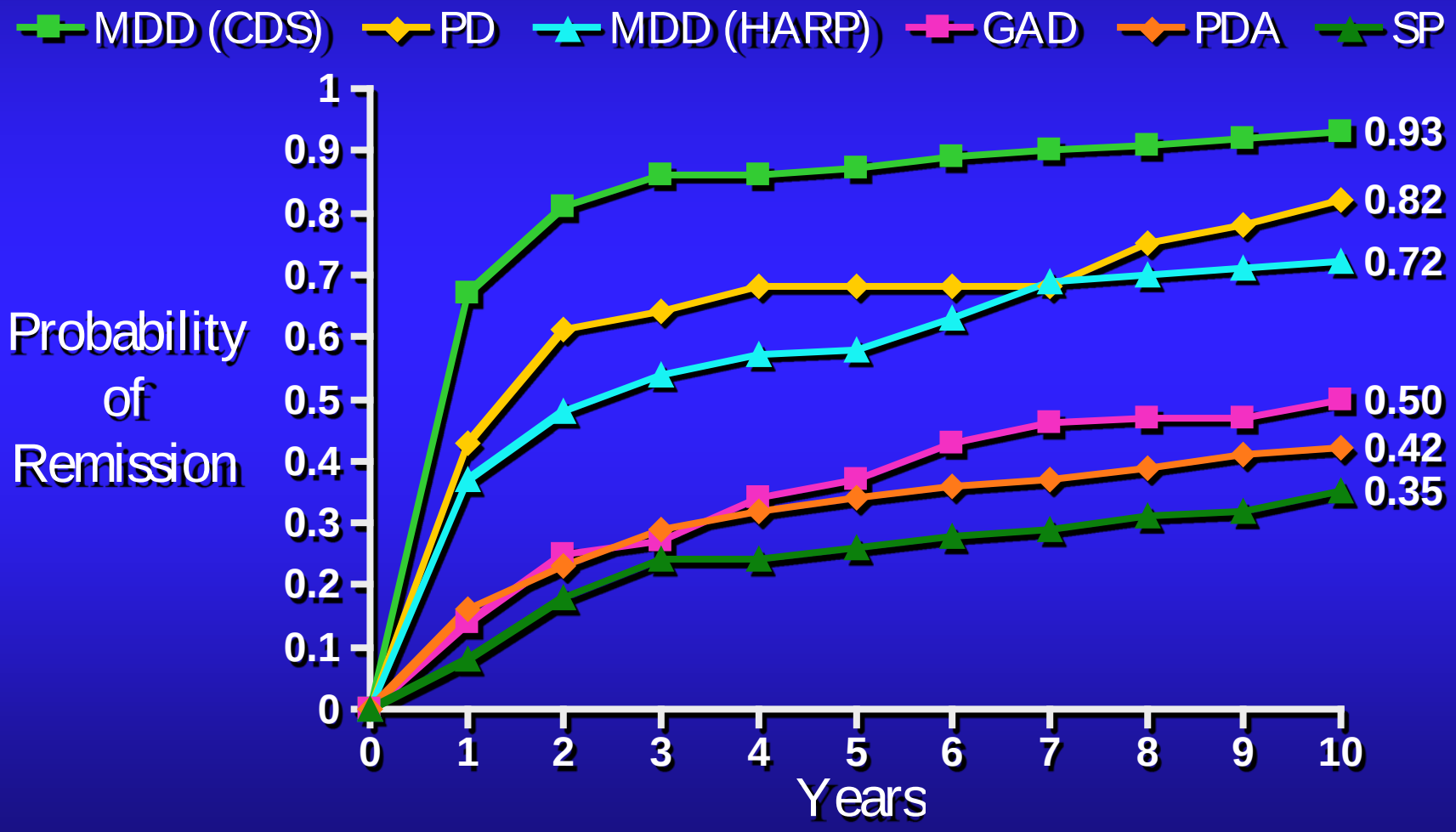
Course of GAD

Chronic course (mean > 20 yrs)

- **Low rate of spontaneous remission (25% at 2 yrs)**
  - **For each add'l Axis I disorder 50% lower**
  - **For each add'l Axis III disorder 19% lower**

Sartorius N et al. Br J Psychiatry. 1996;168(suppl 30):38-43.
Maier W et al. Acta Psychiatr Scand. 2000;101:29-36.

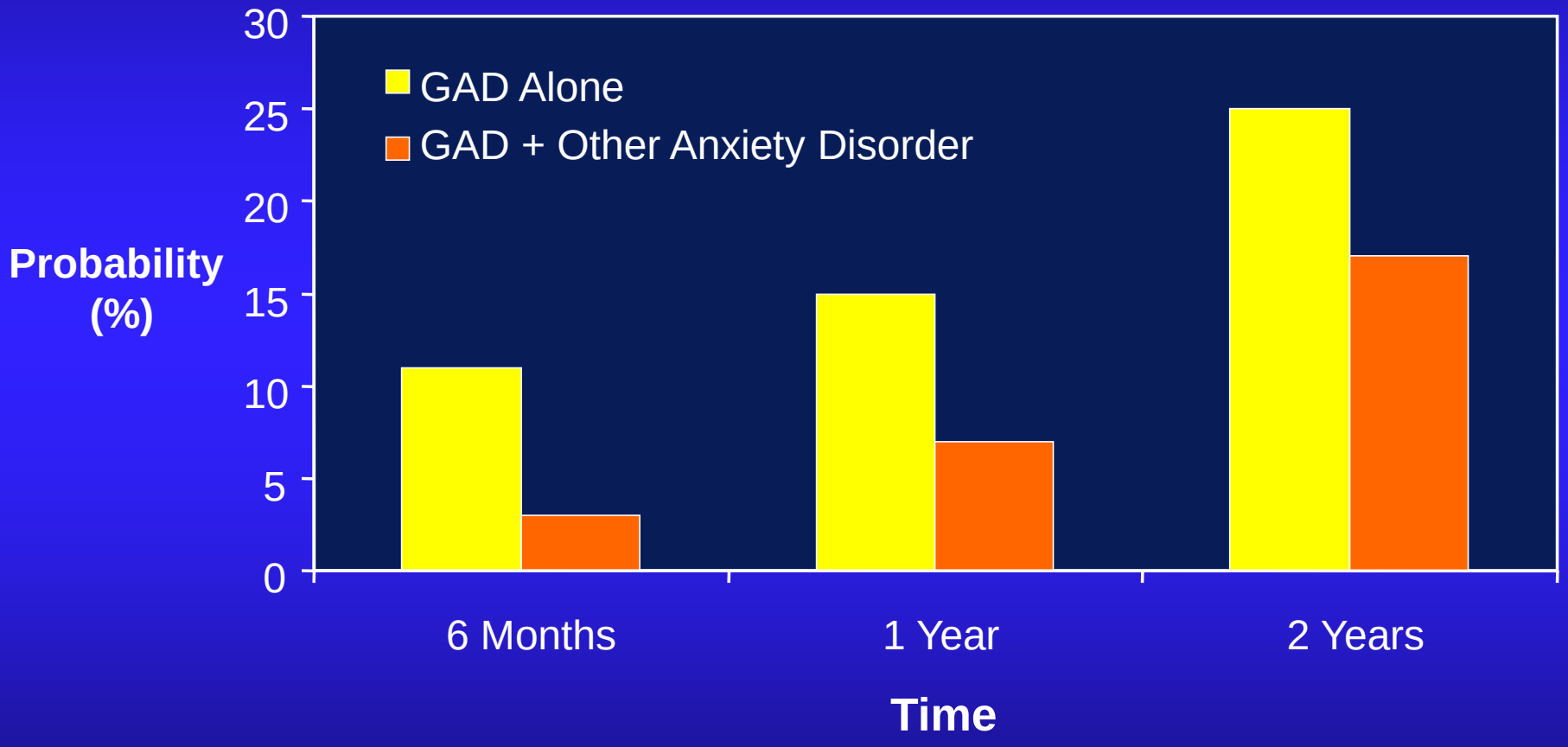
10-Year Anxiety Disorder and Major Depressive Disorder Remission Rates



Keller, MB, Culpepper L, Data on file; CDS- Collaborative Depression Study

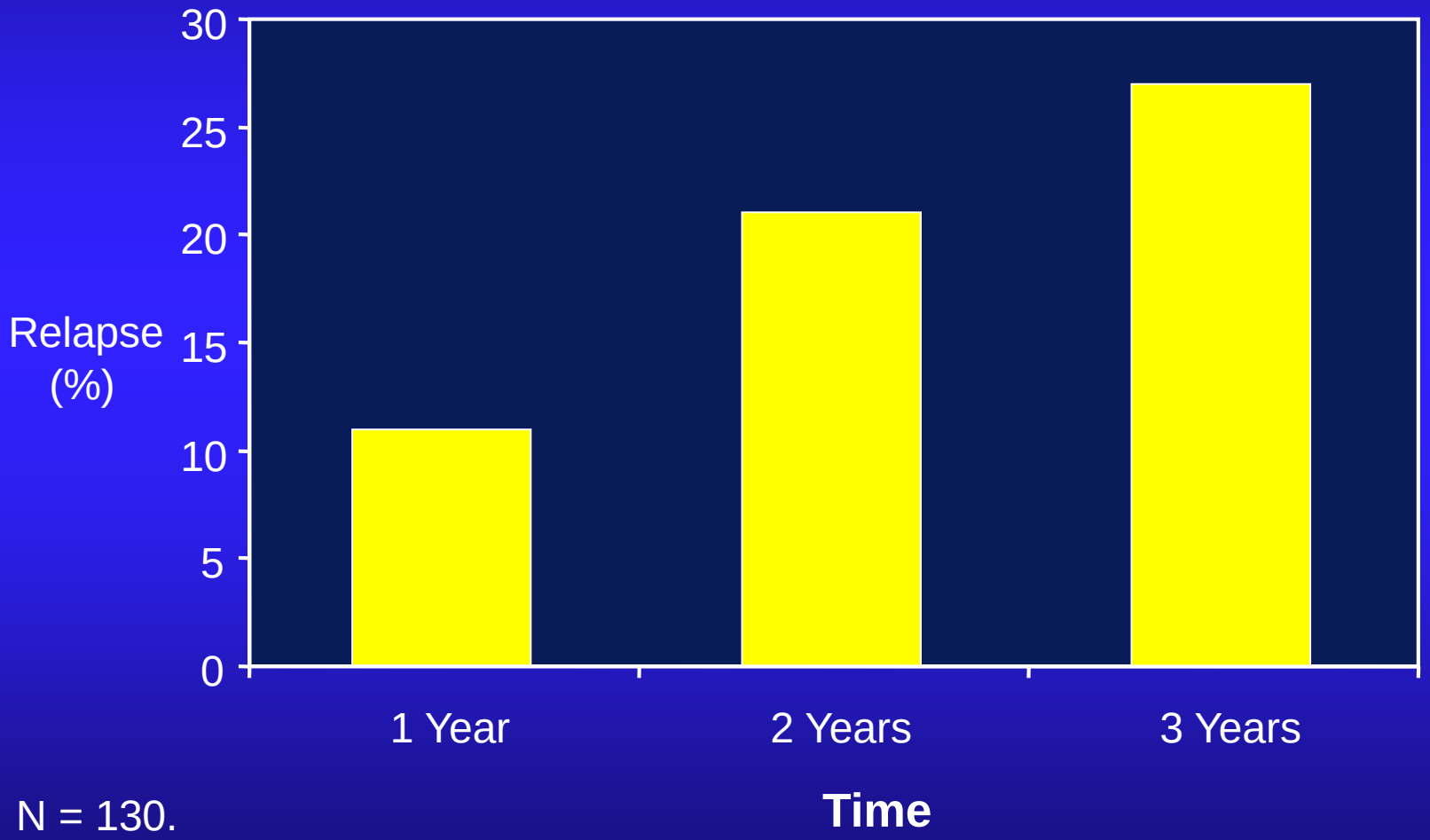
Low Probability of Remission in GAD*

Patients in treatment (HARP)



Yonkers KA et al. *Br J Psychiatry*. 1996;168:308-313.

Relapse Rates in GAD After Full Remission



N = 130.

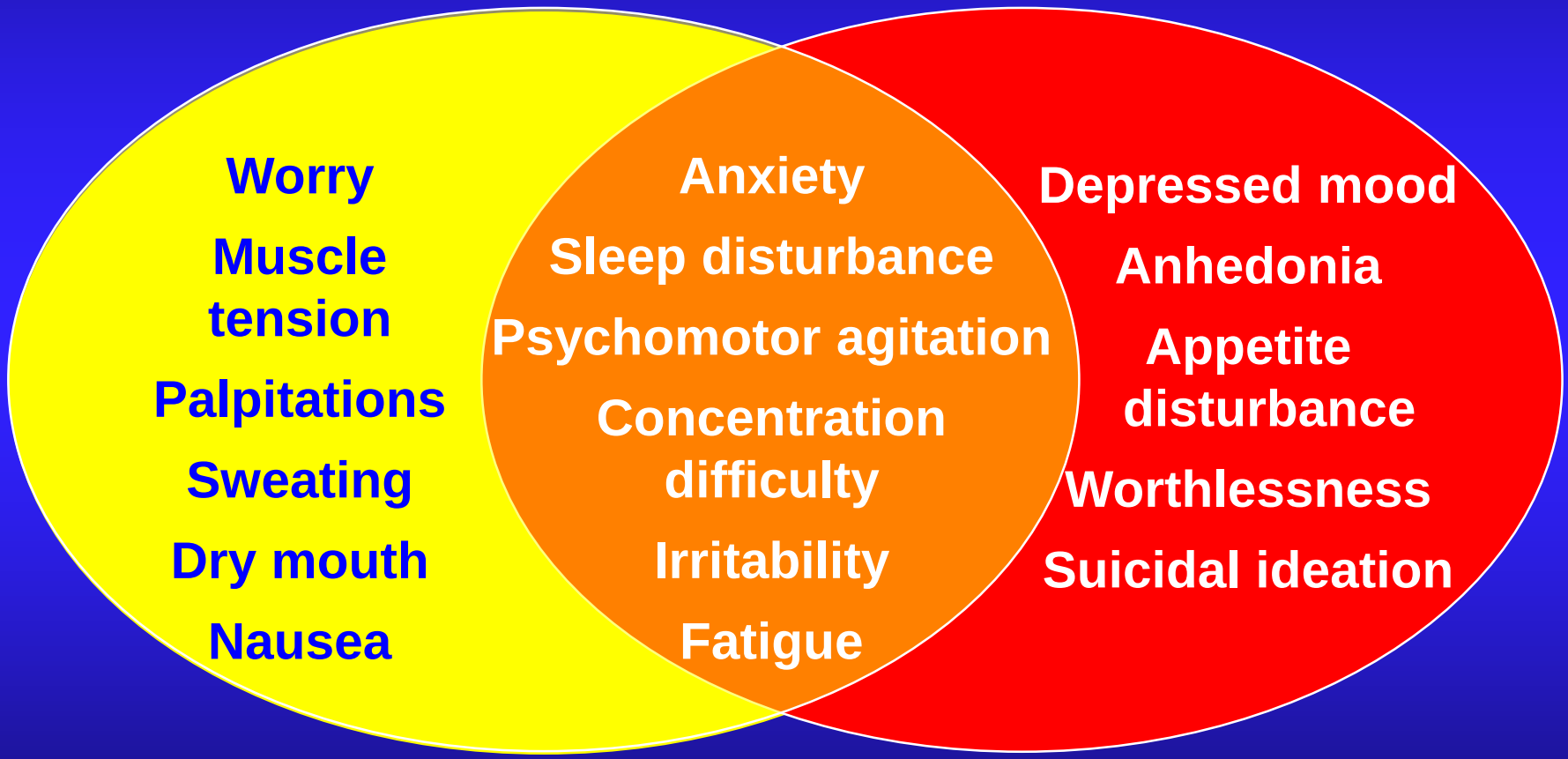
Yonkers KA et al. *Br J Psychiatry*. 2000;176:544-549 Depress Anxiety 2003 17:173-9.

GAD Patients: Comorbidity

- 90% have another psychiatric disorder
- In patients with GAD
  - 62% have lifetime major depression
  - 40% have dysthymia
- Anxiety disorders predict greatest risk of secondary MDD
- 58% of patients with lifetime MDD have an anxiety disorder

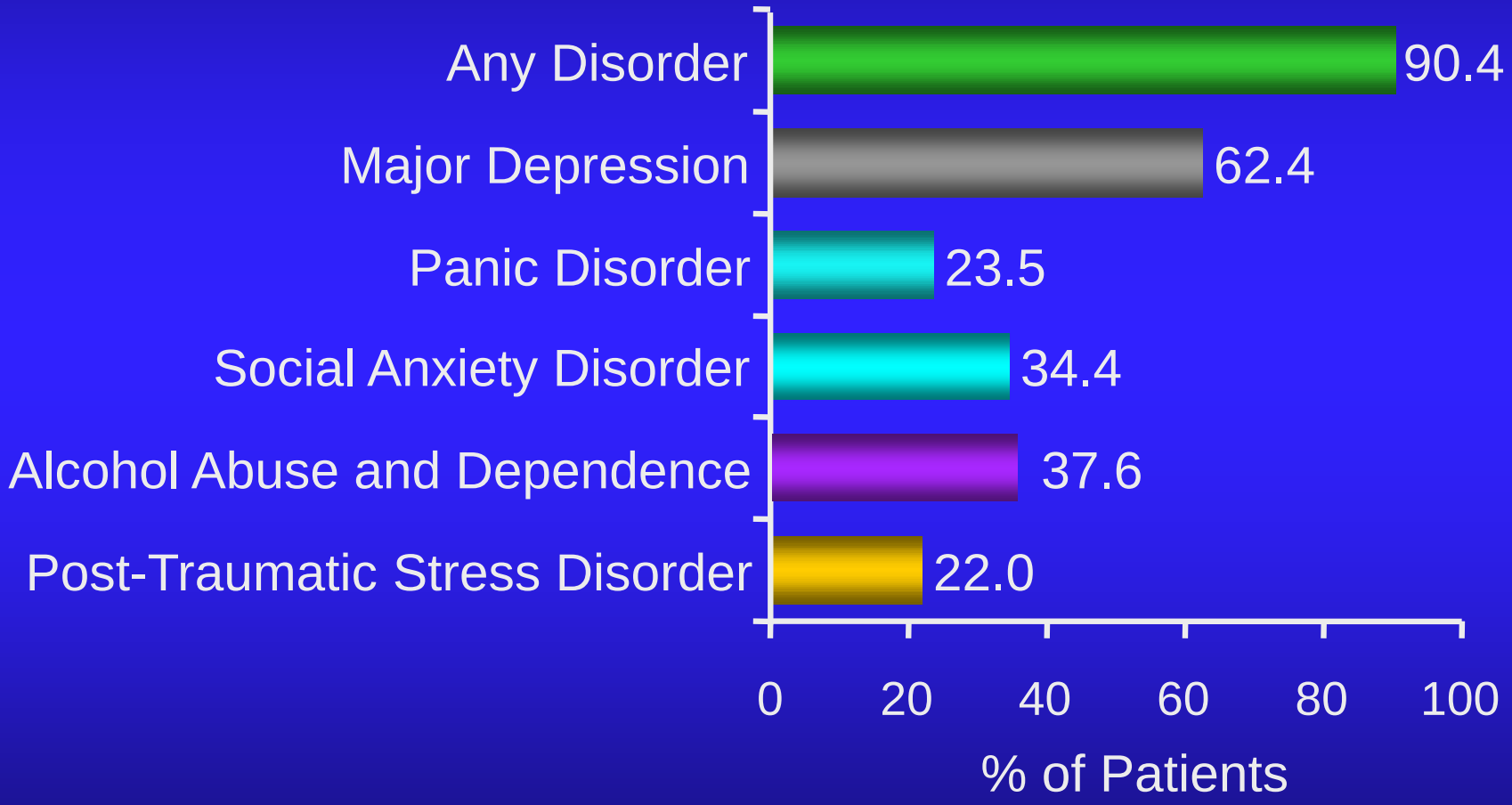
Kessler RC et al. Br J Psychiatry. 1996;168(suppl 30):17
Wittchen H-U et al. Arch Gen Psychiatry. 1994;51:355

Overlapping Symptoms of MDD and GAD



DSM-IV-TR. Washington, DC: American Psychiatric Association. 2000.

Lifetime Prevalence of Comorbid Disorders in Patients with GAD

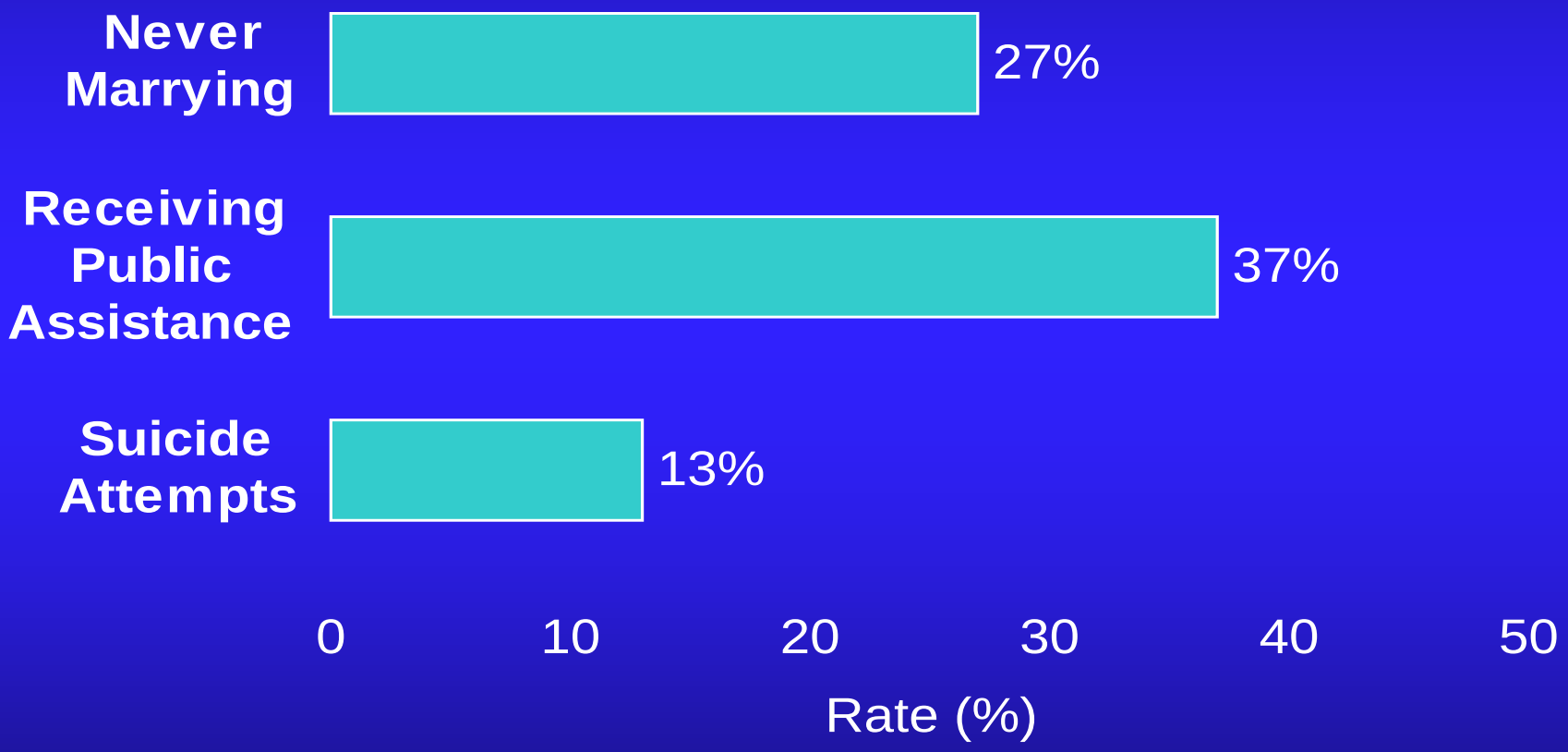


Wittchen HU, et al. Arch Gen Psychiatry. 1994;51(5):355-364; Kessler et al, Arch Gen Psychiatry, 2000.

GAD+MDD: Implications

- Treatment resistance or delayed response
- Increased suicidal behavior
- Antidepressants indicated
- One open-label clinical practice reports effectiveness of venlafaxine in comorbid state
- CBT efficacy for comorbid state less clear, needs study
- Much written, little known
- Brown et al AJP 1996; 153: 1293-1300; Gaynes et al, Gen Hosp Psych 1999; 21:158-67; Goodnick et al, JCP199; 60: 446-48; Silverstone et al JCP 1999; 60: 22-8; Peruigi et al, Neuropsychobiology, 2002

GAD: *Complications*

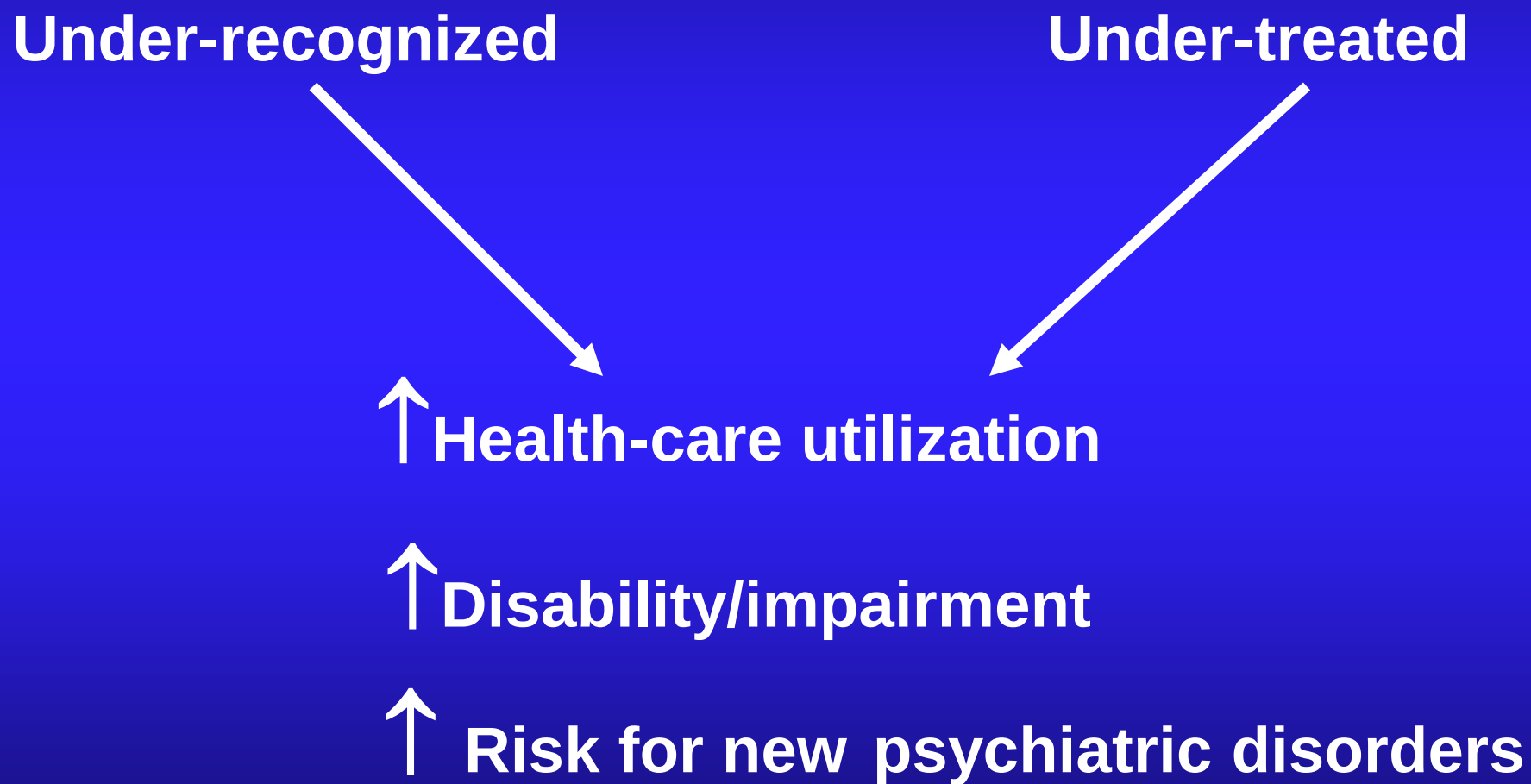


Massion AO et al. *Am J Psychiatry*. 1993;150:600-607.

GAD Often Perceived as Physical by Patients--High Health Care Utilization and Low Recognition

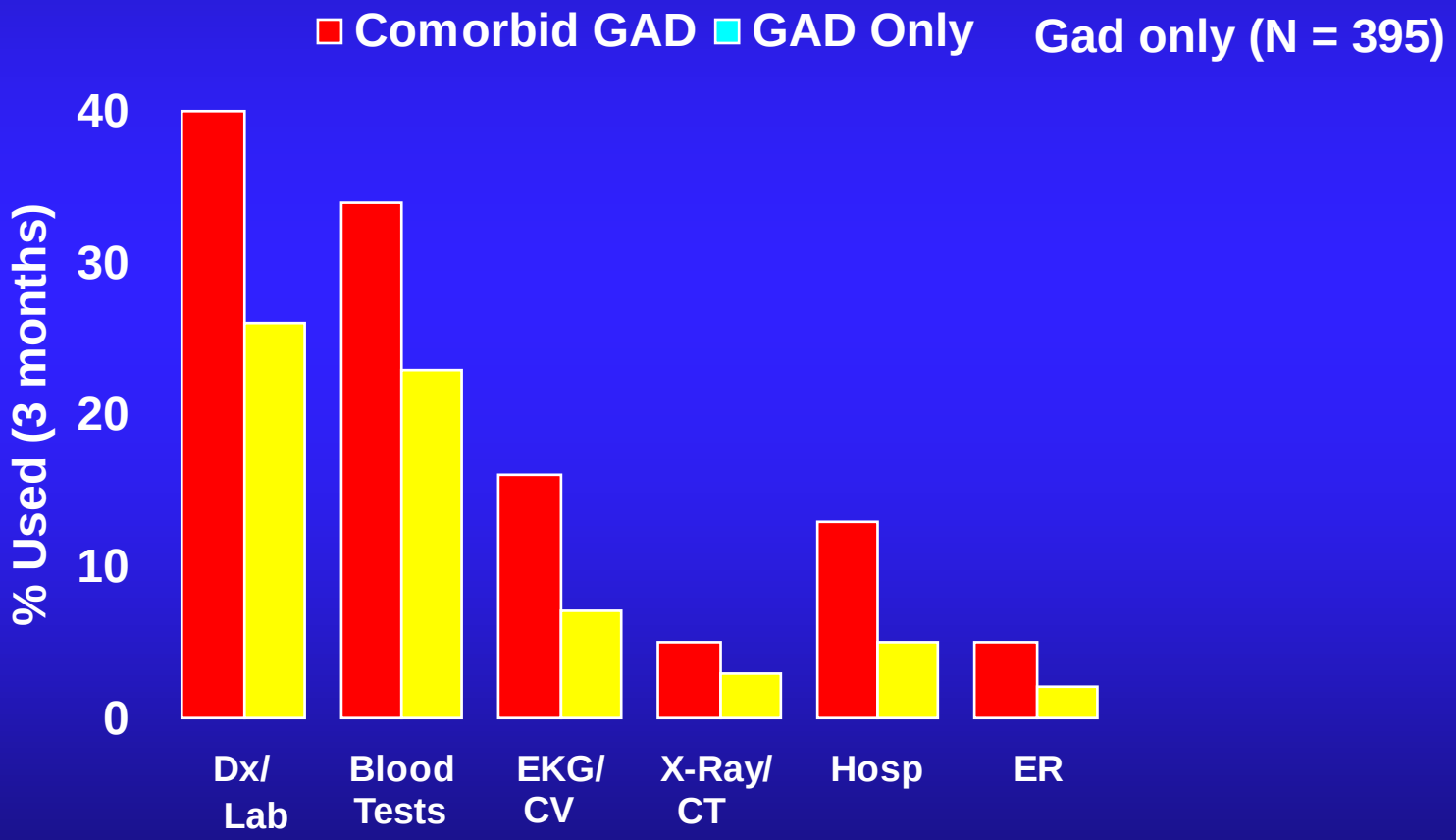
- Gastrointestinal distress
- Insomnia
- Fatigue
- Musculoskeletal complaints
- Headache
- Cardiovascular complaints

Generalized Anxiety Disorder (GAD)



Generalized Anxiety Disorder

Services Utilization and Comorbidity



Souetre et al, *J Psychosom Res* 1994;151

GAD in Cardiology

Cardiovascular Evaluation Sought by GAD Patients

Logue et al, *Psychiatr Res* 1993;27:55

GAD
Differential Diagnosis

- **Adjustment disorders**
  - With anxiety
  - With depression
  - With mixed symptoms
- **Anxiety disorders**
  - Generalized anxiety disorder (GAD)
  - Panic disorder
  - Phobias
  - Post-traumatic stress disorder (PTSD)
  - Obsessive-compulsive disorder (OCD)

Patient Assessment

- Establish Diagnosis
- Comorbid diagnosis present?
  - Current or past depression
- Natural History of Illness
- Treatment History
- Family History
- Medical History and exam
  - Review medications, *including herbal medicine*

Differential Diagnosis

Medications Which Can Cause Anxiety Symptoms

- Stimulants (caffeine)
- Thyroid supplementation
- Antidepressants
- Corticosteroids
- Oral contraceptives
- Bronchodilators
- Decongestants
- Abrupt withdrawal of CNS depressants
  - Alcohol
  - Barbiturates
  - Benzodiazepines

Fernandez et al. J Clin Psychiatry. 1995;56(suppl 2):20–29.
Kirkwood et al. Anxiety disorders. In: DiPiro et al, eds. Pharmacotherapy: A Pathophysiologic
Approach. 3rd ed. 1997:1443–1462.

Differential Diagnosis

Medical Conditions with Secondary Anxiety Symptoms

- Endocrine disorders
  - Thyroid disease
  - Parathyroid diseases
  - Hypoglycemia
  - Cushings Disease
- Cardio-respiratory disorders
  - Angina
  - Pulmonary embolism
- Autoimmune disorders
- Neurological
  - Seizure disorder
- Substance-related dependence/ withdrawal
  - Nicotine
  - Alcohol
  - Benzodiazepines
  - Opioids

Goals of Treatment in GAD

Response	Remission*
≥ 50% decrease from baseline in HAM-A scores or CGI score of 1 or 2	HAM-A score ≤ 7 Patient asymptomatic Psychosocial/occupational functioning restored

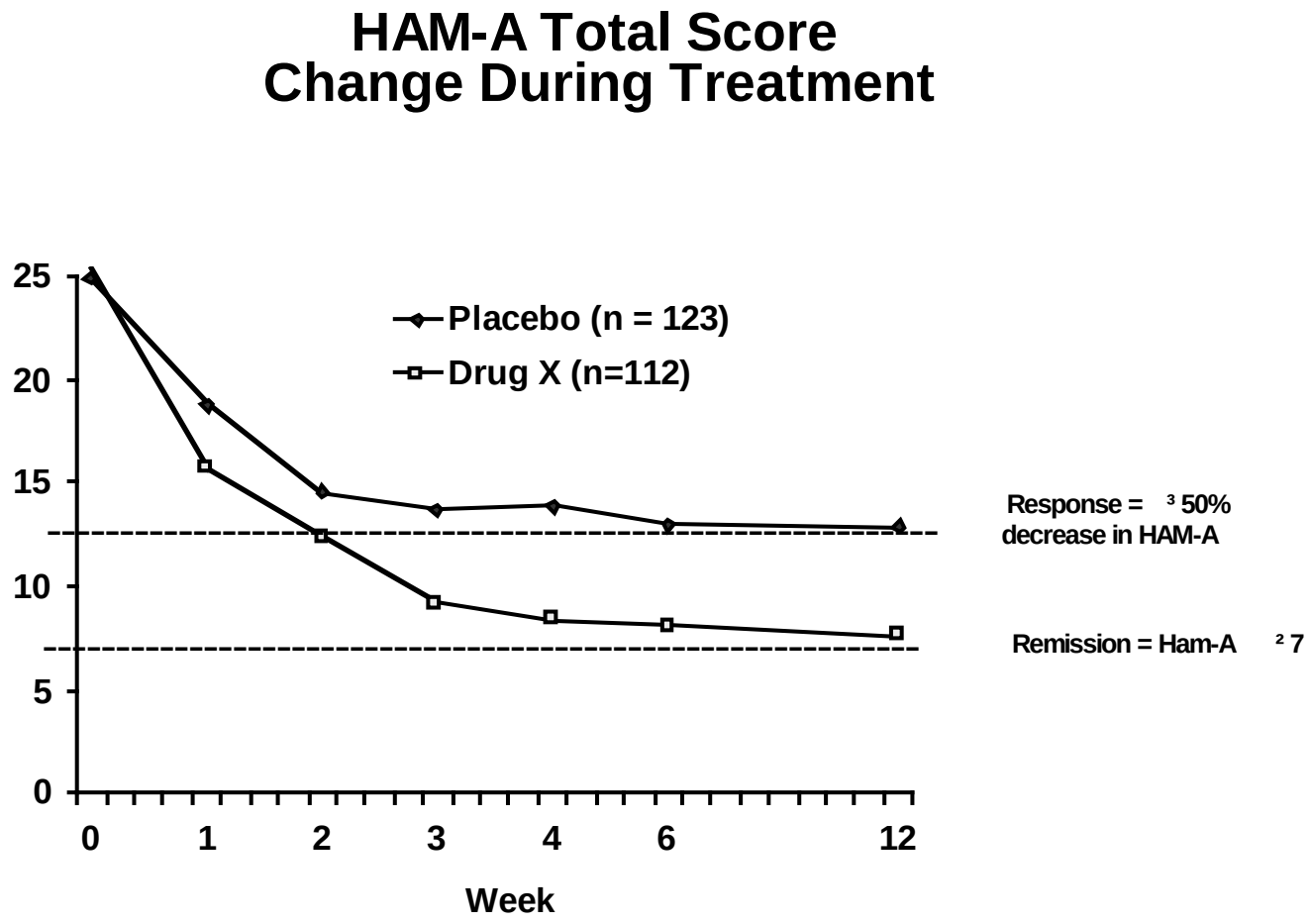
*Peer-reviewed published studies on remission in GAD not yet available.

Allgulander C et al. *Br J Psychiatry.* 2001;179:15-22.
Pollack MH et al. *J Clin Psychiatry.* 2001;62:350-357.

Outcomes Assessment in GAD

- Hamilton Anxiety Rating Scale
  - Traditionally used in clinical trials
- Hospital and Anxiety Rating Scale
  - Patient rated 14 items
    - 7 items for anxiety
    - 7 items for depression
    - Sensitive to change
    - Equivalence to Hamilton Anxiety Scale shown in large patient sample

Response vs Remission



Treating Anxiety Disorder May Reduce Risk of MDD

- National Comorbidity Survey
  - Sept. 1990 - Feb. 1992 (interview and re-interview 2y later)
- Respondents with GAD w/o prior MDE
- ≥4 doses psychotropic medication for GAD
  - Lower risk of depression
    - » 5.73% vs. 18.9%, $p<0.0001$
  - Receiving any medication for GAD or consulting mental health specialist was not.

Goodwin RD and Gorman JM, Am J Psychiatry 2002;159(11):1935-37

Treatments for GAD

- Anxiolytic agents and antidepressants are effective in the treatment of GAD
  - BZDs
  - Buspirone
  - TCAs
  - SSRIs
  - SNRIs Venlafaxine XR (extended release)
    - (duloxetine in clinical trials 2006)
- Some forms of psychotherapy are effective in the treatment of GAD

*

GAD Psychosocial Treatments

- Cognitive-Behavior Therapy*
  - Manualized treatment developed
  - Limited data
  - Behavioral alone (eg relaxation, imaginal exposure) vs Cognitive alone better outcome
  - Combined cognitive and behavioral
- Other Psychotherapy
  - Insight-oriented
  - Family/group
- Support
- Education

*Unclear for comorbid states

Deacon and Abramowitz J Clin Psychol 2004; 60:429-41

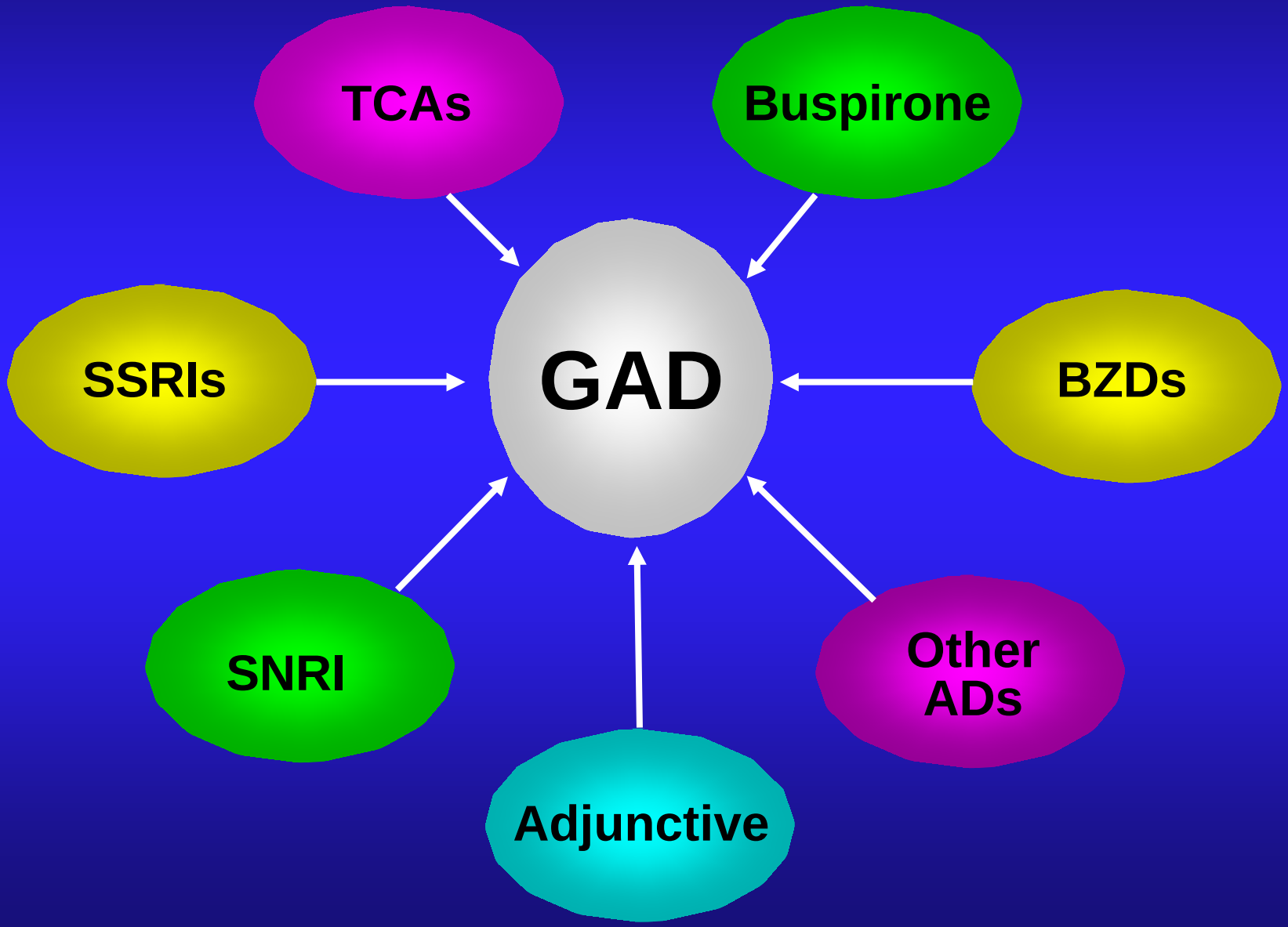
Lydiard et al J Consult Clin Psychol, 64:660-68, 1996

Psychotherapy in GAD

- **Recovery rates at 6-month follow-up**
  - **Cognitive behavioral therapy: 44 of 87 patients = 51%**
  - **Applied relaxation: 23 of 38 patients = 60%**
  - **Analytical psychotherapy: 1 of 23 patients = 4%**

Fisher PL, Durham RC. *Psychol Med.* 1999;29:1425-1434.

Pharmacotherapy for GAD



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Traditional Anxiolytics

Limitations

- **Poor tolerability (TCAs, MAOIs)**
  - ***SSRIs-Less than ideal***
- **Limited breadth of efficacy (TCAs, BZDs, MAOIs?)**
- **Lack of antidepressant efficacy (buspirone?, BZDs)**
- **Safety (TCAs, MAOIs)**

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Initiating therapy: treatment considerations

Ease of management

- Safety
- Concomitant meds
- Pregnancy
- Age
- Washout

- Compliance
- Ease of switching
- Ease of discontinuation

GAD Treatments
SSRIs and SNRIs+

Advantages

- **Effective**
- **Safety**
- **Tolerability**
- **No dependence issues**
- **Once-daily dosing**

Disadvantages

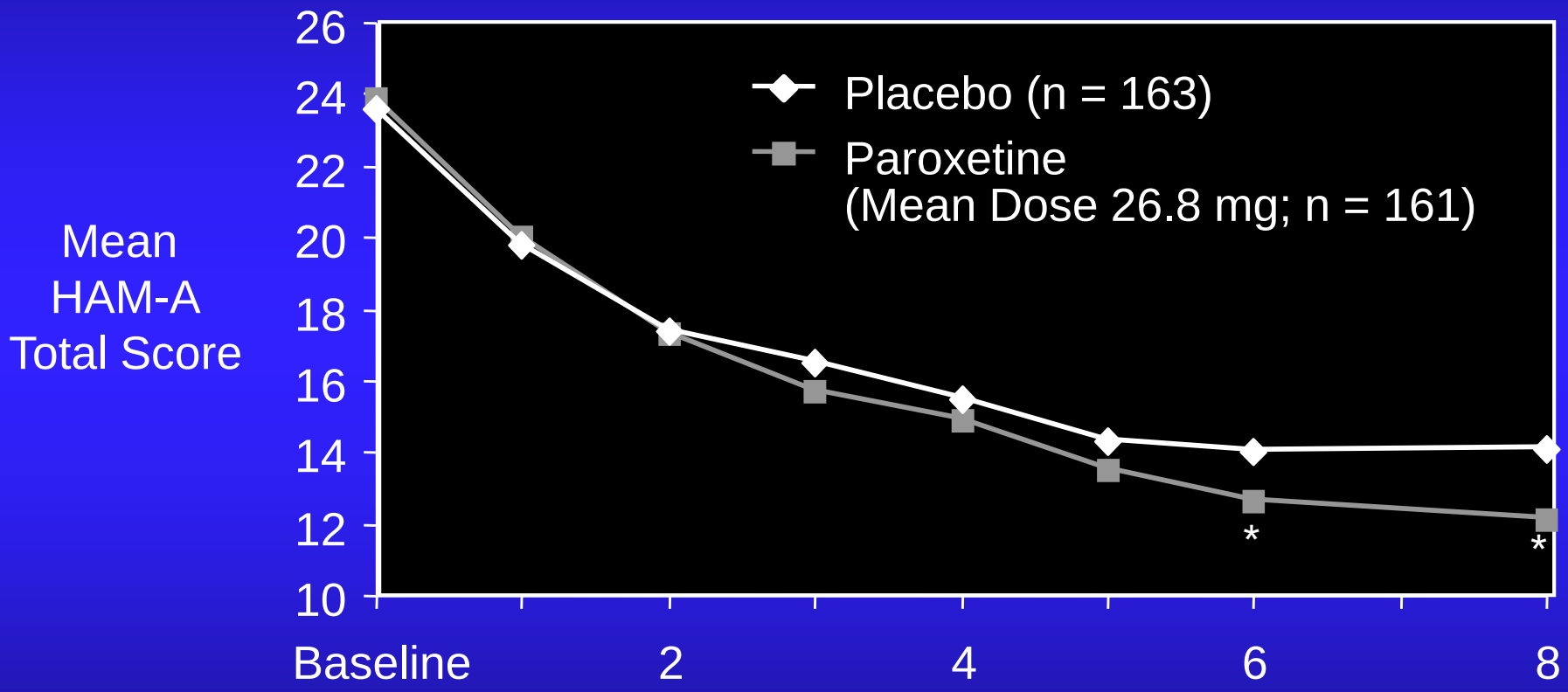
- **Delayed onset of action**
- **Early anxiogenic effect**
- **Sexual side-effects**
- **Usually requires dose titration**

*

+venlafaxine

SSRIs: Paroxetine for GAD

Flexible Dosing



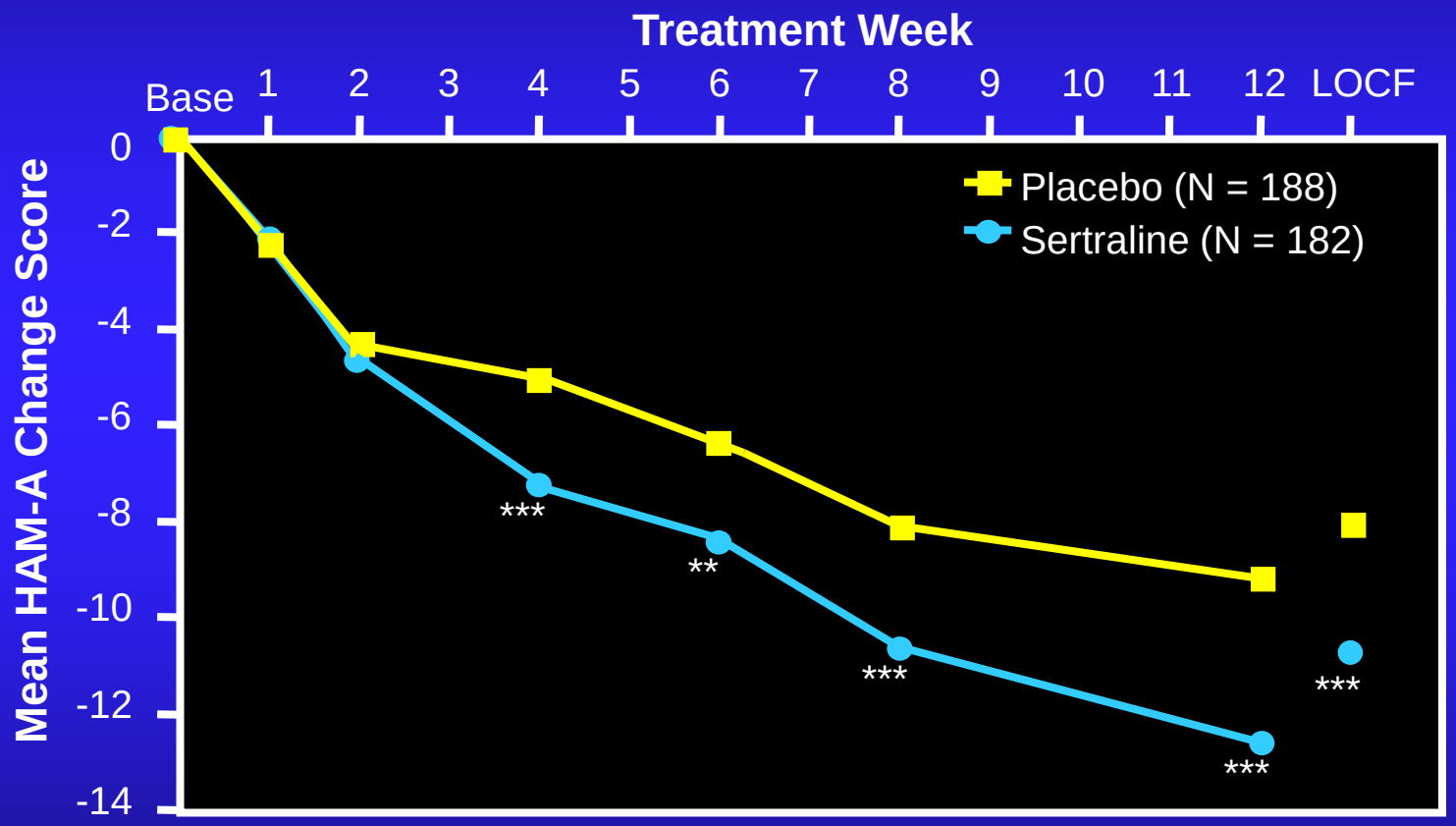
LOCF dataset.

*P < .05 vs placebo.

Pollack MH et al. *J Clin Psychiatry.* 2001;62:350-357.

SSRIs for GAD: Sertraline vs Placebo

ITT sample

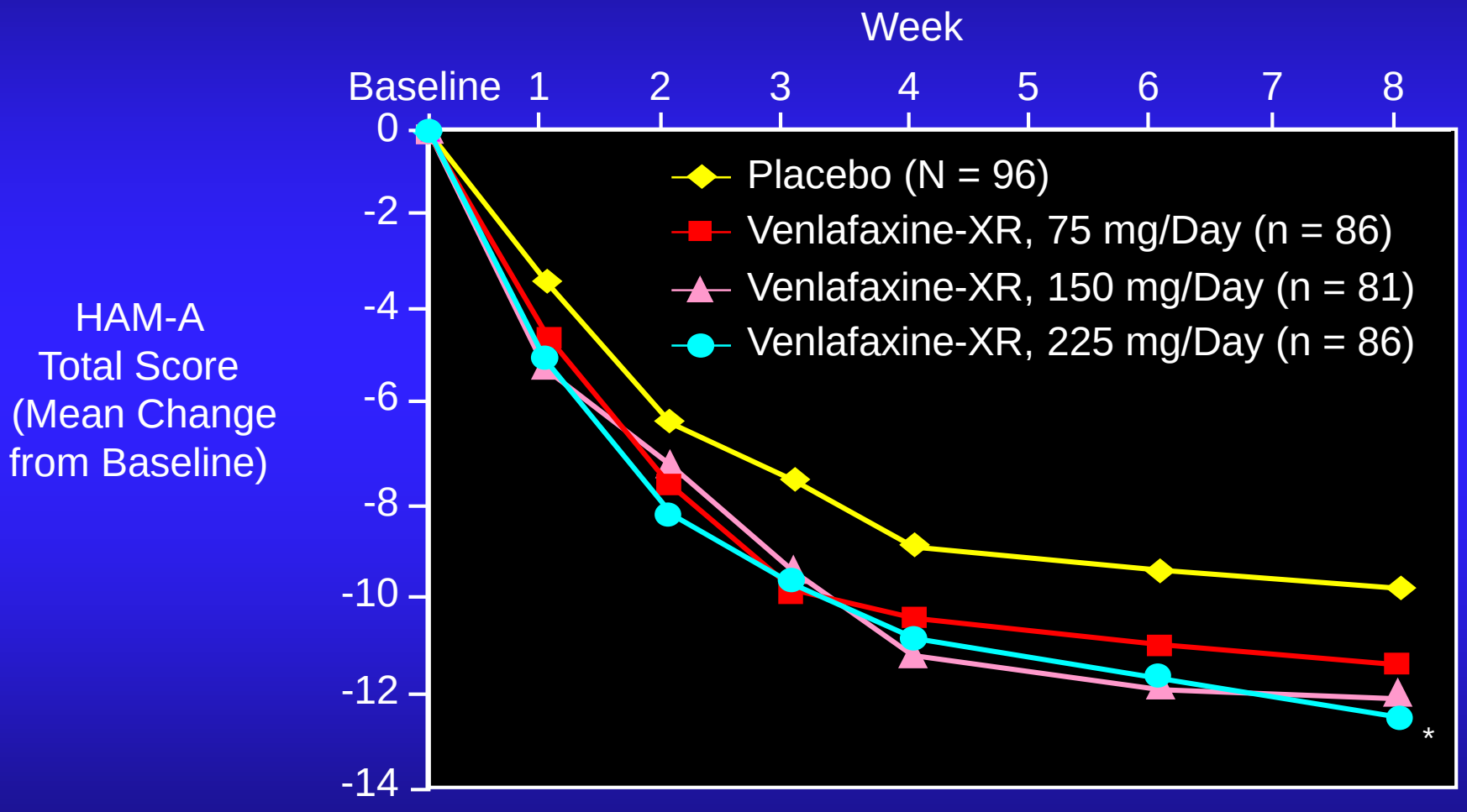


**P < .01
***P < .0001

Adapted from Dahl AA et al. Acta Psychiatrica Scand 2005; 111:429-35

Venlafaxine Treatment of GAD

Fixed-dose Study



*P = .03.

Rickels K et al. *Am J Psychiatry.* 2000;157:968-974.

Duloxetine

- SNRI: binds with high affinity to serotonin and norepinephrine transporters
- Mimics physiologic effects of antidepressants
- More potent than fluoxetine as inhibitor of serotonin reuptake
- FDA-approved for MDD
- GAD studies in Phase III now

Karpa KD. *CNS Drug Rev.* 2002;8:361-376.

*

GAD Treatment
Benzodiazepines

Advantages

- **Rapid onset**
- **Effective**
- **Well-tolerated**
- **General anti-anxiety effects**
- **Safe in overdose**
- **Generics available**

Disadvantages

- **Withdrawal reactions**
- **Sedation**
- **Multiple daily dosing often required**
- **Abuse potential in patients w/ Hx abusing**
- **Poor antidepressant effect**

*

GAD Treatment
Benzodiazepines

Agent	Daily Dosage
Benzodiazepines	**Range (mg)**
Alprazolam	2-6
Clonazepam*	1-3
Lorazepam	4-10
Diazepam*	15-20

*Slow elimination, longer to steady-state

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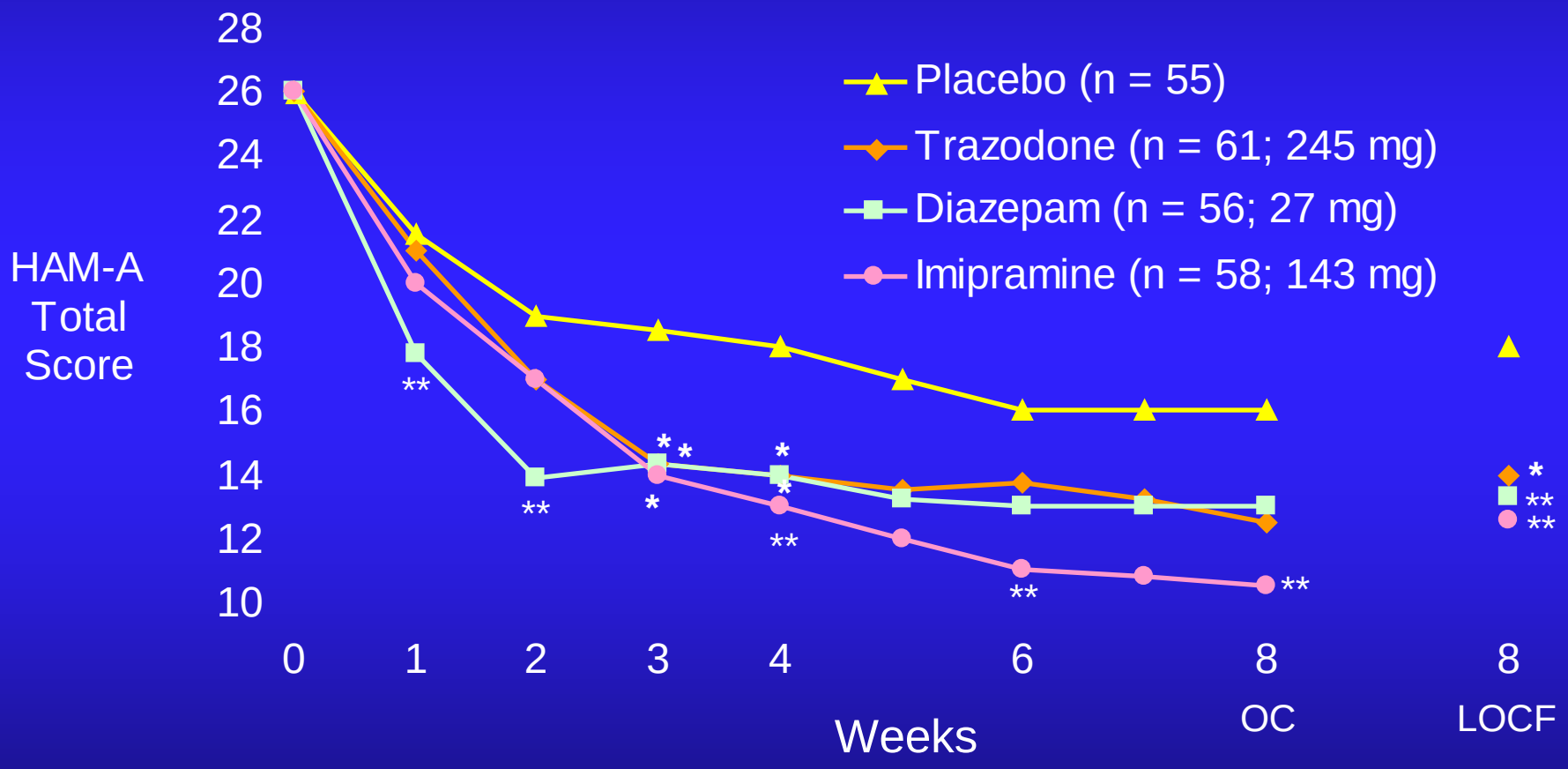
Imipramine, Diazepam, and Trazodone Treatment of GAD



OC = observed cases; OC dataset.
*$P < .05$. **$P < .01$.
Rickels K et al. *Arch Gen Psychiatry*. 1993;50:884-895.

BZ for GAD-Considerations

- No long-term studies with BZ monotherapy
- GAD
  - Highly comorbid with depression
  - Often requires long-term therapy
- Benzodiazepines
  - Not effective for depression
  - Not considered ideal as *monotherapy* treatment
    - This is based on zero data
  - Useful as adjunctive medication for many patients

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Buspirone

- Buspirone-Partial 5HT1a agonist
  - Early studies showed efficacy at 15 mg comparable to diazepam 15 mg
  - Limited breadth of efficacy in comorbid patients limits enthusiasm
  - Outcomes of various studies are uneven
  - Higher dose (at least 30 mg daily) probably necessary

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Long-Term Treatment of GAD

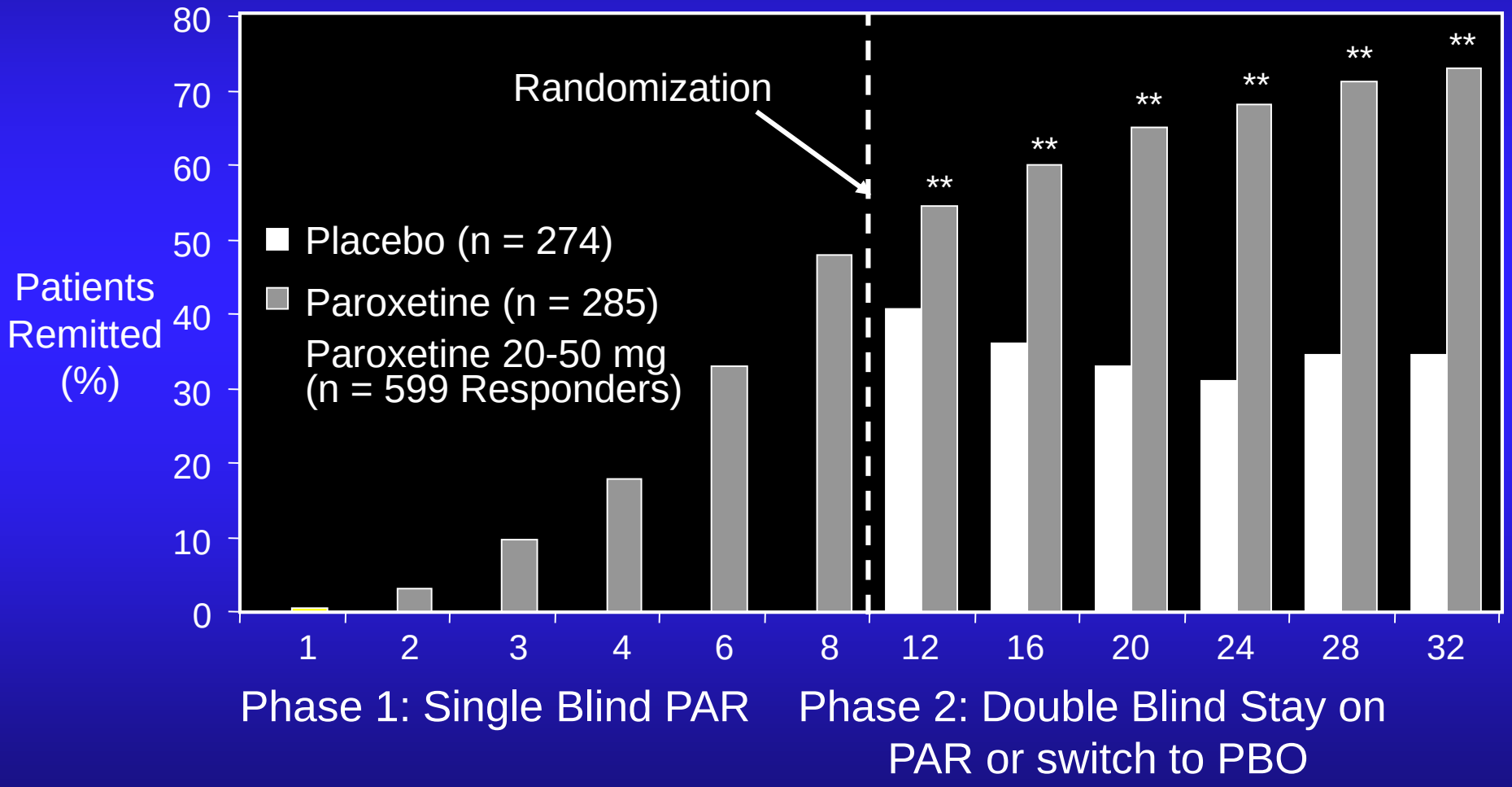
- Need to treat for long term
- Full relapse in approximately 25% of patients 1 month after stopping treatment
- 60%-80% relapse within 1st year after stopping treatment

*

Hales RE et al. *J Clin Psychiatry*. 1997;58(suppl 3):76-80.
Rickels K, Schweizer E. *J Clin Psychopharmacol*. 1990;10(3 suppl):101S-110S.

Paroxetine Long-Term GAD Treatment

Remission Takes Time

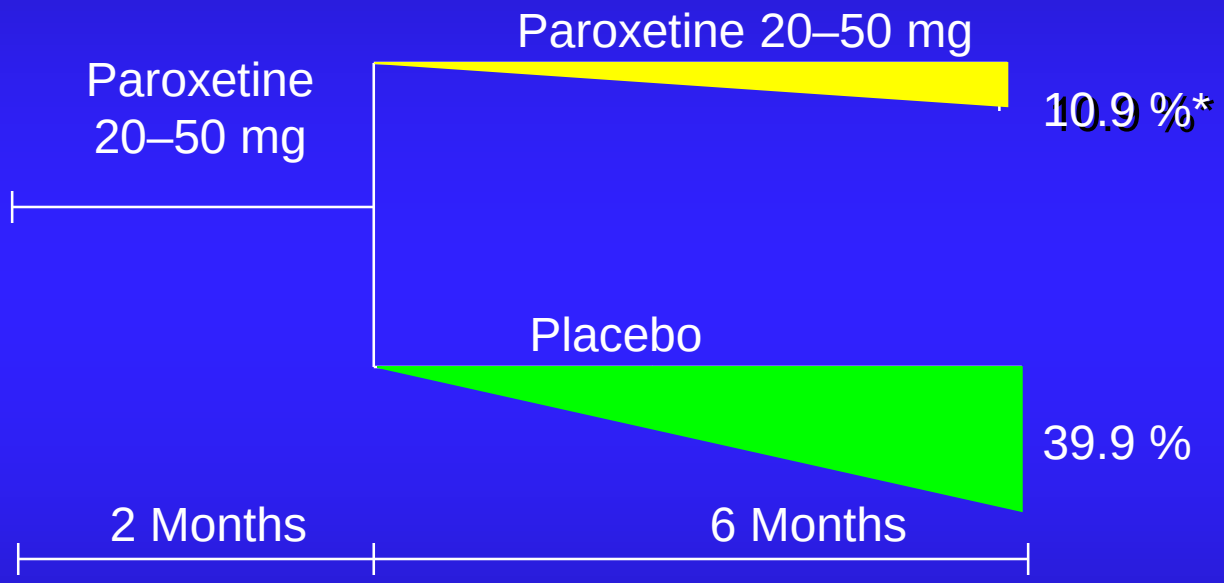


*

**$P < .01$ vs placebo. Remission = HAM-A ≤ 7; LOCF dataset. Pollack, M. APA; May 2002

Paroxetine Long-Term GAD Treatment

Relapse Prevention



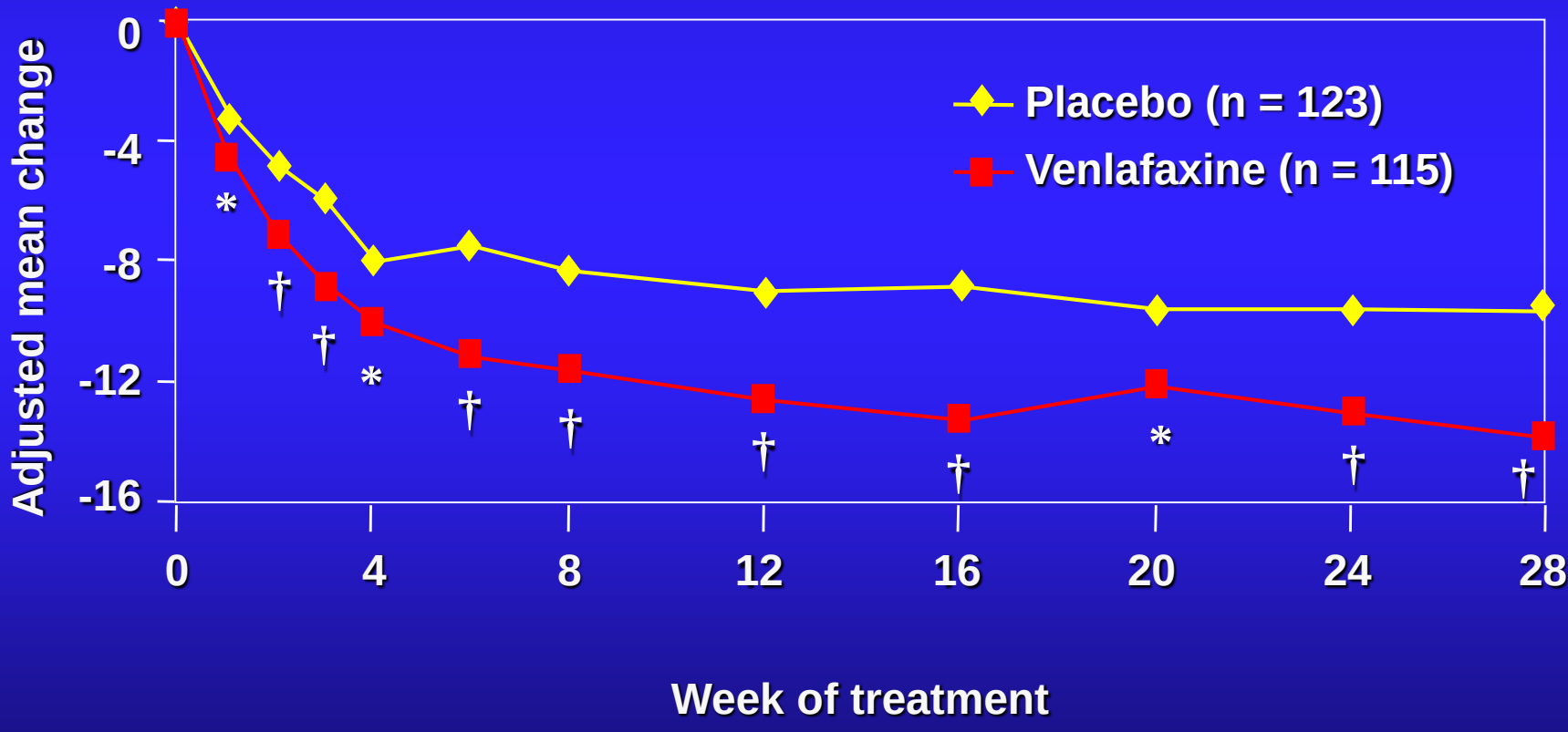
***P* <.001; N = 286/274; LOCF**

Stocchi et al J Clin Psychiatry 2003; 64: 250-58.

*

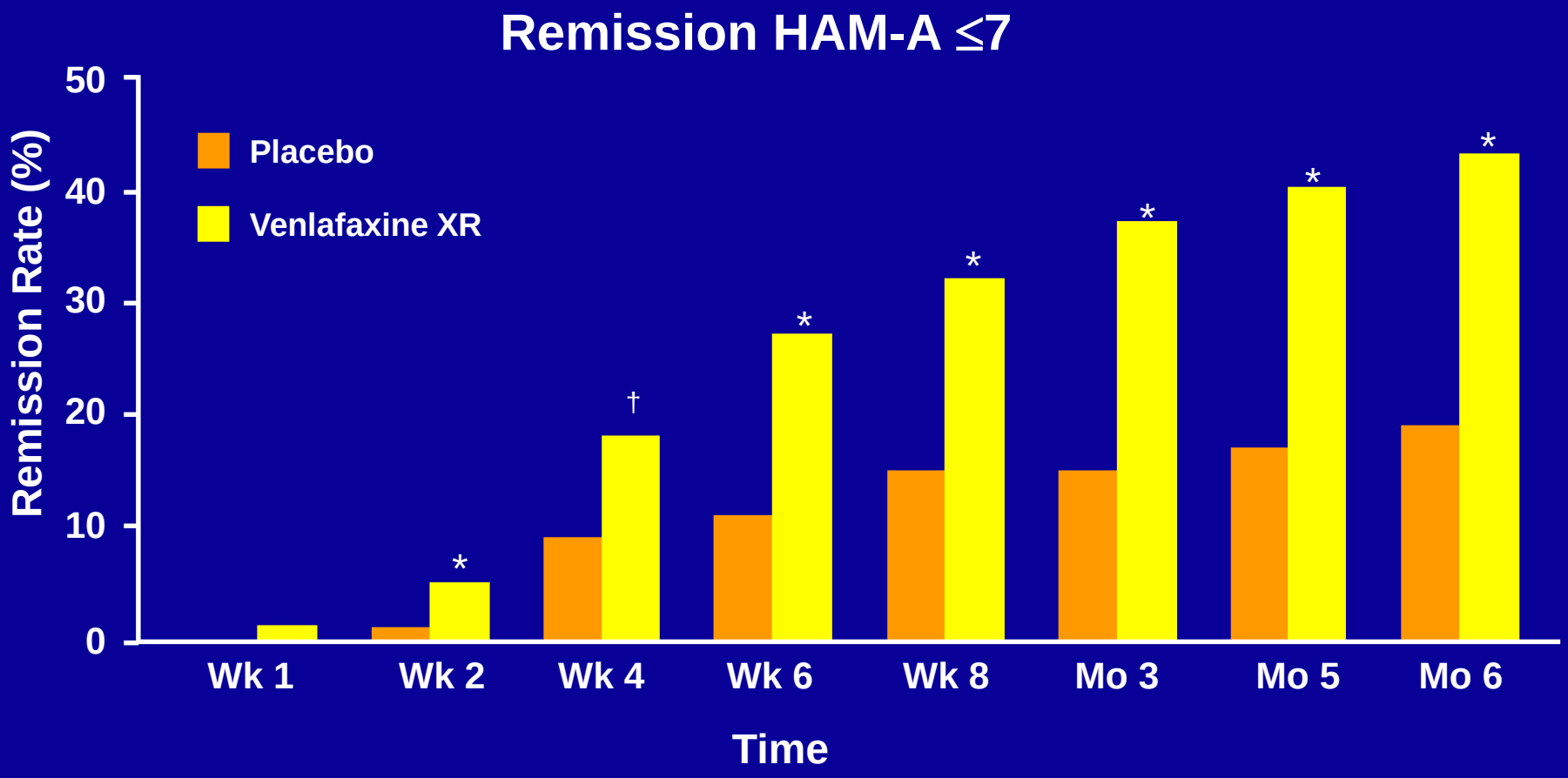
6-Month, Placebo-Controlled Trial of Venlafaxine XR in GAD

HAM-A Total—Observed Cases Analysis
(Mean Baseline HAM-A Total Score 25.0, Mean Daily Dose 176 mg)



* *P* < 0.05 vs. placebo †; *P* < 0.001 vs. placebo Gelenberg AJ et al. *JAMA*. 2000;283:3082-3088.

Remission Takes Time
GAD Pooled Analysis (N=767)



*P<0.001 vs. placebo. †P<0.01 vs. placebo.

Montgomery SA, et al. *J Psychiatr Res*. 2002;36:209-217 .

Placebo-Controlled Trial of Sertraline in the Treatment of Children with GAD

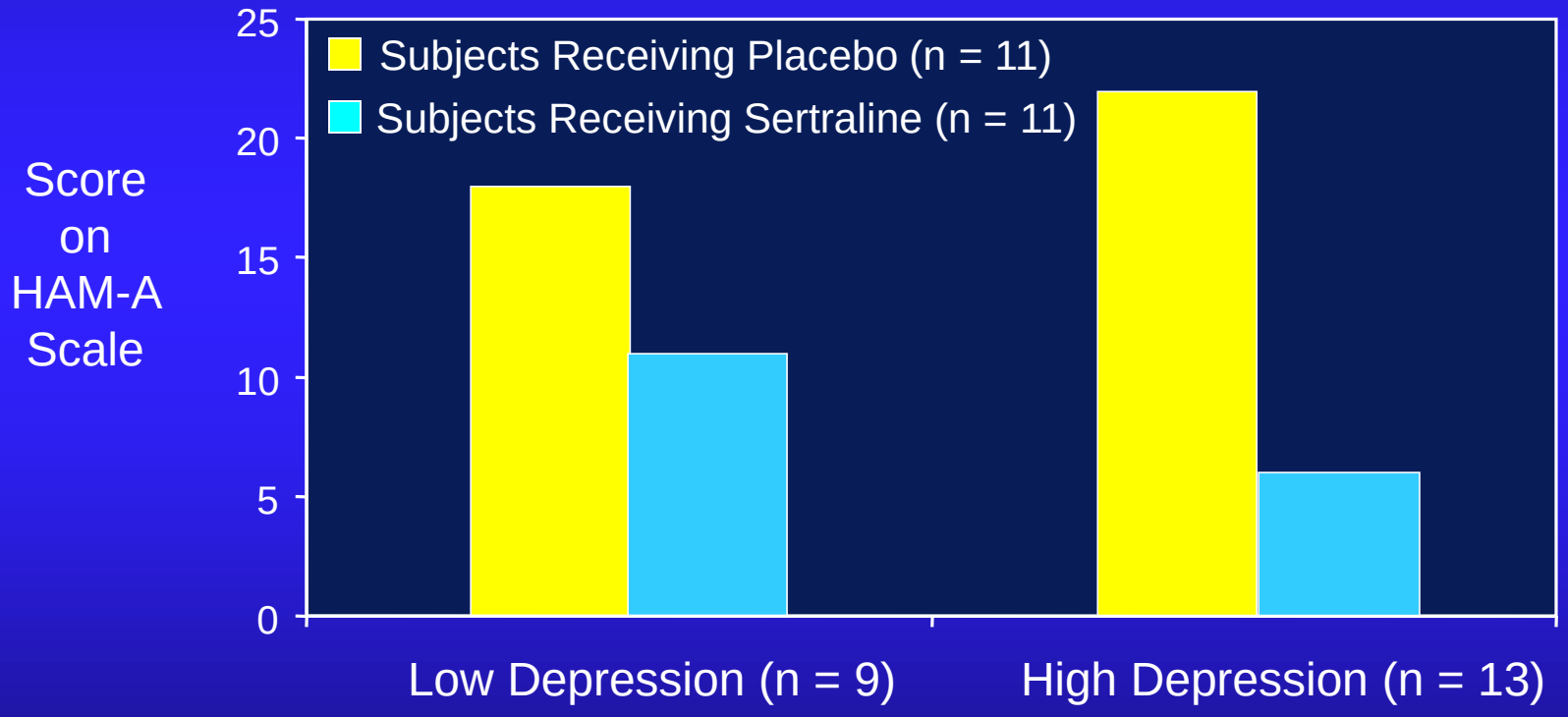
- N = 22
- 2-3 week run-in, 9 weeks of double-blind treatment with sertraline or placebo
- Primary diagnosis of GAD; excluded MDD, OCD, MR, ADD
- Ages 5-17 years (mean 11.7 ± 3.9 years)
- Sertraline dose: 25 mg/d for week 1; 50 mg/day weeks 2-9

*

Rynn MA et al. *Am J Psychiatry.* 2001;158:2008-2014.

Placebo-Controlled Trial of Sertraline in the Treatment of Children with GAD

*Mean Total Scores on Hamilton Anxiety Rating Scale at 9 Weeks**



*LOCF. Low and high depression severity indicated by Hamilton Depression Rating Scale scores ≤ 10 and > 10, respectively.

Rynn MA et al. *Am J Psychiatry.* 2001;158:2008-2014.

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Summary: GAD Antidepressant Dosing

Category	Usual Dosage Range (mg/d)
SSRIS	
Fluoxetine	20-60
Sertraline*	100-200
Paroxetine*	20-40
Fluvoxamine	100-300
Citalopram*	20-40
Escitalopram*	10-20
SNRIs	
Venlafaxine**	75-225
Duloxetine	60-120
Tricyclic Antidepressants	
Imipramine*	100-300
Clomipramine*	50-100

*Controlled data , **FDA approved

Anticonvulsants Potentially Useful as Adjunctive GAD Treatment

- Vigabatrin
  - Inhibits GABA transaminase
- Topiramate
  - Acts at ion-gated channels
- Tiagabine
  - Inhibits GABA reuptake
- Gabapentin
  - GABAergic anxiolytic, novel mechanism
  - Pilot study evidence of efficacy in PD, SP, EtOH withdrawal

- Pregabalin-clearly effective for GAD but not FDA-approved for GAD

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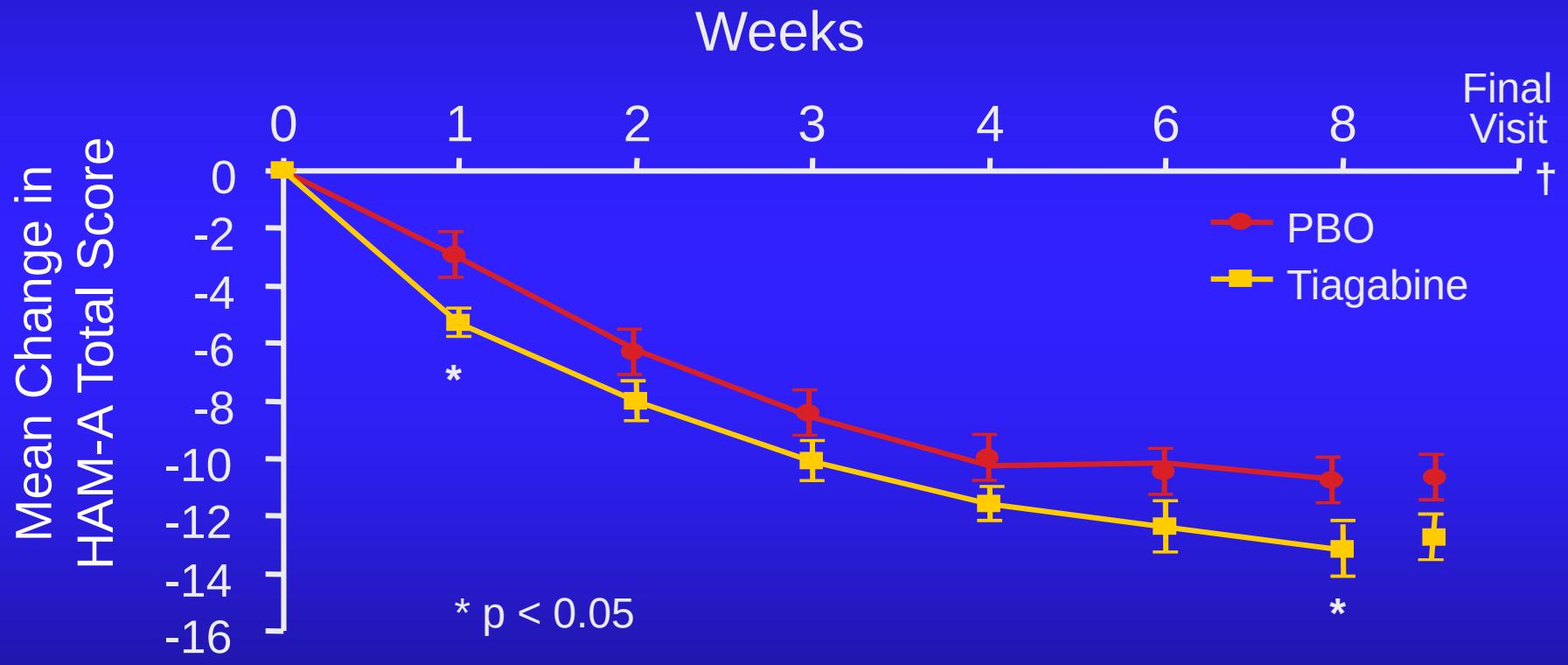
Selective GABA Reuptake Inhibitor Tiagabine for GAD :

HAM-A Total Scores--marginal effect possibly due to design--Phase III in progress in 2006



† Final visit was calculated using last post-baseline observation for each patient.

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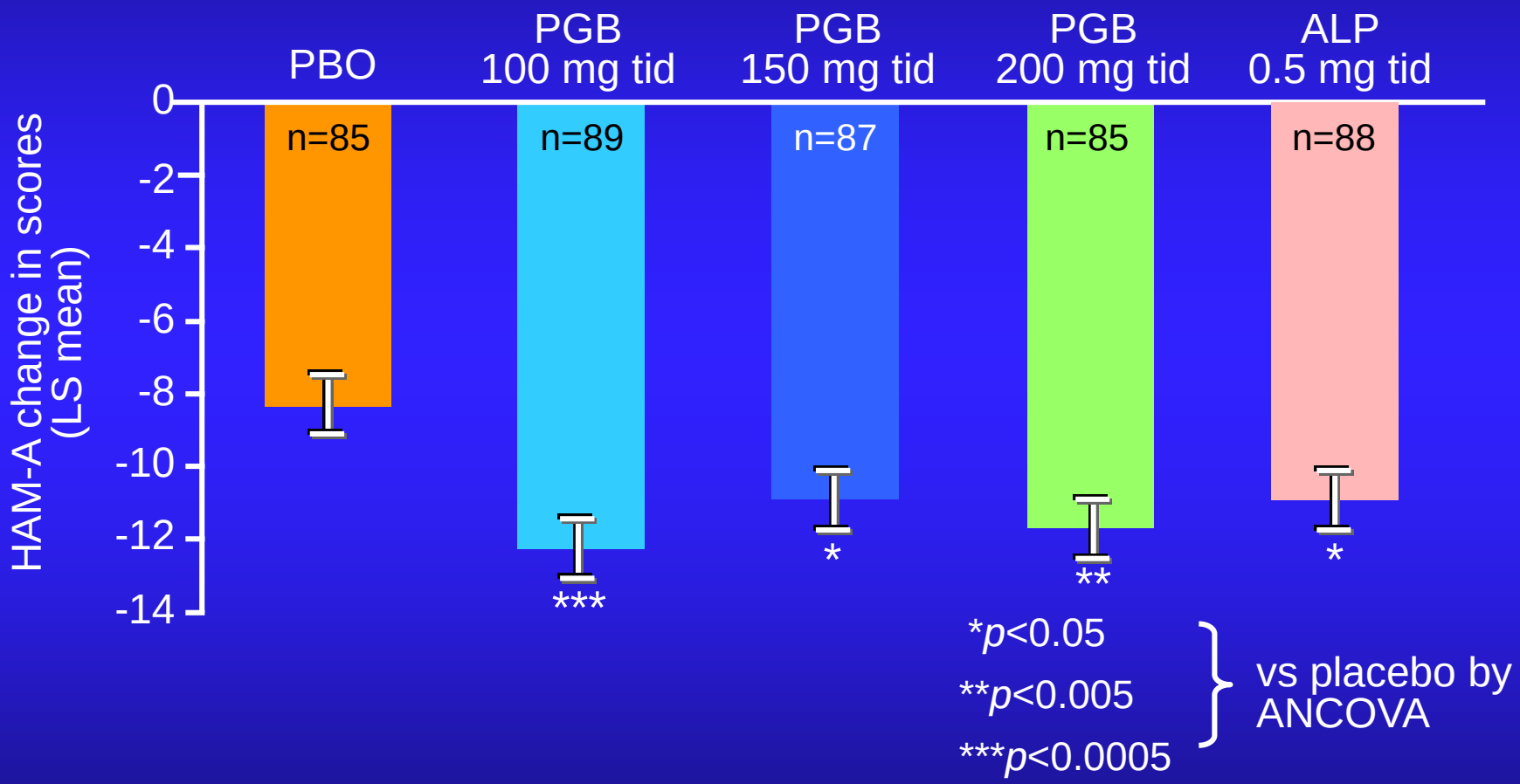
Van Ameringen M, Pollack MH, et al. Poster presented at CINP, 2004.

Pregabalin vs. Alprazolam in GAD



Mean baseline HAM-A score (SD): 25.0 (3.4); 4 weeks

Does not have FDA approval

Pollack et al (2001) ACNP

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Strategies for Refractory GAD

- Evaluate treatment intensity
  - Dose and duration of antidepressant Rx?
- Switch to a second SSRI/antidepressant
- Add
  - benzodiazepine
  - buspirone
  - GABAergic anticonvulsants
    - Gabapentin, tiagabine, vigabatrin, topiramate,
  - low dose atypical neuroleptics
- Review psychosocial variables for stress management
  - Add CBT

Most suggestions from clinical experience
Coplan et al JCP 154 (supp) 63-74,1993

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Summary

- GAD is common
- Remission is the goal
  - Identification of target symptoms, including physical symptoms
- Careful evaluation, patient education key aspects of treatment
- Medication: start low and go slow
  - Adequate dosages for adequate lengths of time
  - May require long-term treatment

*

Question #1

True or False

Women have a HIGHER Lifetime Prevalence of GAD as compared to Men.

Answer #1

TRUE!

Question #2

Which Psychiatric Illness has the HIGHEST LIFETIME PREVALENCE of COMORBIDITY with GAD?

Answer #2

Major Depressive Disorder

Question #3

What Anxiety Assessment Scale is commonly used to Assess Outcomes in GAD?

and…

A decrease of ___% or greater on this scale defines RESPONSE while a score of ___ or less on this scale defines REMISSION.

Answer #3

Hamilton Anxiety Rating Scale

A decrease of 50% or greater on this scale defines RESPONSE while a score of 7 or less on this scale defines REMISSION.

Question #4

What PHARMACOLOGIC TREATMENTS are Effective in Treating GAD?

Answer #4

- Benzodiazepines
- Buspirone
- Tricyclic Antidepressnts
- Selective Serotonin Reuptake Inhibitors
- Serotonin Norepinephrine Reuptake Inhibitors

Question #5

What Percentage of Patients with GAD Relapse Within the First Year After Stopping Pharmacotherapy?

Answer #5

60-80%

Part II-May be used separately or used with Part I

Future Strategies for Anxiety Disorders

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Traditional Anxiolytics

Limitations

- **Poor tolerability (TCAs, MAOIs)**
  - ***SSRIs-Less than ideal***
- **Limited breadth of efficacy (TCAs, BZDs, MAOIs?)**
- **Lack of antidepressant efficacy (buspirone?, BZDs)**
- **Safety (TCAs, MAOIs)**

Anticonvulsants

- **Carbamazepine**
- **Valproic acid**
  - ***Both have some GABAergic action (VPA > CBZ)***
  - ***Marginal antidepressants***
  - ***Breadth of efficacy not clear***

(cont)

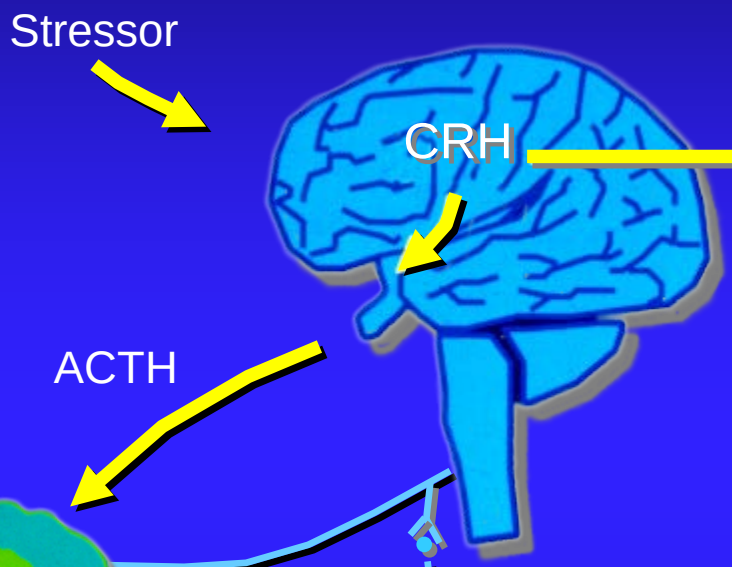
Anticonvulsants

- Vigabatrin
  - Inhibits GABA transaminase
- Topiramate
  - Acts at ion-gated channels
- Tiagabine
  - Inhibits GABA reuptake
- Gabapentin
  - GABAergic anxiolytic, novel mechanism
  - Pilot study evidence of efficacy in PD, SP, EtOH withdrawal
- *Utility in anxiety disorders not known*

Bad News Peptides

- Corticotropin-releasing factor (CRF)
- Cholecystokinin (CCK)
- Substance P

CRF and Acute Stress

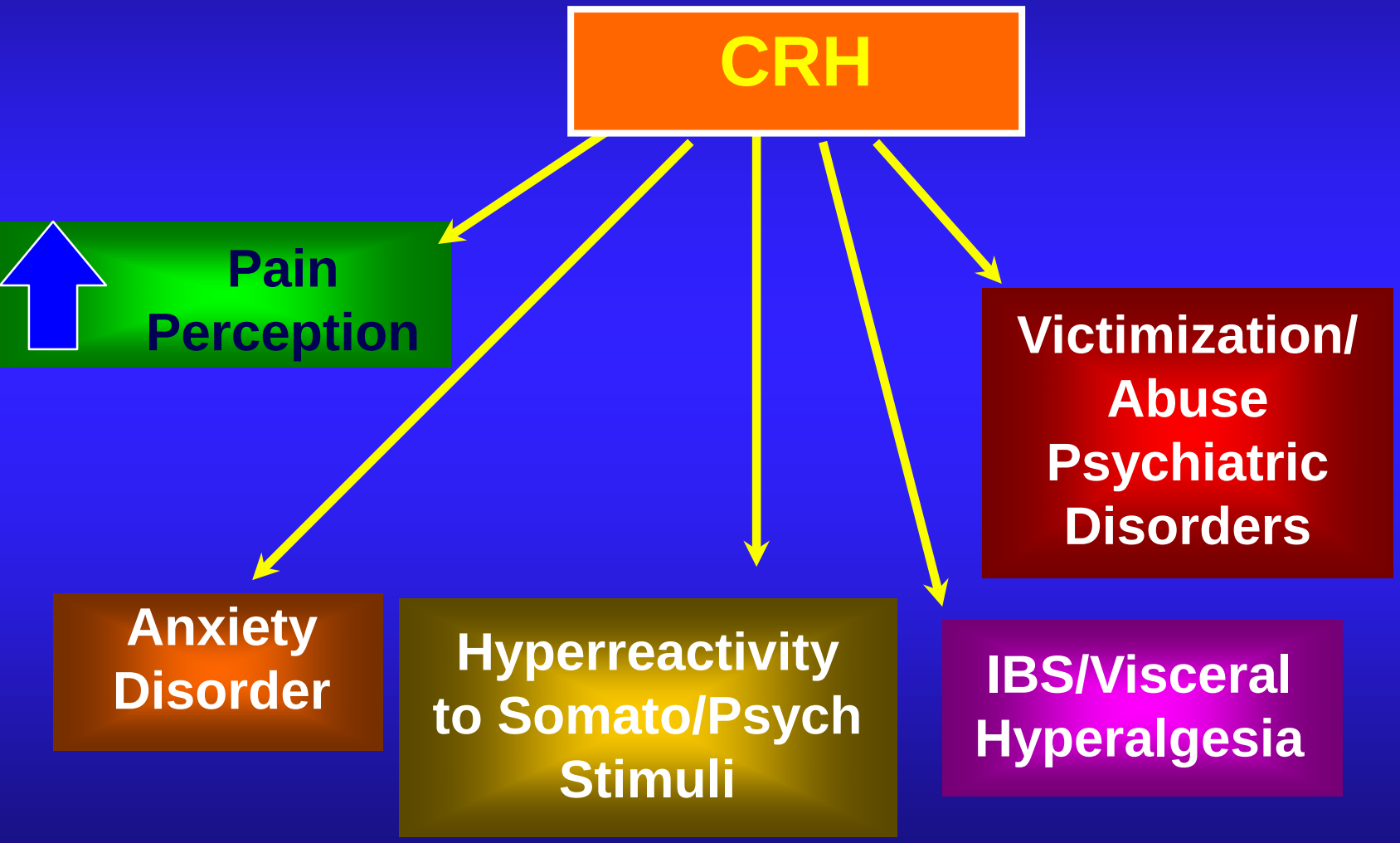


- ↓ Eating
- ↓ Reproduction
- ↓ SW Sleep
- ↑ Grooming
- ↑ Neophobia (novel environ)
- ↑ Locomotor activity (familiar environ)
- ↑ Behavioral despair
- ↑ Seizure/kindling
- ↑ Locus coeruleus FR
- ↑ Pyramidal FR

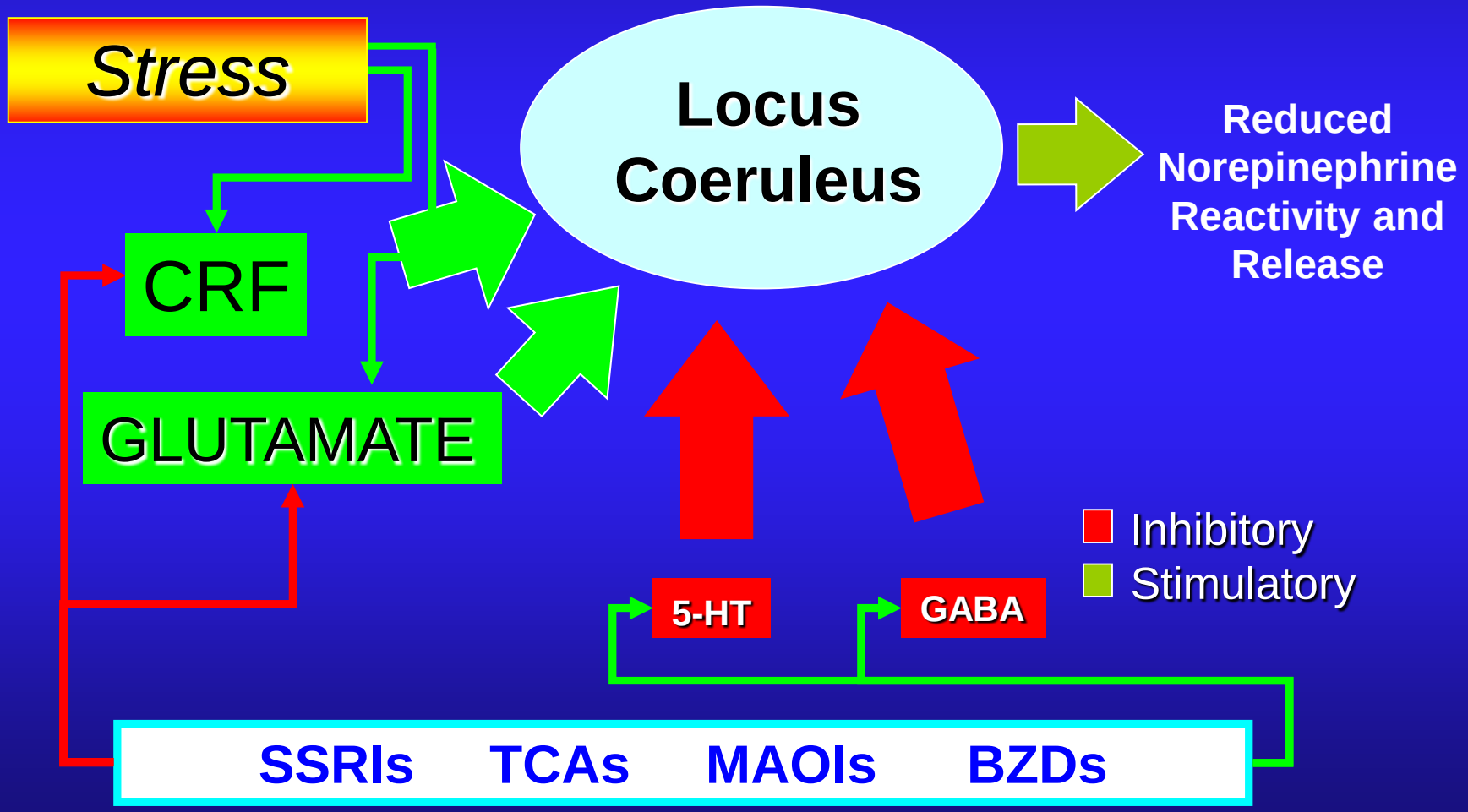
- ↑ Blood pressure
- ↑ Heart rate
- ↑ Blood sugar
- ↓ GI blood flow

- ↑ Gluconeogenesis
- ↑ Lipolysis
- ↑ Proteolysis
- ↑ Insulin resistance
- ↓ Inflammation
- ↓ Immune function

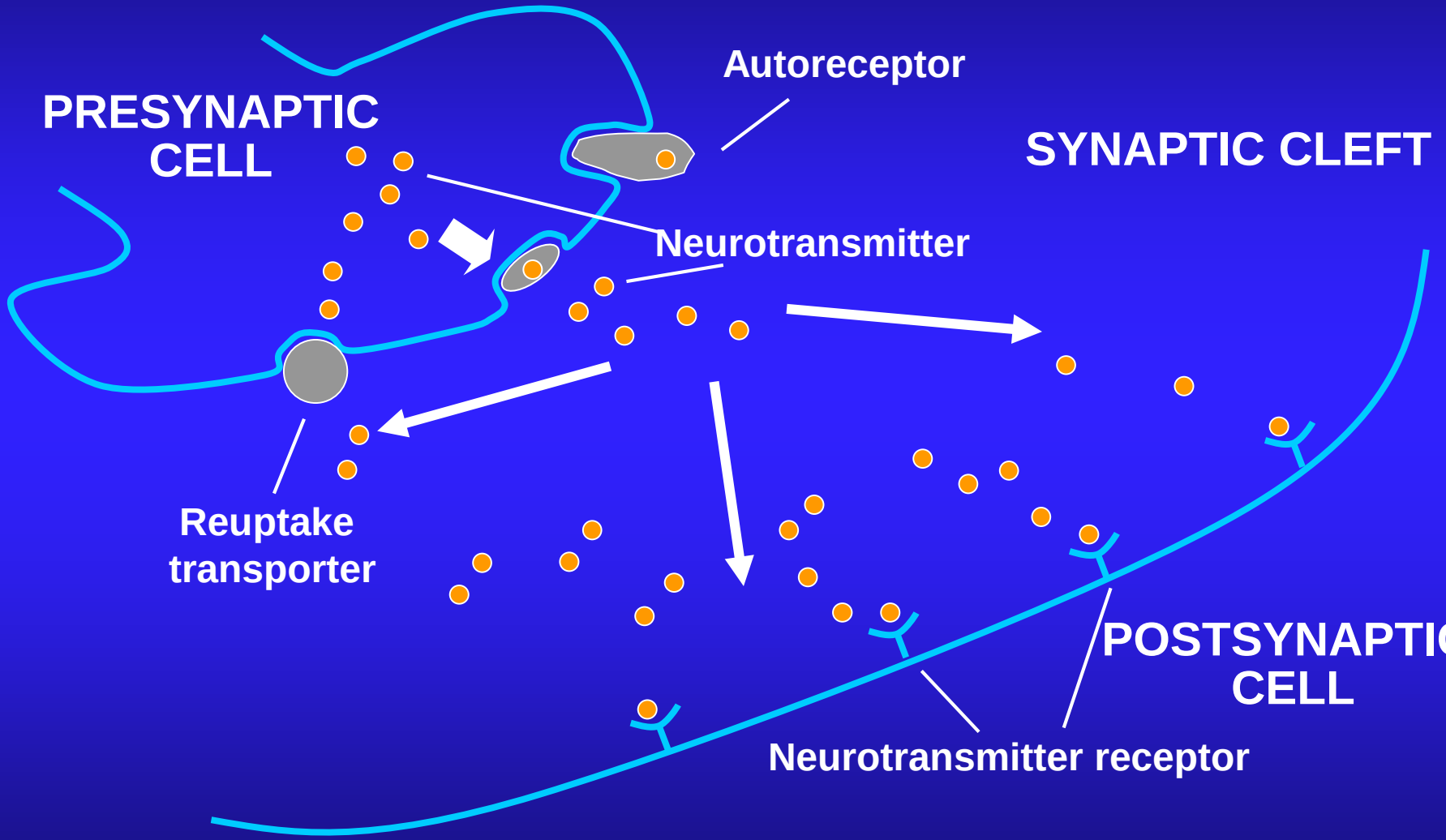
CRF Role in Stress Related Illnesses



Locus Coeruleus System as a Site of Action for Psychotropics



Neurotransmitters—Mechanisms of Action

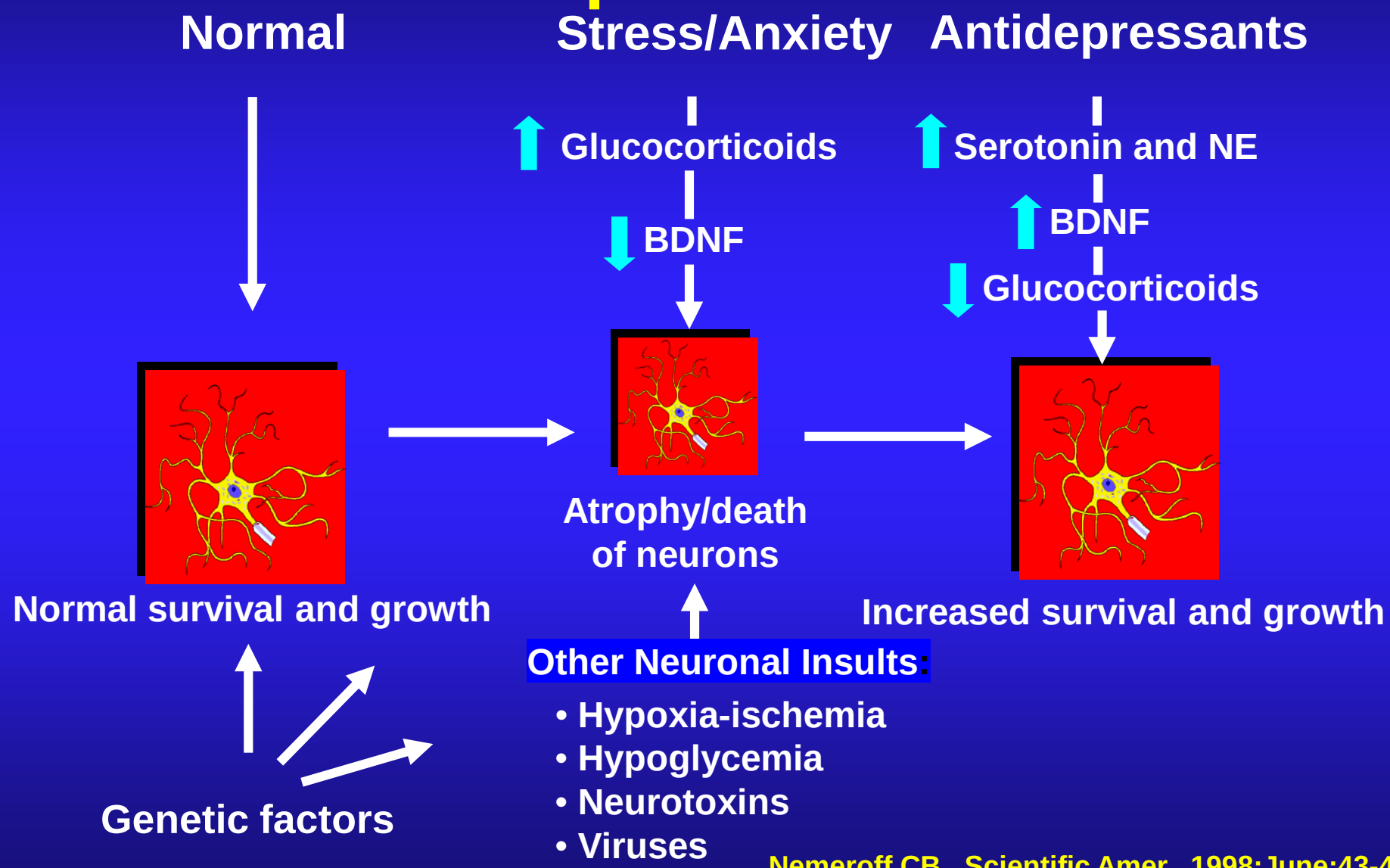


Nemeroff CB. Scientific Amer. 1998;June:43-49.

Antidepressants: Transductional Targets of Action

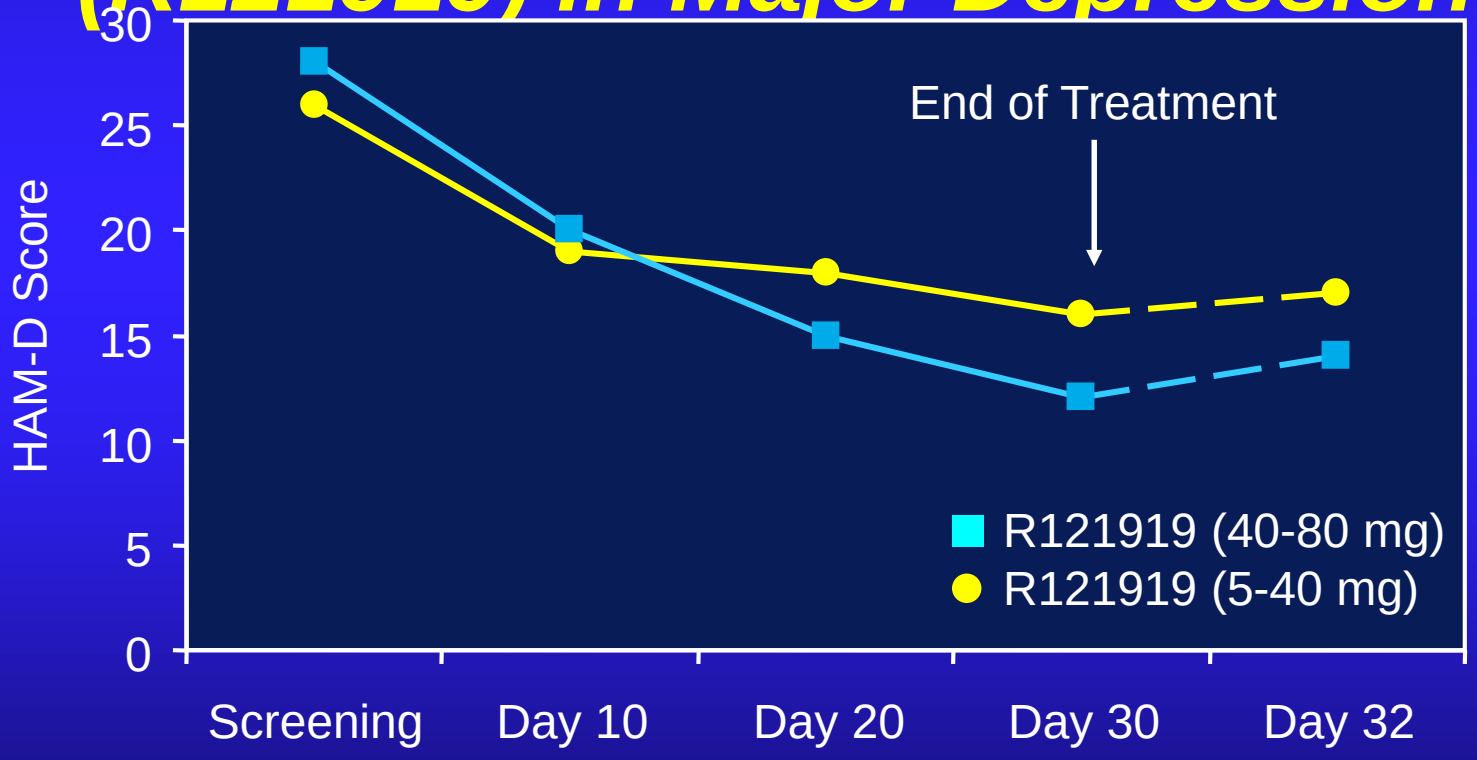
- Antidepressants increase NE, 5-HT or both
- Activate transductional cascades
  - Activate or inhibit the synthesis of specific gene products
- Multiple, synergistic mechanisms likely

Hypothesis of Stress, Anxiety and Depression



Nemeroff CB. Scientific Amer. 1998;June:43-49.

The First 20 Patients: *Effects of the High-Affinity CRF 1 Antagonist (R121919) in Major Depression*



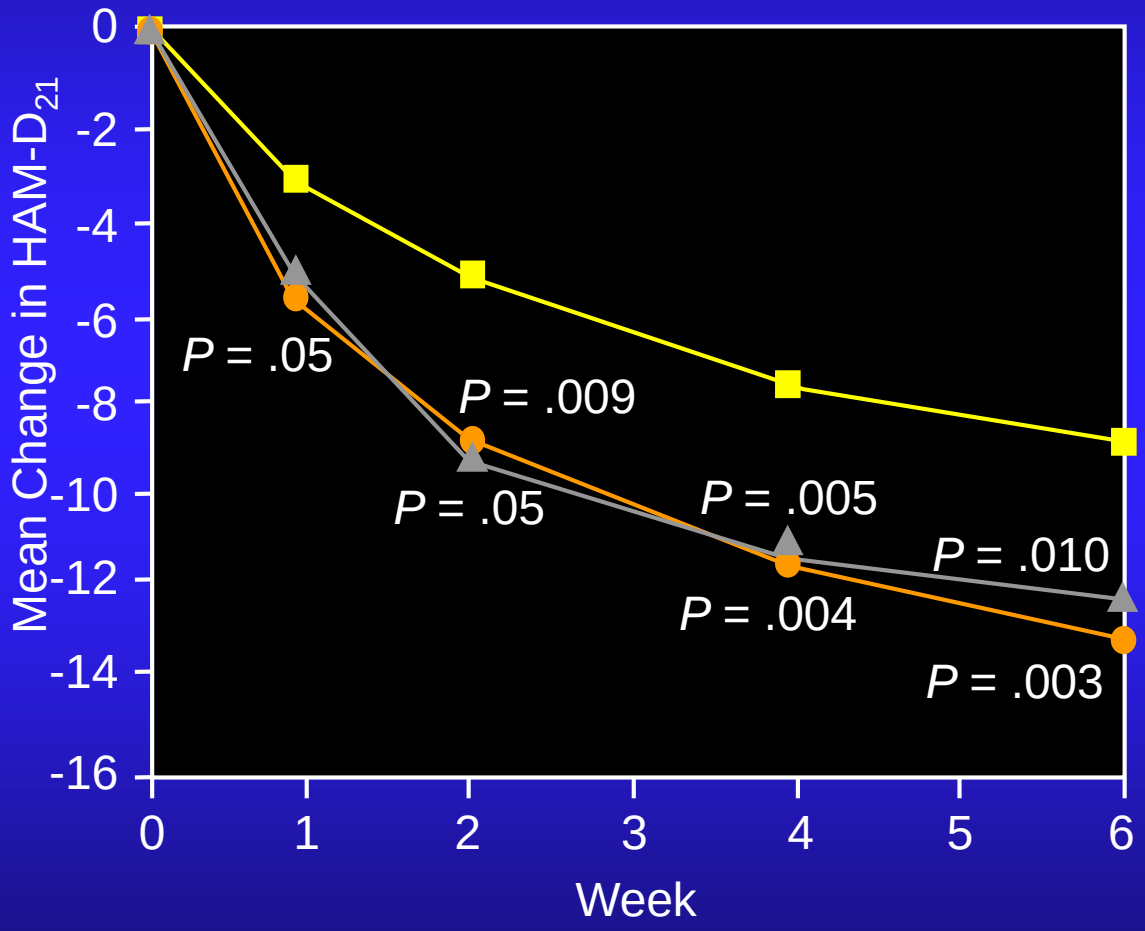
Zobel AW et al. *J Psychiatr Res*. 2000;34:171-181.

Substance P Antagonists

- Substance P $\Rightarrow$ anxiety, depression, pain
- Three receptors identified in CNS
- MK-869: nonpeptide NK_1 receptor antagonist
- Oral, once-daily formulation

Kramer MS et al. *Science*. 1998;281:1640-1645.

Effect of MK-869 and Paroxetine on Depression



Placebo (n = 70)

Paroxetine 20 mg (n = 72)

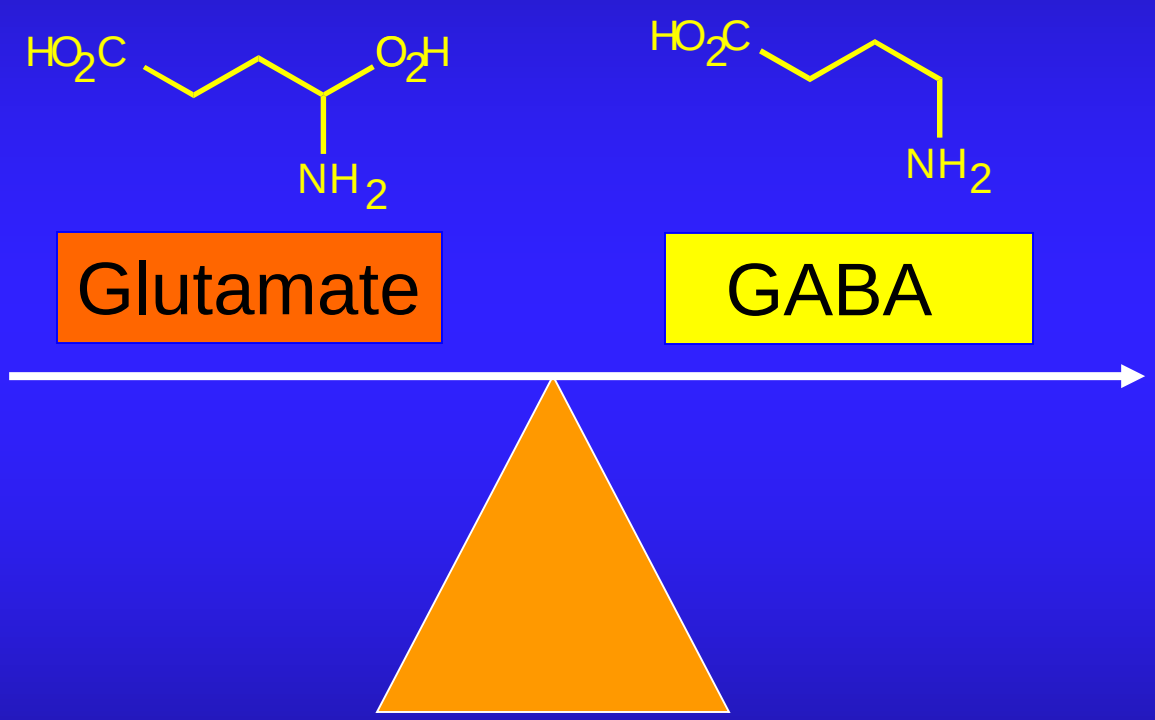
MK-869 300 mg (n = 71)

Kramer MS et al. *Science*. 1998;281:1640-1645.

Glutamatergic System mGLU Agonists

- Novel presynaptic mechanism
- Decreases excitatory neurotransmitter glutamate release
- May modulate GABA transmission

Glutamatergic-GABAergic Interactions



Pathology

Hyperexcitability

mGlu Receptors

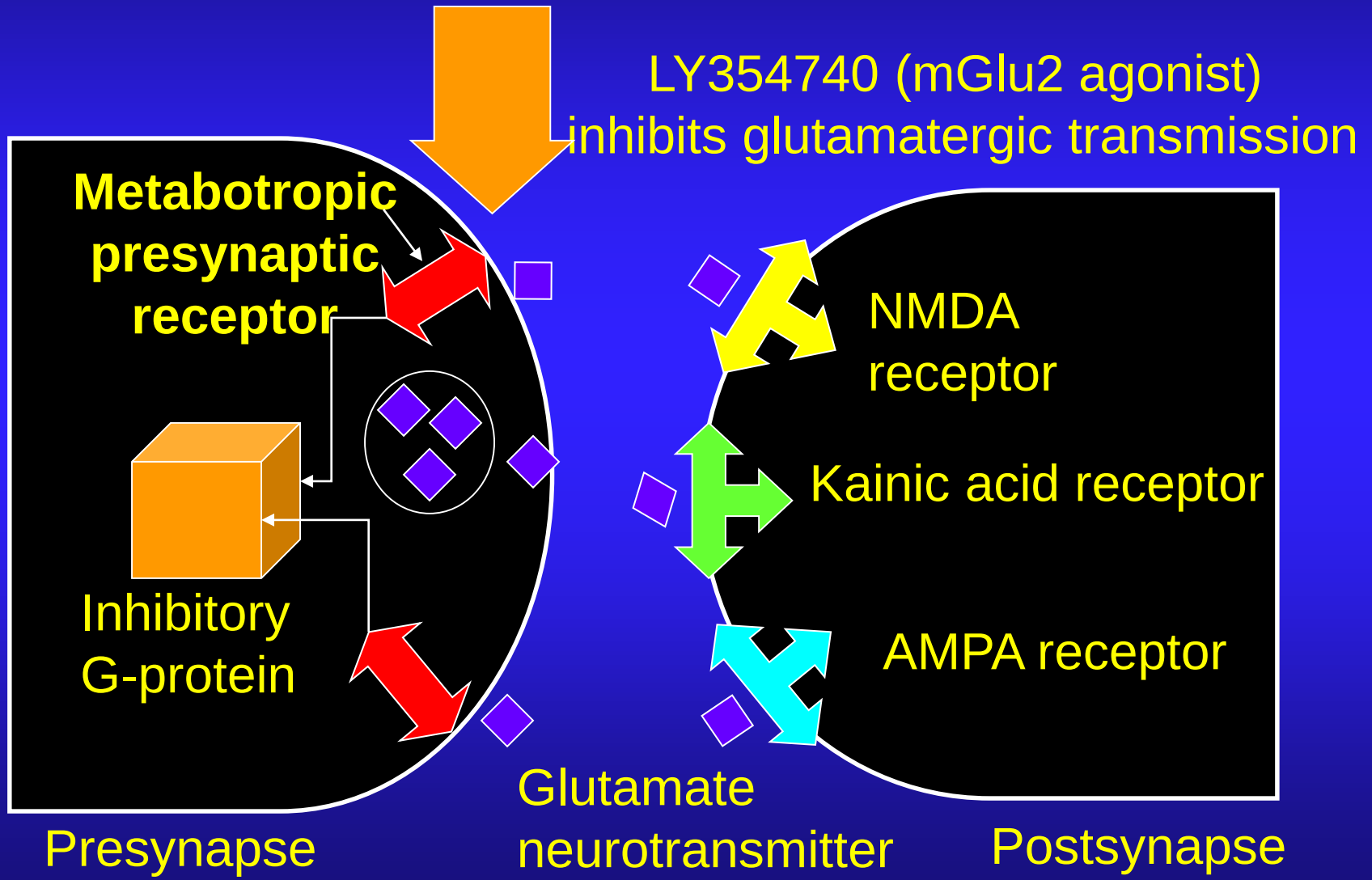
Physiological Range

mGlu Receptors

Hypoexcitability

Pathology

Schema of Glutamatergic Neurotransmission



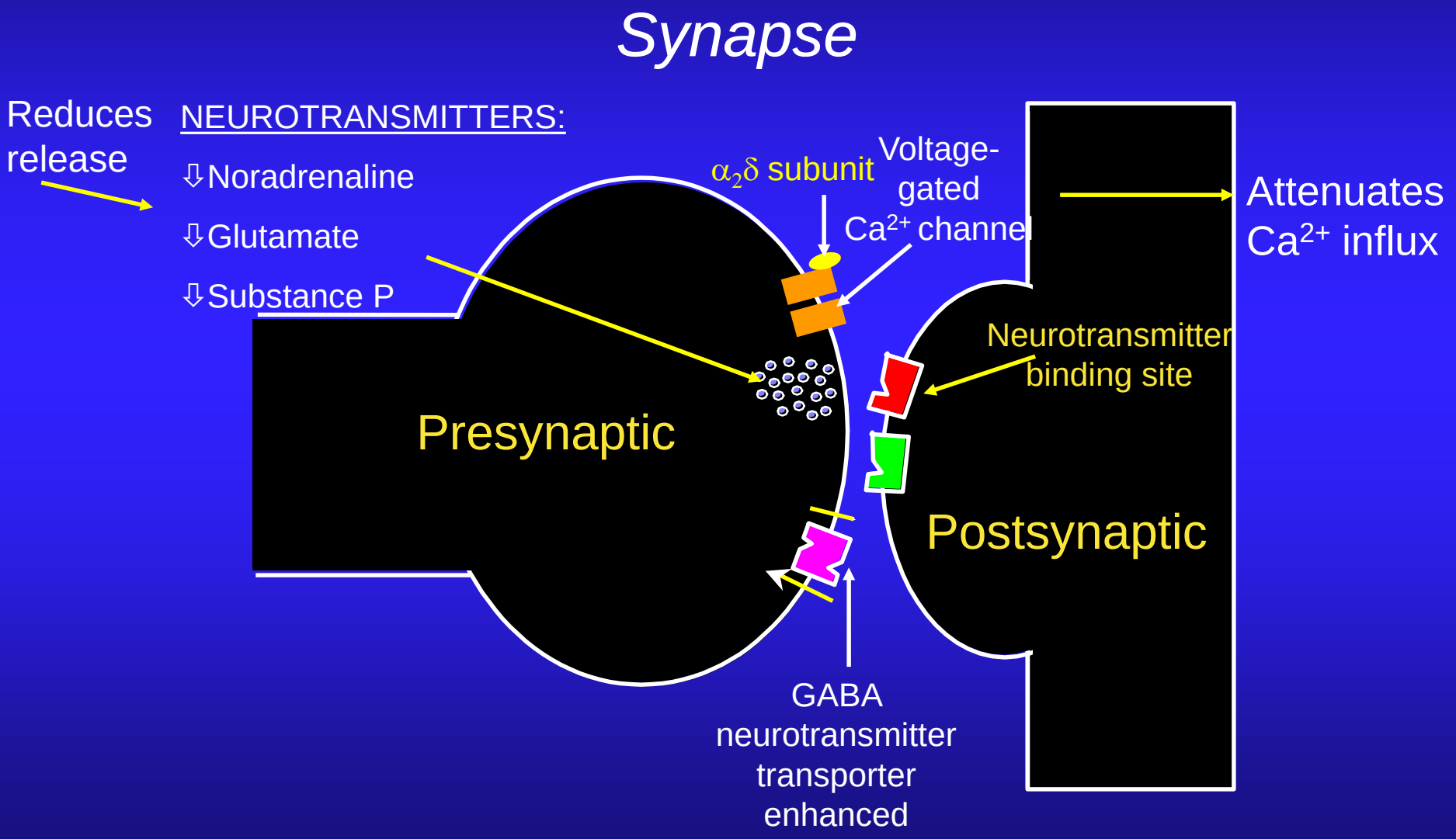
Partial BZD Agonists

- Pagoclone
  - Effective in panic disorder
  - In development
- Abecarnil
  - Some effect in GAD, not sustained?
- Others in pipeline

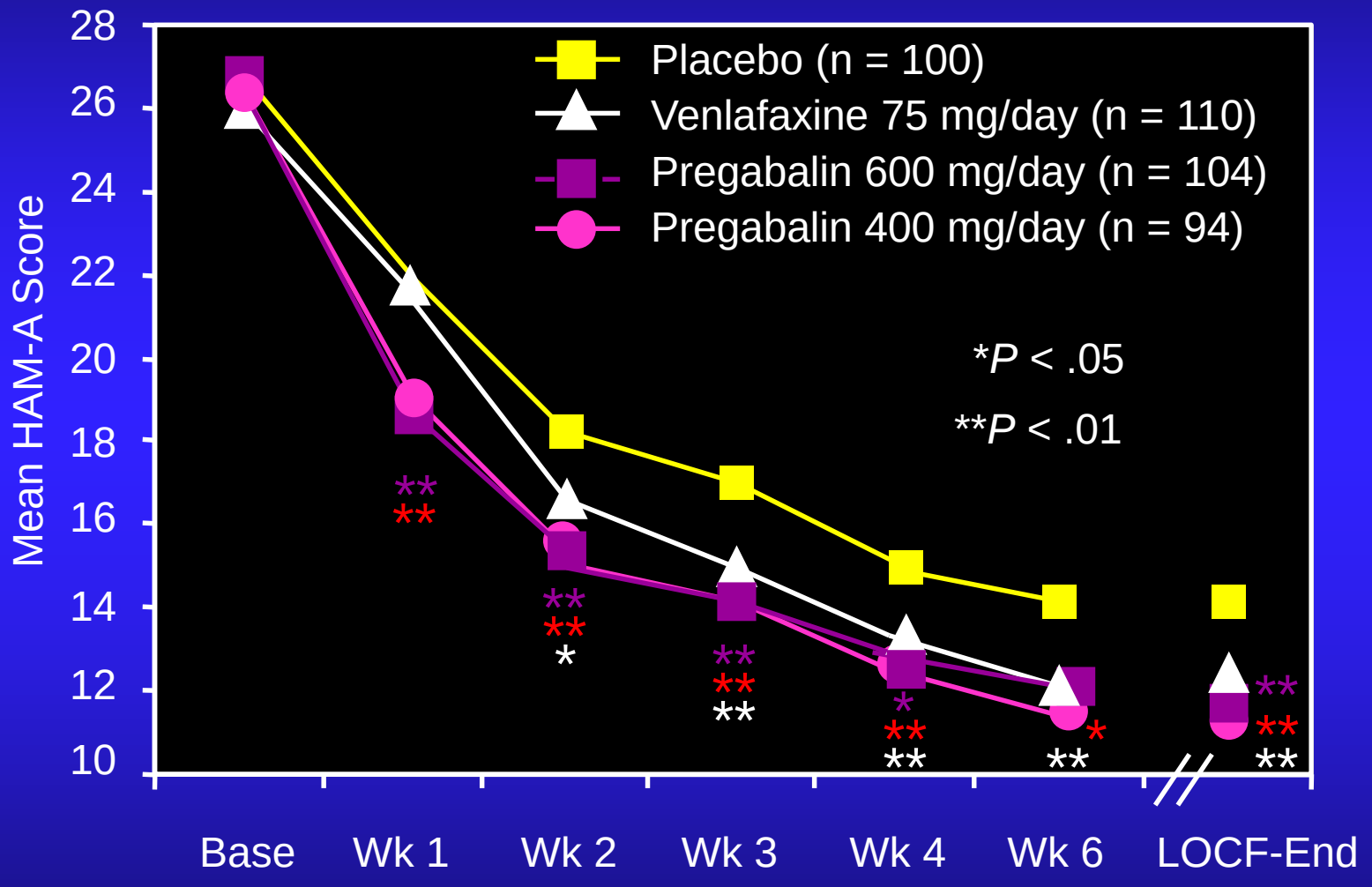
BZD Receptor Subunit Agonists

- GABA-A_{1a}
  - Sedation, anxiolytic
- GABA-A_{2a}
  - Anxiolytic
- GABA-A_{3a}
  - Muscle relaxation
- GABA-A_{5a}
  - Memory, muscle relaxant

Pregabalin Novel Mechanism: $\alpha_2\delta$ *Binding Inhibitory Effect*



Pregabalin vs Venlafaxine IR Study in GAD



All medication doses b.i.d.

Data on file, Pfizer Inc.