Generalized Anxiety Disorder

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Generalized Anxiety Disorder (GAD) Pharmacotherapy Lecture Outline

- Questions
- Diagnosis, DSM-V
- Epidemiology, Course of Illness
- Neurobiology
- Morbidity and Comorbidity
- Assessment
- Treatment
- Summary
- Questions and Answers

Question #1

The lifetime prevalence of GAD in women is how many times the lifetime prevalence in men?

a) 0.5
b) 0.75
c) 1.0
d) 1.5
e) 2.0

Question #2

Which of the following disorders is not commonly comorbid with GAD?

a) Major depression
b) Panic disorder
c) Social anxiety disorder
d) Schizophrenia (prodromal)
e) Alcohol abuse or dependence

Question #3

In treaing GAD, the efficacy of which drug(s) is *not* well-supported by controlled trials?

a) SSRIs
b) SNRIs
c) Atypical antipsychotics
d) Pregabalin
e) Benzodiazepines

Question #4

What % of GAD patients achieve *remission (HAM-A ≤ 7, or CGI-I = very much improved)* during an 8-week SSRI or SNRI trial?

a) 10%
b) 20%
c) 25-35%
d) 40-50%

Question #5

Relapse rates in GAD after 12 months of successful drug treatment are decreased if the patient has also received CBT aimed at GAD.

a) True
b) False
c) Unknown

DSM-5 GAD Diagnostic Criteria

- Excessive or difficult-to-control anxiety and worry (apprehensive expectation)
- More days than not for ≥ 6 months
  - 6-month criterion affects prevalence figures, but not course or disability.
  - 6-month criterion is somewhat controversial*
- Symptoms impair social, occupational, or other important role functioning and/or cause significant distress

DSM 5. Washington, DC: American Psychiatric Association. 2013.
*Kessler RC, et al. Psychol Med 2005; 35:1073-82 - see notes

DSM-5 GAD Diagnostic Criteria (cont.)

- Associated with ≥ 3 of the following
  - restlessness/feeling keyed-up
  - being easily fatigued
  - difficulty concentrating
  - irritability
  - muscle tension
  - sleep disturbance
- The symptoms are not attributable to another Axis I disorder (such as PTSD) or due to a substance or a medical condition

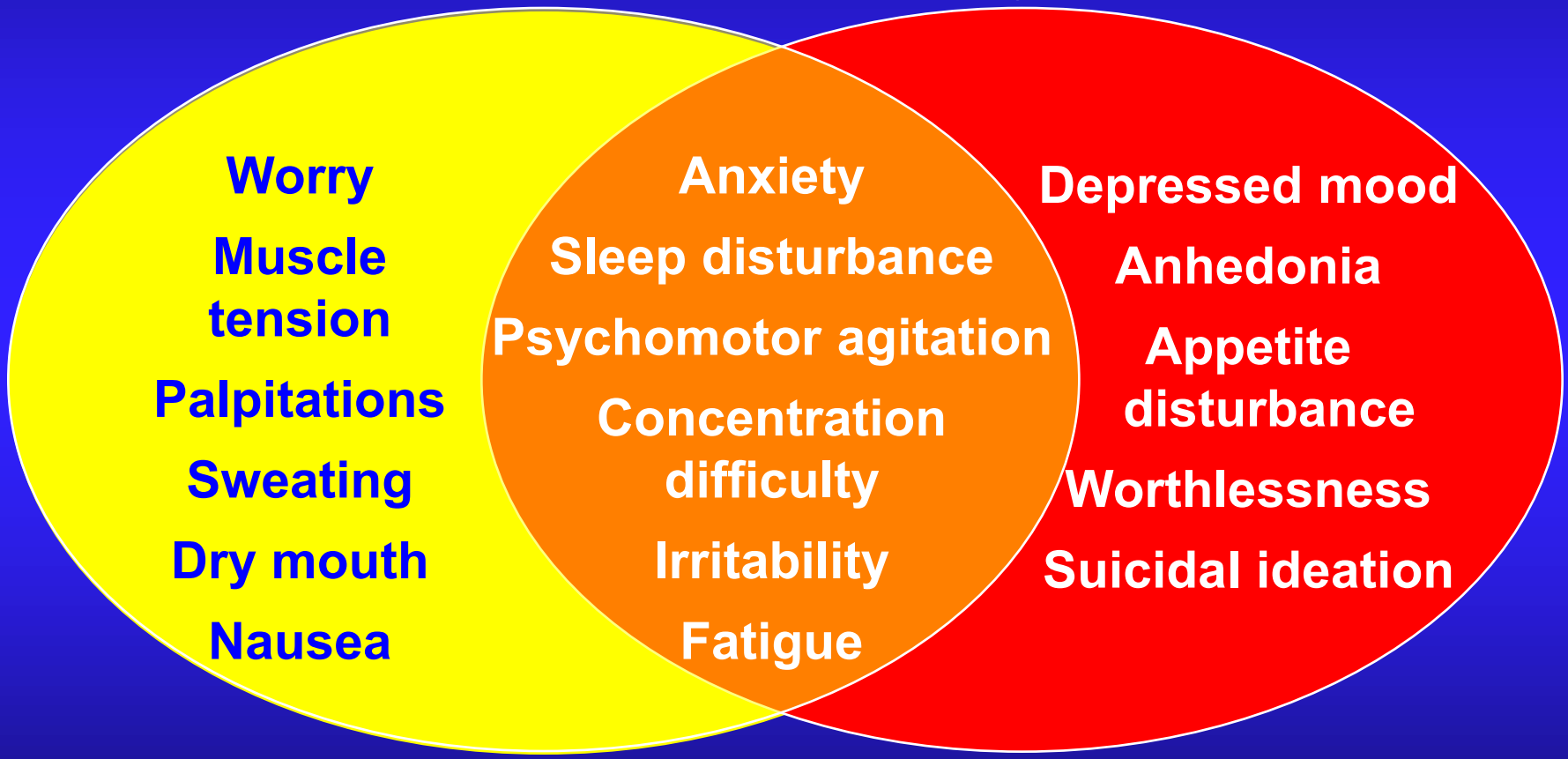
DSM 5. Washington, DC: American Psychiatric Association. 2013.

GAD - Other Associated Symptoms

- **Psychic symptoms**
  - **Impaired memory**
  - **Concern over health**
- **Somatic symptoms**
  - **Trembling**
  - **Twitching**
  - **Muscle aches**
  - **Nausea or diarrhea**
  - **Sweating**
  - **Urinary frequency**
  - **Palpitations**
  - **Pain**

DSM-5. Washington, DC: American Psychiatric Association. 2013.
Schweizer E, et al. J Clin Psychiatry. 1997;58(suppl 3):27-31.

Overlapping Symptoms of GAD and MDD



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

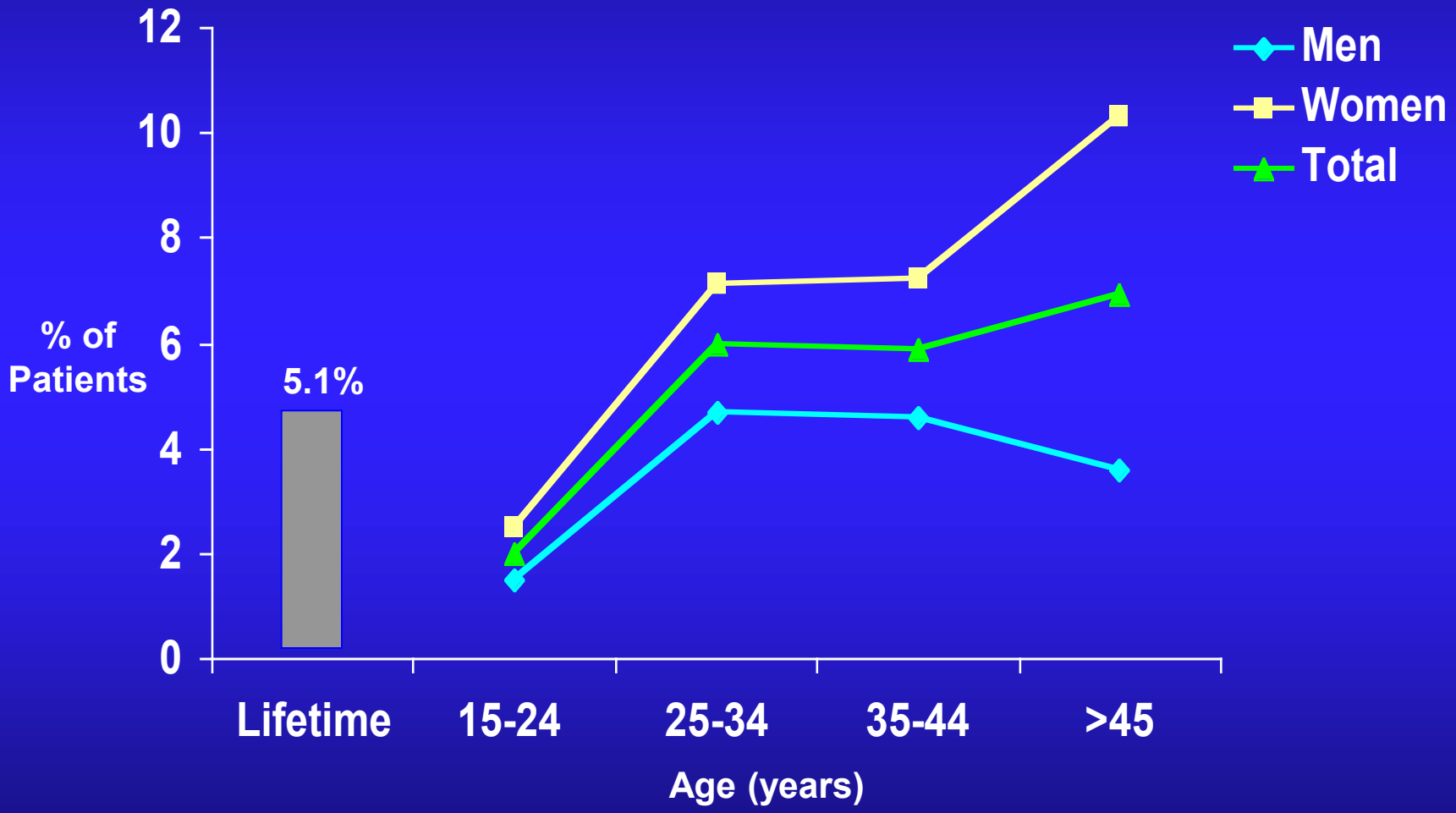
Epidemiology of GAD

- Lifetime prevalence ~ 9.0 %
- 12-month prevalence ~ 2 - 3%
- Women/Men = 2/1
- Median age of onset is 30 years
  - 25% < age 20; 50% between ages 20 and 47.
- High comorbidity in clinical and community samples. "Pure" GAD is rare (10% lifetime).

Kessler RC, et al. Arch Gen Psychiatry. 1994;51:8; Kessler RC, et al. Arch Gen Psych. 2005;62:593; Weisberg RB. J Clin Psych 2009;70 (suppl 2):4-9; DSM-5. Washington, DC: American Psychiatric Association, 2013

GAD Increases Later in Life in Women

Lifetime Prevalence of GAD: National Comorbidity Survey



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

GAD Longitudinal Course

- Chronic course, so chronic treatment is indicated
- Overlap with Major Depression is substantial
  - each increases the risk for the other
- Low rate of remission
- Remission rate is further reduced (additive):
  - with each add'l Axis I disorder (50% less likely)
  - with each add'l Axis III disorder (19% less likely)

Sartorius N, et al. Br J Psychiatry. 1996;168(suppl 30):38-43; Maier W, et al. Acta Psychiatr Scand. 2000;101:29-36; Keller MB. J Cin Psych 2002; 63 (suppl):11-16; Yonkers KA, et al. Br J Psychiatry. 2000;176:544-549; Yonkers KA, et al. Depress Anxiety 2003 17:173-9; Rodriguez BF, et al. J Nerv Ment Dis 2006;194:91-7; Keller MB and Lydiard RC, Psych CME Reports 2005;1:1-7; Moffitt TE, et al. Arch Gen Psych 2007;64: 651-60

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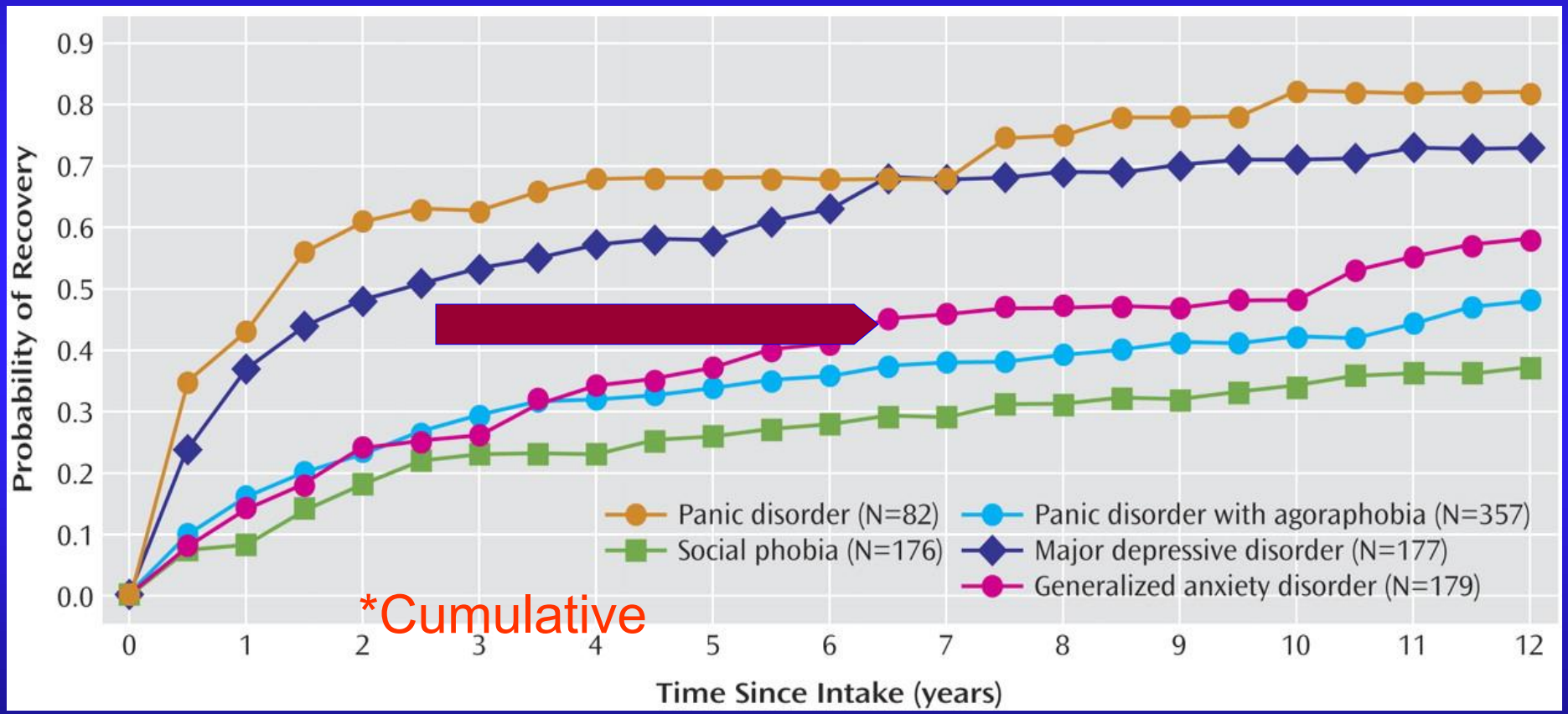
12-Year Probability of Remission in GAD

Low rate of recovery, and high recurrence rate (See notes)



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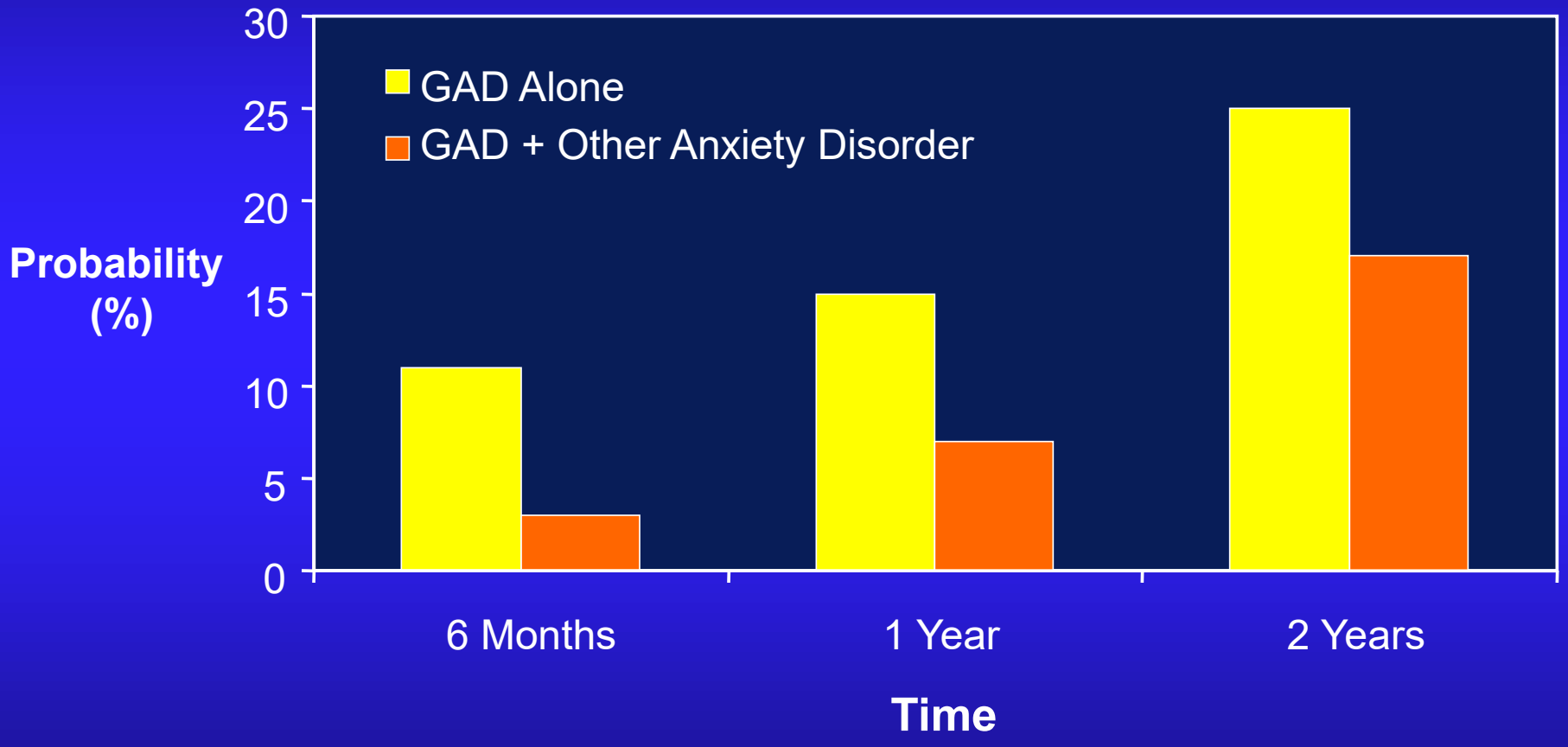
Bruce SE, et al. Am J Psychiatry. 2005;162:1179-87

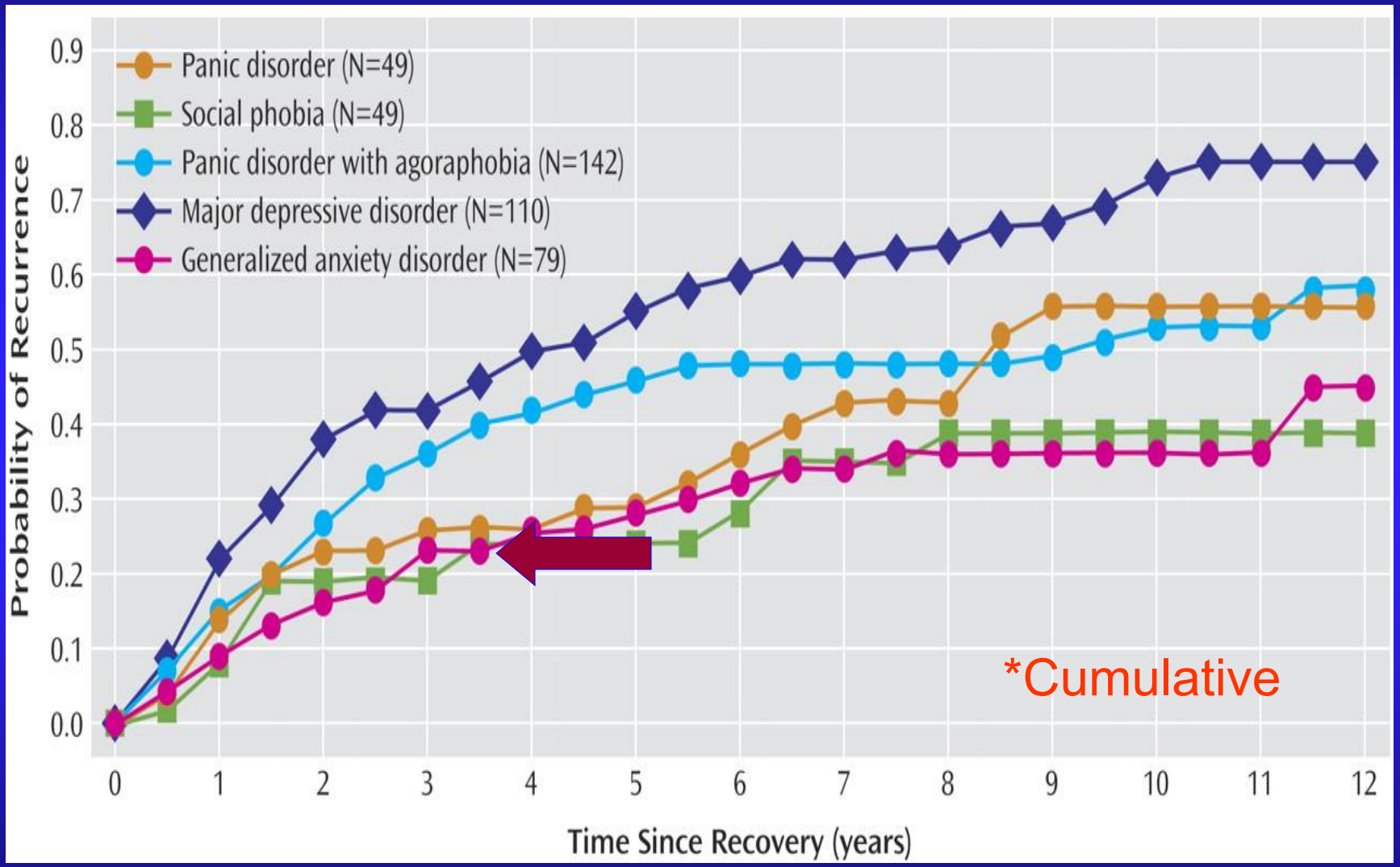
GAD - Low Probability of Remission

Patients in Harvard Anxiety Research Program
Strict criteria for remission



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

12-Year Probability of Recurrence



Bruce SE, et al. Am J Psychiatry 2005 162:1179-87

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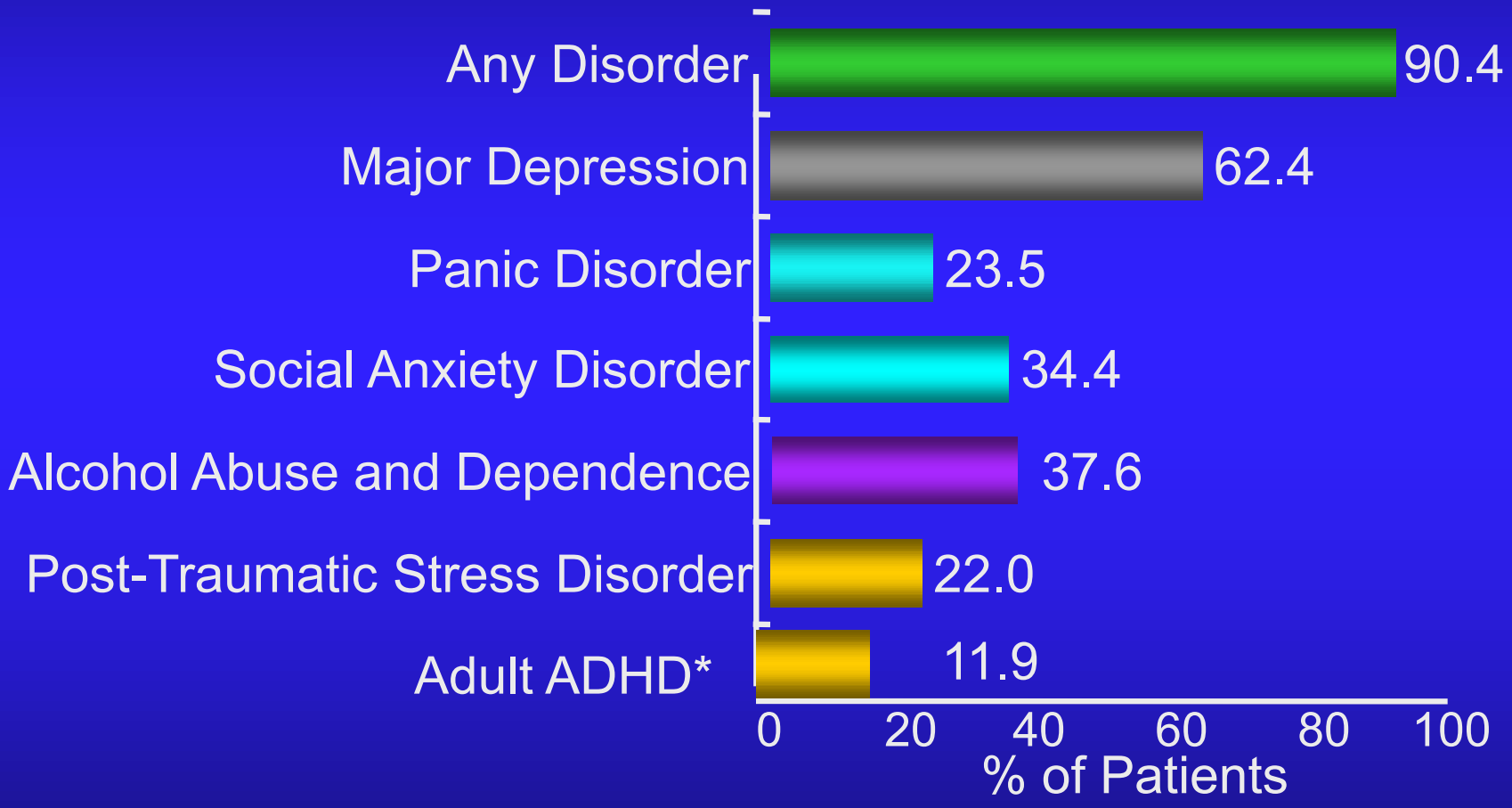
Lifetime Prevalence of Comorbid Disorders in GAD



Wittchen HU, et al. Arch Gen Psychiatry. 1994;51:355-364; Kessler R, et al. Arch Gen Psychiatry. 2000; *Kessler R, et al. Am J Psychiatry. 2006;163:716-23

GAD with coexisting MDD

- ↑'d treatment resistance or delayed response
- ↑'d suicidal behavior

- Antidepressants are indicated
  - An open-label series reports effectiveness of venlafaxine in comorbid state
  - CBT efficacy for comorbid conditions is less clear, needs study
  - Much written, little known

Brown GA, et al. American J Psychiatry. 1996; 153:1293-1300; Gaynes BN, et al. Gen Hosp Psych 1999;21:158-67; Goodnick PJ, et al. J Clin Psych 1999; 60:446-48; Silverstone PH, et al. J Clin Psych. 1999;60: 22-8; Perugi G, et al. Neuropsychobiology, 2002;46;145-9

Treating GAD
May Reduce Risk of Major Depression

- National Comorbidity Survey (Sept.1990 – Feb.1992)
  (interview, with re-interview 2 years later)
- Respondents with GAD w/o prior major depression

- Receiving ≥ 4 doses psychotropic medication for GAD
  - Lowered risk of depression:
    to 5.7% vs. 18.9%, $p<0.0001$

- Receiving a medication for GAD or consulting a mental health specialist did not lower this risk.

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

*

Consequences of Untreated Depression-Anxiety-Stress

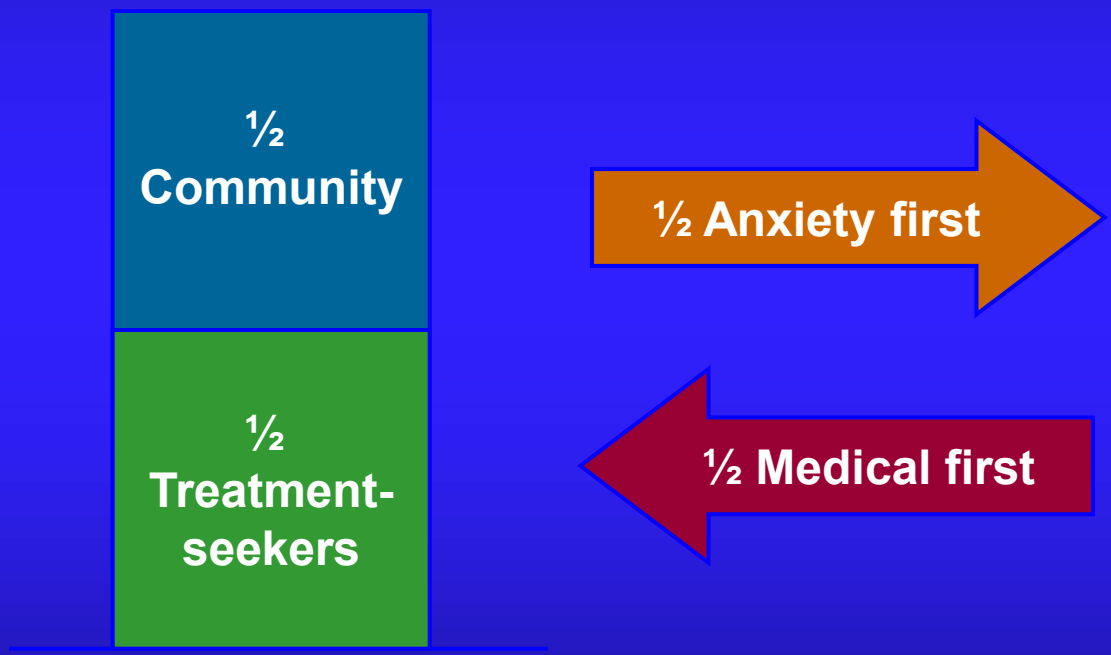
- Metabolic Syndrome
  - Hypertension, Coronary artery disease
  - Central obesity, Type 2 diabetes
  - Hyperlipidemia/hypercholesterolemia
- Immuno-dysregulation
- Neurodegenerative effects
  - (Reversible?)
  - Hippocampal, prefront cortex, amygdala

Raison CL, Miller AH. Am J Psychiatry. 2003;160:1554-1565
Pace T, et al. Brain Behav Immun. 2007; 21:9-19

Anxiety: Worse Long-term Health

German Health Survey (n = 4,181)

~300 Individuals with GAD or Panic Disorder



2 to 6 times as many medical disorders as controls*

- **Cardiovascular disorders**
- **Respiratory disorders**
- **Endocrine-metabolic disorders**
- **Autoimmune disorders**
- **Allergic disorders**

***Controlled for gender, depression, substance abuse.**

Harter MC, et al. Eur Arch Psychiatry Clin Neurosci. 2003;253:313-320; McEwen BS. Biol Psychiatry. 2003;54:200-207; Sareen J, et al. Arch Intern Med 2006;166:2109-16

*

Generalized Anxiety Disorder

↑ Health-care utilization

↑ Disability/impairment

↑ Risk for subsequent psychiatric disorders

GAD Neurobiology
Partial List

- Stress reactivity > normals
- Genetic factors
  - Gender differences: risk for women 2x risk for men
  - Familial inheritance pattern
  - Same gene, different environments?
  - Polymorphism
- Neurotransmitter differences
  - NE over-activity
  - BZ receptor differences
- Immune dysfunction
  - Immunosuppression
  - Worry --> pro-inflammatory cytokine release
- Imaging results
  - Lower BZ receptor density
  - Increased rCBF following worry

*

GAD – Psychiatric Differential Diagnosis

Anxiety disorders

- Social anxiety disorder
- Post-traumatic stress disorder (PTSD)
- Obsessive-compulsive disorder (OCD)
- Adjustment disorder with anxious mood

Major depression and bipolar disorders

Psychotic disorders

*

GAD - Differential Diagnosis
Medical Disorders

- Endocrine
  - Thyroid disease
  - Hypoparathyroidism
  - Hypoglycemia
  - Cushing's Disease
- Cardio-respiratory
  - Angina
  - Pulmonary embolism
- Autoimmune
- Neurological
  - Seizure disorder

GAD – Medication-induced anxiety

- Stimulants
- Caffeine
- Thyroid meds
- Antidepressants
- Bronchodilators
- Decongestants
- Corticosteroids
- Oral contraceptives

- Abrupt withdrawal of:
  - Alcohol
  - Barbiturates
  - Benzodiazepines
  - Nicotine
  - Opioids

Fernandez F, et al. J Clin Psychiatry. 1995;56(suppl 2):20–29; Kirkwood et al. Anxiety disorders. In: DiPiro J, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 3rd ed. 1997:1443–1462; Culpepper L. J Clin Psych 2009;70(suppl 2):20-24

Patient Assessment and Education

- Establish the diagnosis and its effects
- Is a comorbid disorder present?
  - Current or past major depression?
- History of the illness
- Treatment history
- Family history
- Medical history and exam
  - Review medications, *including herbal medicines*

- Educate the patient and family
  – www.adaa.org

*

Assessing GAD Treatment Effects

Response

≥ 50% decrease from baseline in HAM-A score or CGI score of 1 or 2

Remission

HAM-A score ≤ 7
Patient asymptomatic
Psychosocial/occupational functioning restored

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

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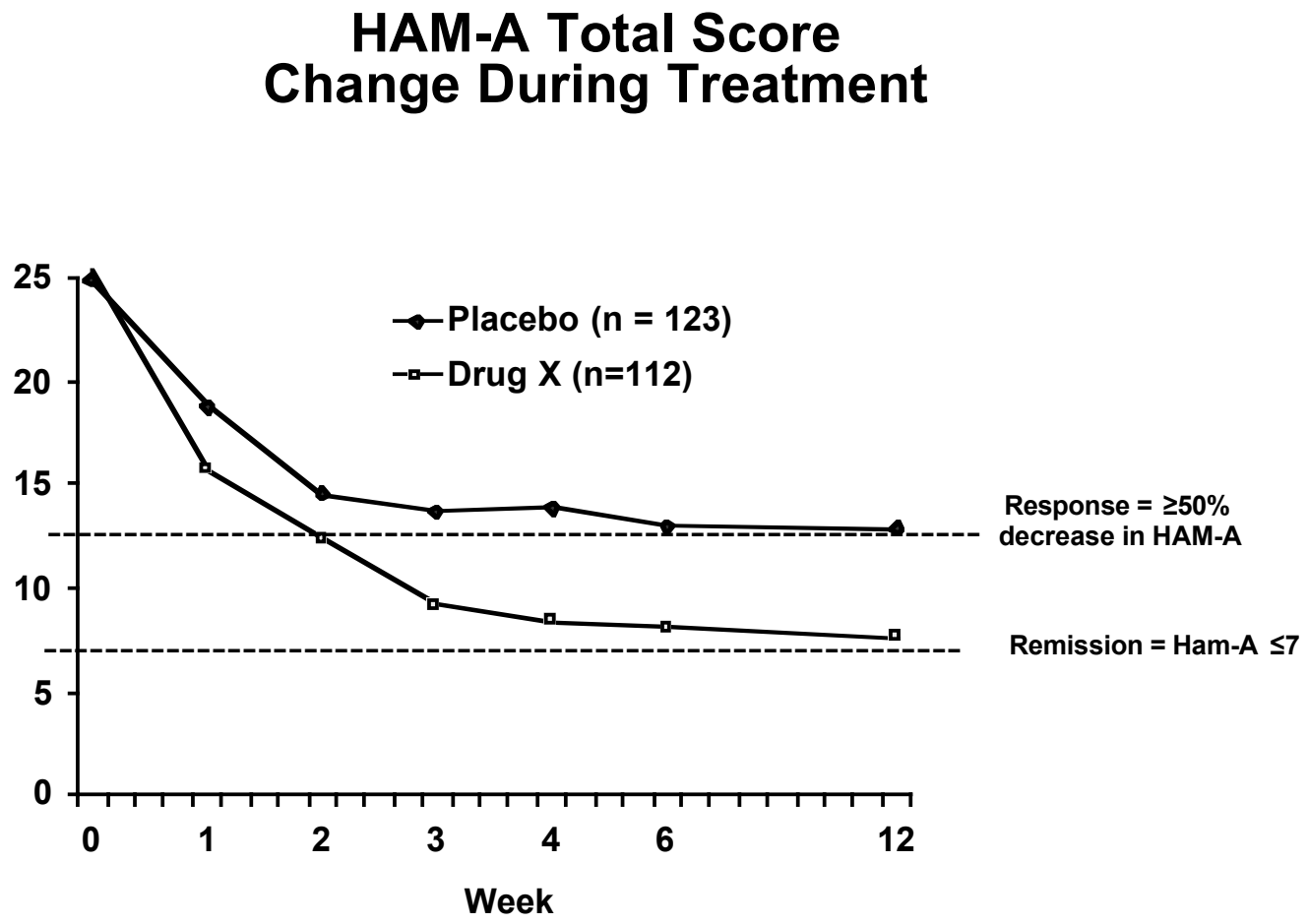
Response vs. Remission



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Interpreting the Literature

- Efficacy (how well Rx works in a trial) ≠ Effectiveness (how well Rx works in clinical practice)
  - e.g. patients with comorbid dx are not in trials
- Improving functioning is most important
- Short-term studies (≤ 12 weeks) can't provide good data re ultimate change in functioning
  - Look for HAM-A ↓ ≥ 10 points
  - Look for HAM-A ↓ ≥ 5 points than placebo ↓
  - These are guidelines only

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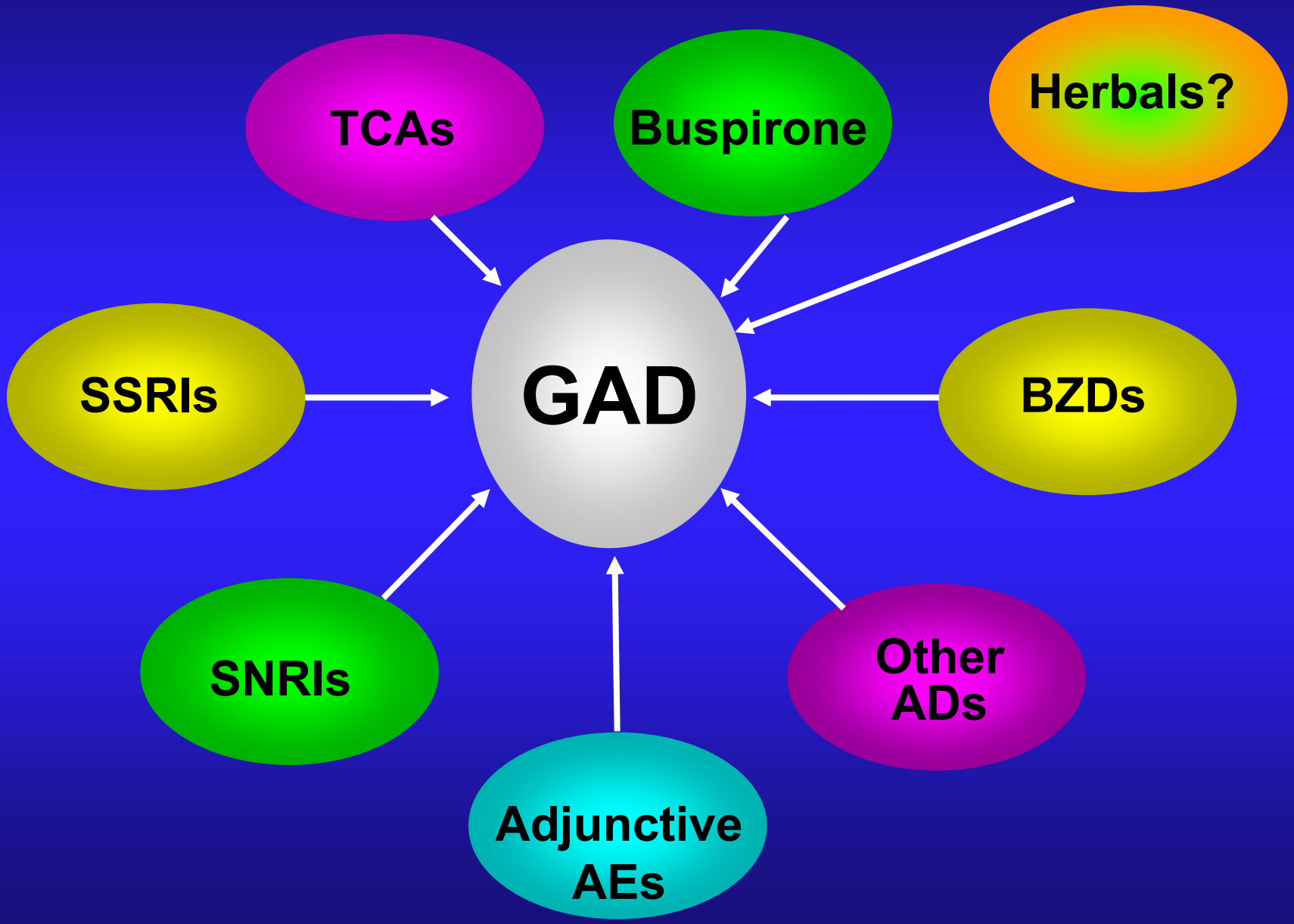
Pharmacotherapy for GAD

Ravindran LN, Stein MB. J Clin Psychiatry. 2010;71:839-54.



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Initiating therapy: considerations

Ease of management

- Safety
- Concomitant meds
- Pregnancy
- Age
- Washout

- Compliance
- Ease of switching
- Ease of discontinuing

*

First-line GAD Treatments
SSRIs and SNRIs

Advantages

- Effective
- Good Safety
- Tolerability
- Once-daily dosing
- Sustained long-term efficacy

Disadvantages

- Delayed onset of action
- Early anxiogenic effects
- Sexual side-effects
- Dose titration needed
- Discontinuation Sx

*

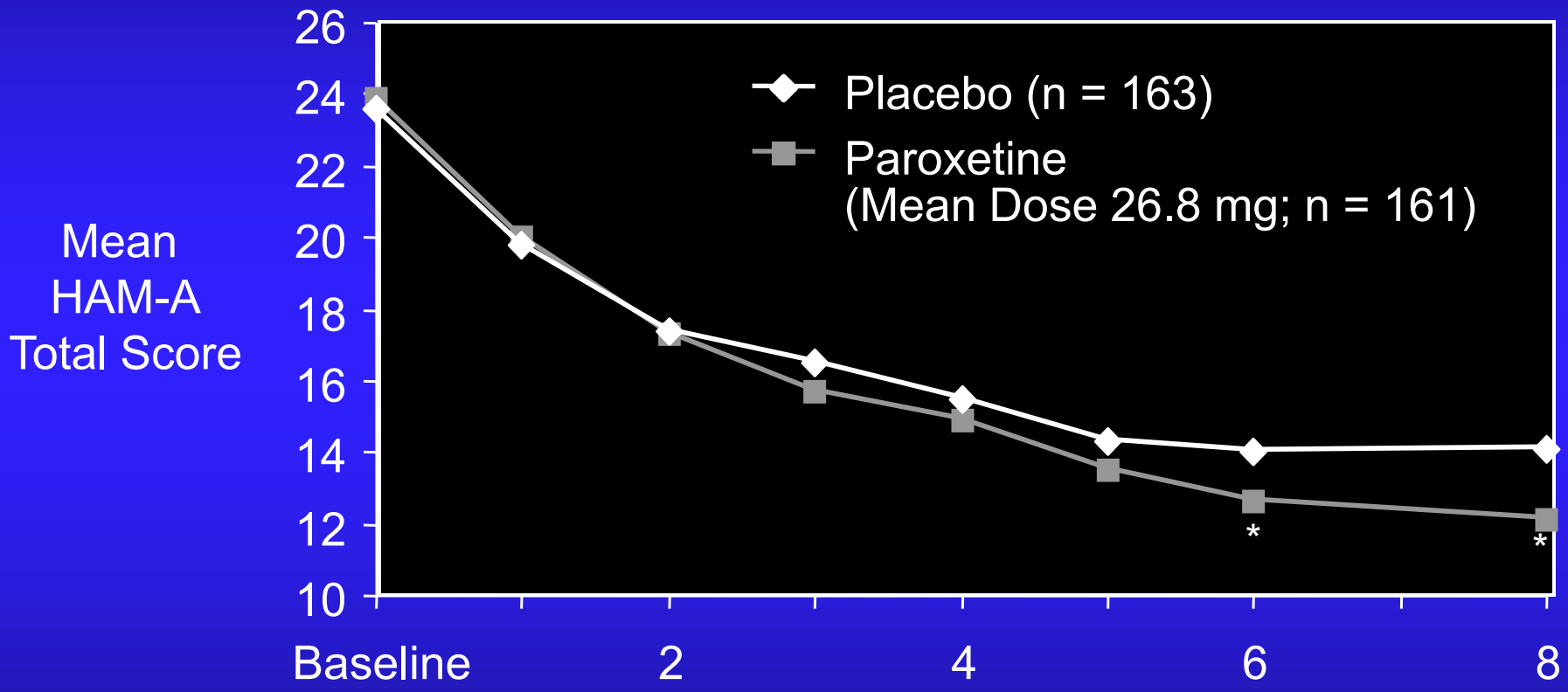
GAD: FDA-Approved SSRIs/SNRIs

- Citalopram
- Escitalopram
- Paroxetine
- Venlafaxine
- Duloxetine

- None is demonstrably more effective than the others

SSRIs for GAD: Paroxetine

Flexibly Dosed



LOCF dataset.

*$P < .05$ vs placebo.

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

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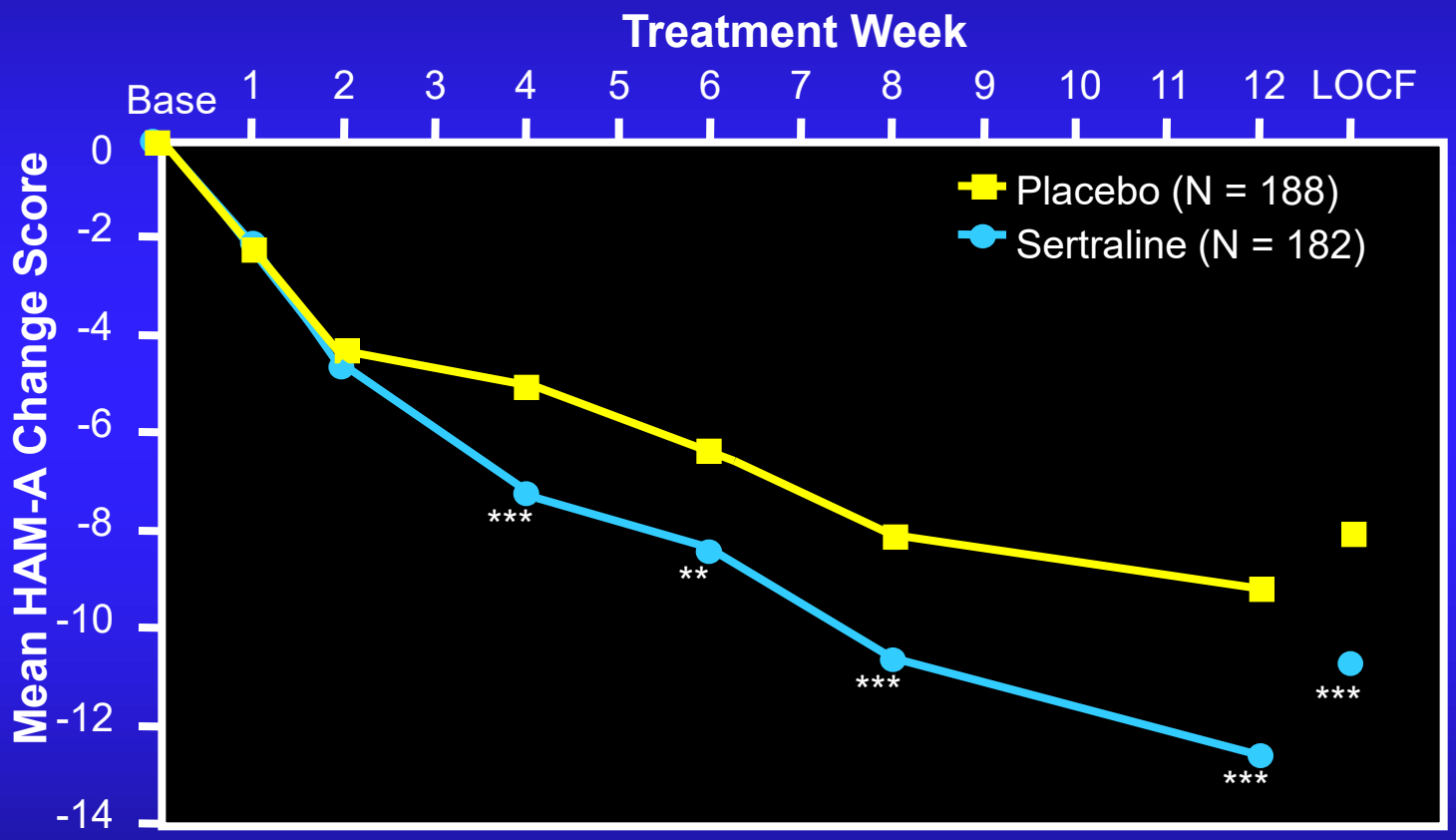
SSRIs for GAD: Sertraline vs. Placebo

ITT sample



$^{**}P < .01$
$^{***}P < .0001$

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

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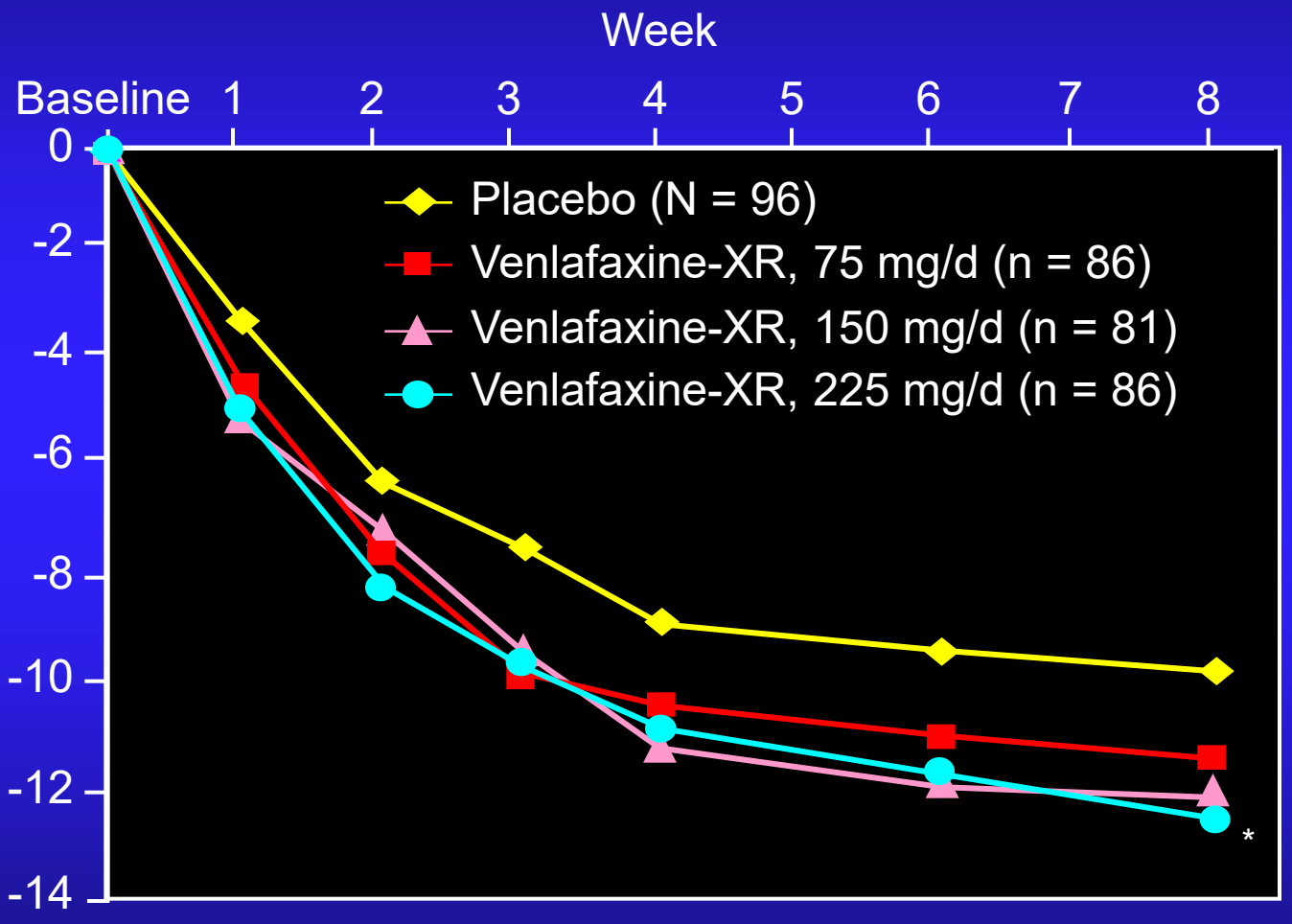
SNRI for GAD: Venlafaxine

Fixed-dose Study



HAM-A Total Score (Mean Change from Baseline)

*P = .03.

Rickels K, et al. Am J Psychiatry. 2000;157:968-74.

*

SNRI for GAD – Duloxetine

- Binds with high affinity to 5HT and NE transporters

- 3 placebo-controlled RCTs, 9-10 weeks
  - one fixed-dose 60 and 120mg/d vs. placebo
  - 2 flexible dosing 60-120mg/d vs. placebo
- Results: ↓ anxiety, ↓ disability and ↑ quality of life
- Effective in preventing GAD relapse

Karpa KD. CNS Drug Rev. 2002;8:361-376;
Endicott J, et al. J Clin Psychiatry 2007;68: 518-24

*

GAD - Antidepressant Dosing

Category	Usual Dose 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

GAD Treatment
Benzodiazepines

Advantages

- Rapid onset
- Effective
- Well-tolerated
- Safe in overdose
- Generics available

Disadvantages

- Withdrawal symptoms
- Sedation
- Multiple daily dosing often required, except for clonzepam
- Abuse potential
- Unreliable antidepressant effect

* Long-term treatment of GAD with BZs has not been systematically studied; far more opinion than fact is reported in the literature

GAD Treatment
Benzodiazepines

Drug	Dose Range (mg/d)
Alprazolam	0.75 - 6
Clonazepam*	1 - 3
Lorazepam	4 - 10
Diazepam*	15 - 20

*Slow elimination, longer time to reach steady-state

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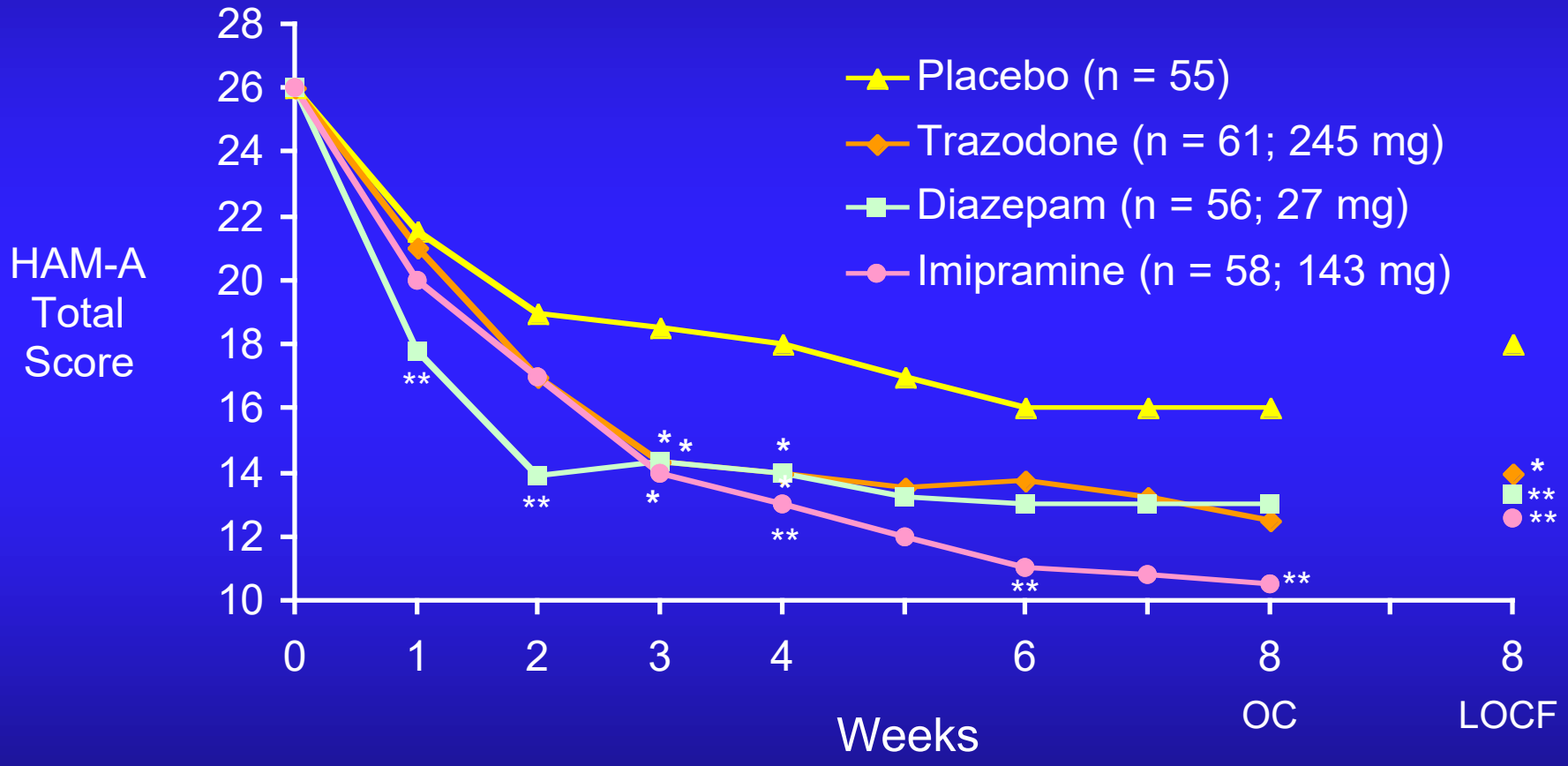
Comparing Imipramine, Diazepam and Trazodone for GAD



OC = observed cases; OC dataset.
*$P < .05$. **$P < .01$.

Rickels K, et al. Arch Gen Psychiatry. 1993;50:884-895.

GAD - Buspirone

- A $5HT_{1a}$ post-synaptic partial agonist and a full agonist at pre-synaptic 5HT receptors
  - Outcomes of 6-week studies of varying design (vs. placebo, ≠ comparators) are uneven
  - No long-term studies
  - Delayed onset of action ≥ 2 weeks)
  - Not effective for most GAD comorbid conditions
  - Dose ≥ 30 mg daily probably usually necessary

Chessick CA, et al. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD006115. DOI 10.1002/14651858.CD006115.

*

GAD - Hydroxyzine

- Double-blind, 12-week study, n=334
- Hydroxyzine 50 mg/d
  = bromazepam 6 mg/d > placebo
- Response rates:
  - Hydroxyzine 57%
  - Bromazepam 60%
  - Placebo 25%
- Useful for GAD patients with alcohol abuse

Llorca PM, et al. J Clin Psychiatry. 2002;63:1020-7

Long-Term Treatment of GAD

- Need to treat long-term (≥ 12 months)
- ≈ 25% of patients relapse within 1 month after stopping treatment
- 60%-80% relapse within 1st year after stopping treatment
- Favorable response to SSRI/SNRI maintenance Rx

Hales RE, et al. J Clin Psychiatry. 1997;58(suppl 3):76-80.
Rickels K, Schweizer E. J Clin Psychopharmacol. 1990;10(3 suppl) 101-110S
Donavan MR, et al. J Affective Disord. 2010;123: 9–16.

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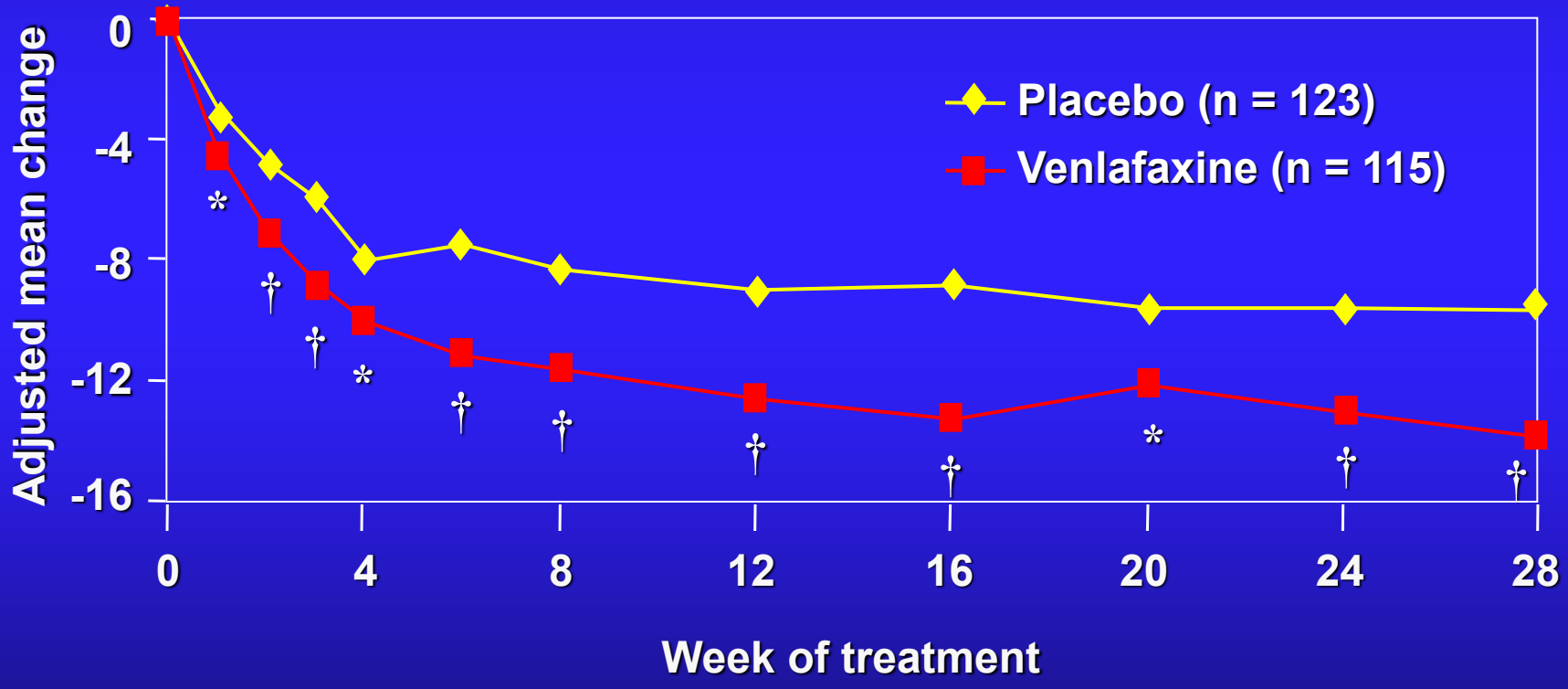
GAD: 6-Month, Placebo-Controlled Trial
Venlafaxine XR

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

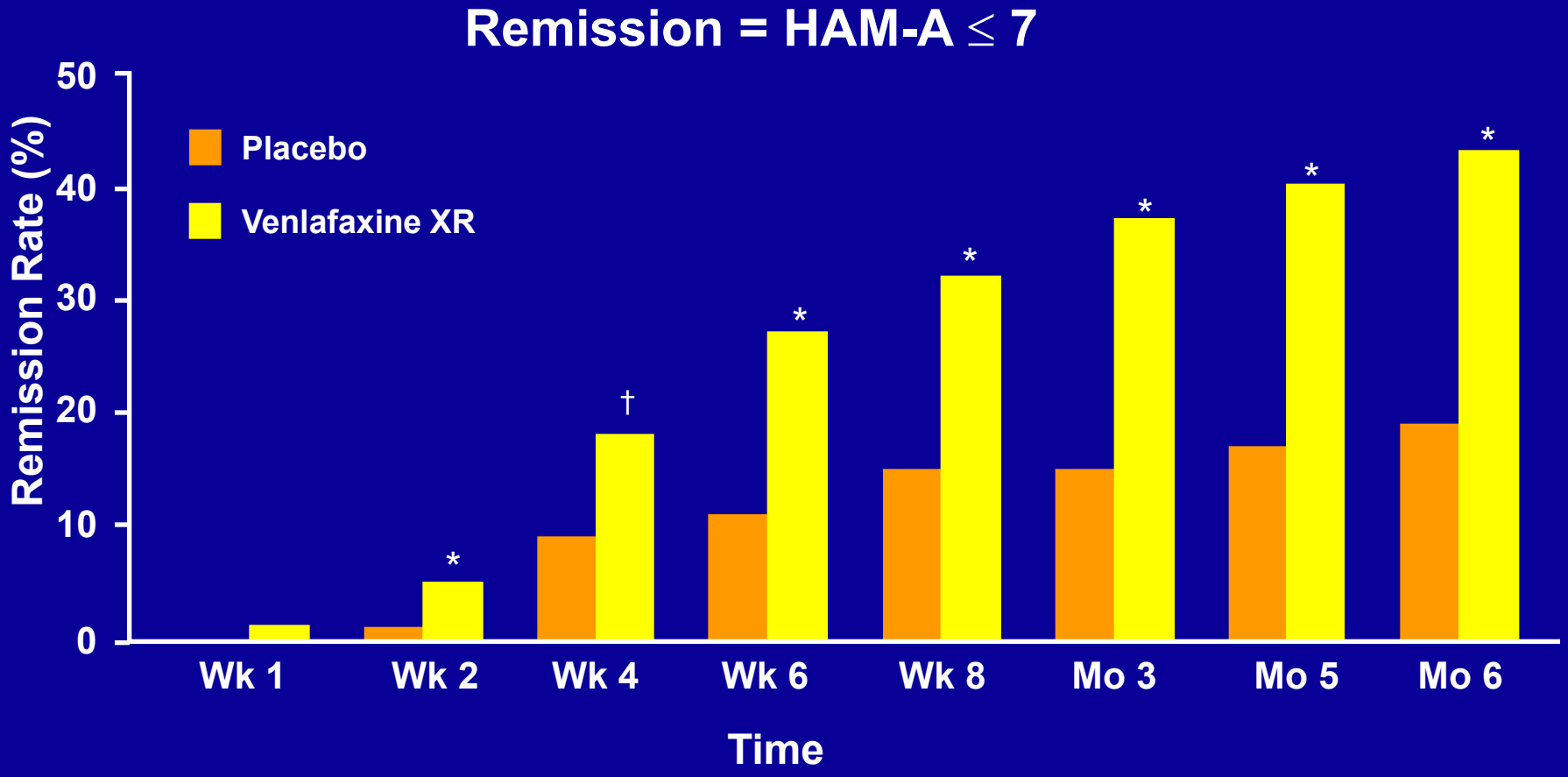


*** p < 0.05 vs. placebo; † p < 0.001 vs. placebo**

*

Gelenberg AJ, et al. JAMA 2000;283:3082-88.

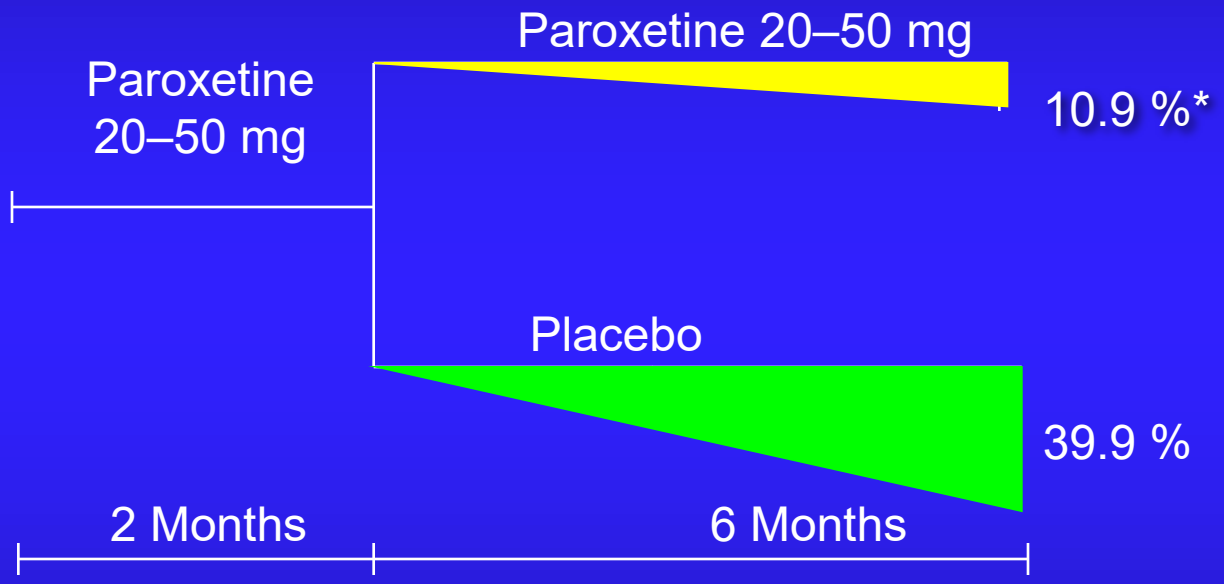
GAD Remission Takes Time: Venlafaxine Pooled Analysis (N=767)



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

Montgomery SA, et al. J Psychiatr Res. 2002;36:209-17 .

GAD: Paroxetine Long-Term Treatment
Relapse Prevention



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

Stocchi F, et al. J Clin Psychiatry. 2003;64:250-8.

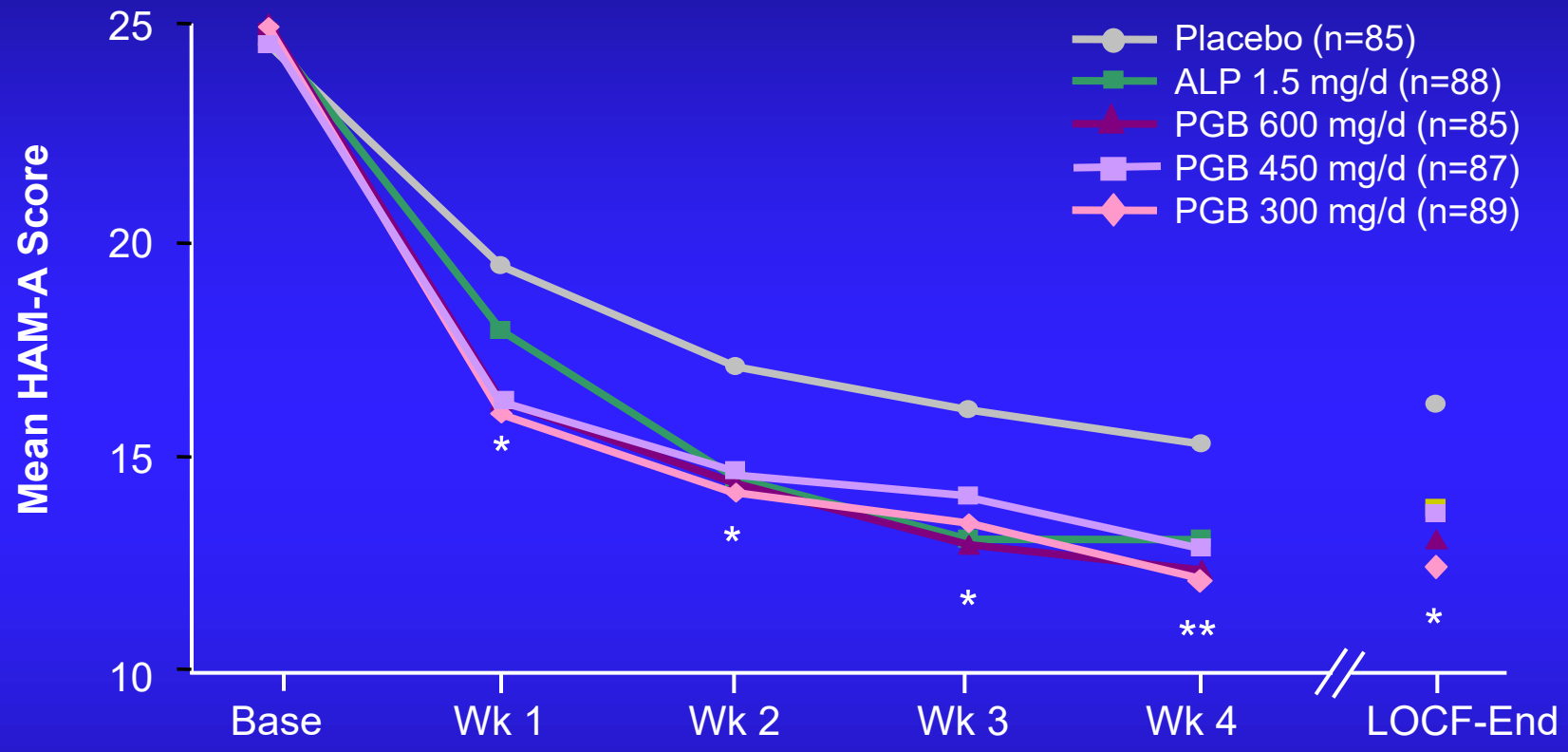
*

GAD – Anticonvulsant: Pregabalin

- **Target**
  - **Binds to $\alpha_2\delta$ subunit of widely distributed voltage-dependent calcium channels**
  - **Like gabapentin, it ↓ CA++ influx through the trans-membrane ion channel, thus ↓ firing rate of neurons that are firing excessively**
- **Downstream effect**
  - **Inhibits release of excitatory neurotransmitters: glutamate, aspartate, NE, DA, 5-HT, substance P, others**

Frampton JE. CNS Drugs. 2014; 28:835-54

Efficacy of Three Doses of Pregabalin vs. Alprazolam in Reducing HAM-A Score



All medications dosed tid.

*$P \leq .05$ vs placebo (ANCOVA) for all medications.

**$P \leq .05$ vs placebo (ANCOVA) for PGB 300 mg/d and PGB 600 mg/d only (OC).

Lydiard RB, et al. Int J Neuropsychopharmacol. 2010;13:229-41

GAD: Pregabalin vs. Venlafaxine N = 421, 6 weeks

- Primary care and psychiatry settings (Europe)
  - Pregabalin (PGB) 400 or 600 mg/d
  - Venlafaxine 75 mg/d
  - placebo
- Both pregabalin doses > placebo by week 1
- Venlafaxine > placebo by week 2
- 75 mg venlafaxine is approved for GAD in Europe
  - Lower dose venlafaxine may be sufficient
  - D/C for side effects:
    - venlafaxine 20.4%,
    - pregabaline 400 mg/d 6.2%; 600 mg/d 13.6%;
    - placebo 9.9%.

Montgomery SA, et al. J Clin Psychiatry. 2006;67:771-82

GAD – Atypical Antipsychotics

- **Mostly studied in small trials as *adjunctive***
  - **Dbl-blnd risperidone, olanzapine effective in achieving response. Ziprazidone and quetiapine ineffective.**
  - **Open-label aripiprazole effective**

- **Quetiapine 50 mg XR and 150 mg XR, 10-week dbl-blnd trial - monotherapy > placebo***

*Bandelow B, et al. Int J Neuropsychopharmacol 2010;13:305-20

CBT for GAD
(Review, N=1,305 patients)

- **CBT vs.**
  - **Treatment as usual (TAU)/waiting list (WL) (13 studies)**
  - **Other psychological therapy (12 studies)**
  - **No studies were long-term**
- **CBT superior to TAU or waitlist in achieving clinical response**
  - **CBT " very effective" for secondary symptoms**
  - **Group CBT Rx in elderly → higher dropout rate**
- **CBT vs. other psychological Rx – unclear if superior, but studies quite heterogeneous**
- **Comparative studies vs. medication have not been done**

Hunot et al, Cochrane Reviews 2007, Issue 1.
Art. No.: CD001848. DOI: 10.1002/14651858.CD001848.pub4

Ginko Biloba (Egb 761) in GAD

- DSM-III-R GAD (n=82) or DSM-III-R adjustment disorder with anxious mood (n=25)
- 4-week placebo-controlled RCT (in Germany)
- HAMA ↓ > placebo (7.8 pts.) for 480 mg-Egb (↓14.3) and 240 mg Egb (↓12.1)
- High dose superior on <u>all</u> measures
  - Possible dose-response effect
- Concerns:
  - Subjects may not have been as ill as those in U.S. RCTs
  - The formulation may be unreliable from many U.S. sources

*

Woelk H, et al. J Psych Res. 2007;41(6):472-80

Kava (Piper methysticum) Is Ineffective for GAD

- **3 placebo-controlled RCTs**
  - **One with active comparator**
- **DSM-IV GAD, ages ≥ 18**
  - Pooled sample: kava 28; placebo 30; venlafaxine 6
- No evidence for efficacy of kava
- Placebo > kava in patients with higher initial anxiety
- Safe, well-tolerated
- Very small sample sizes--Type II error is possible
  - See notes

* **Connor KM, et al. Int Clin Psychopharmacol. 2006;21:249-53**

Strategies for Refractory GAD

- Were dose and duration of antidepressant adequate?
- Review psychosocial stresses for management
- Switch to a second SSRI/SNRI
- Switch to a TCA
- Switch to pregabalin, or
- Add:
  - benzodiazepine
  - buspirone
  - low dose atypical neuroleptic
    - (risperidone, olanzapine, aripiprazole)
  - CBT

Coplan JD, et al. J Clin Psychiatry. 1993;154 (suppl) 63-74; Pollack MH. J Clin Psychiatry. 2009;(suppl) 2:32-8; Snyderman SH, et al. J Clin Psychopharmacol 2005; 25:497-499

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Childhood GAD - Venlafaxine

- 2 RCTs, placebo-controlled
- DSM-IV GAD, ages 6 - 17
  - 59 sites in 2000-2001
- Flexible dosage of extended-release venlafaxine
  - (N=157) or placebo (N=163) for 8 weeks
- Study 1: significant on primary and some secondary outcome measures
- Study 2: significant on some secondary, but not the primary outcome measures
- Pooled sample: Significant primary outcome overall
  - See notes

Rynn, MA, et al. Am J Psychiatry. 2007;164:290-300

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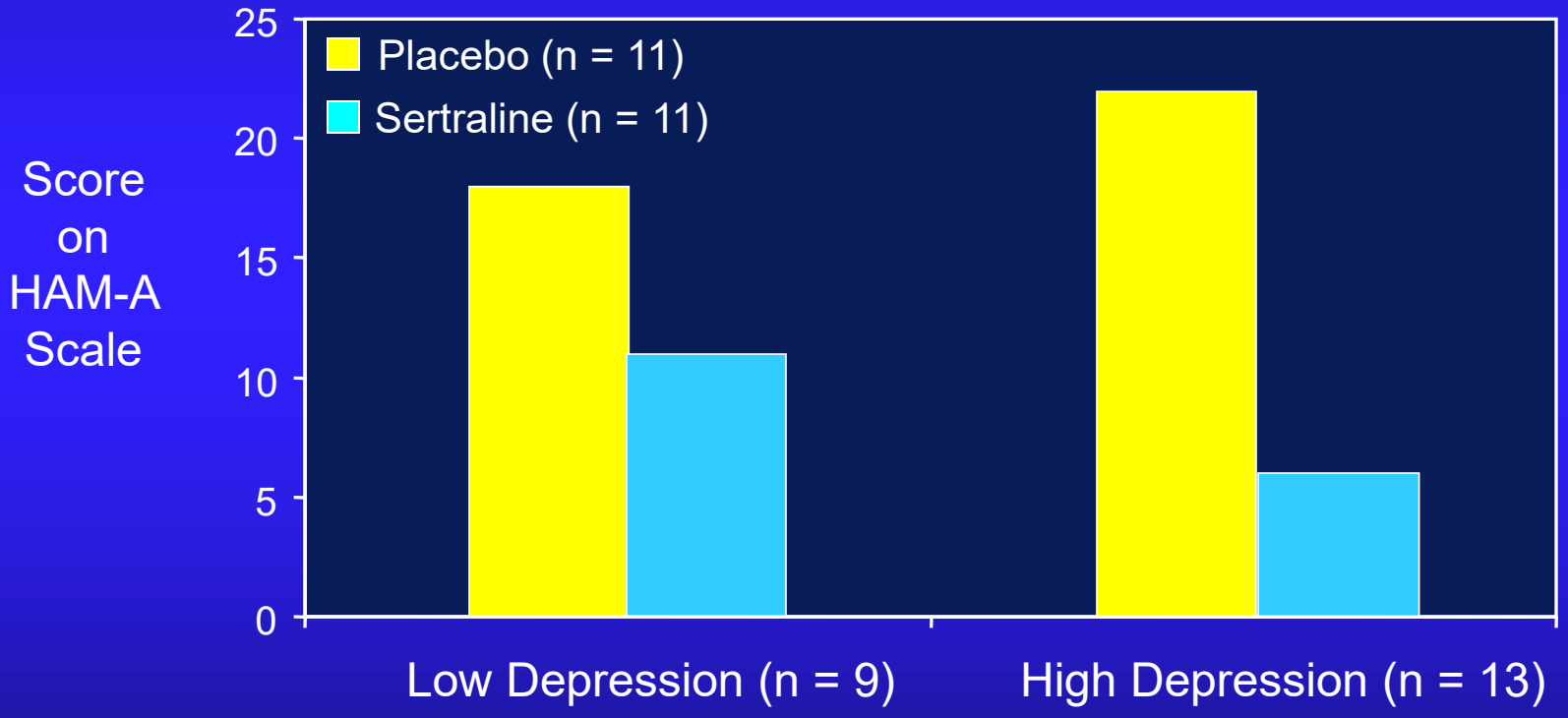
Childhood GAD - Sertraline

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

* Rynn MA, et al. Am J Psychiatry. 2001;158:2008-14.

Childhood GAD - Sertraline

*Mean Total Scores on HAM-A at 9 Weeks**



*LOCF. Low and high depression severity indicated by HAM-D scores ≤ 10 and > 10, respectively.

Rynn MA, et al. Am J Psychiatry. 2001;158:2008-14.

Summary - 1

- GAD is common, F/M prevalence = 2
- Commonly presents to GPs with somatic sx
- Rule out organic causes, including medications
- Comorbid anxiety disorder, major depression, or alcohol abuse/dependence is common

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Summary - 2

- Pharmacotherapy: start low and go slow
  - Adequate doses for adequate time
  - Usually requires long-term treatment
- First-line drugs are SSRIs and SNRIs
  - Benzodiazepines create dependence, long-term data missing
  - Buspirone less evidence, no long-term data
  - Pregabalin supported by large, controlled trials
  - Atypical antipsychotics supported by limited data
- CBT is supported by modest data, but may be less effective than SSRIs/SNRIs

Answers to Questions

- Q1. e. F/M prevalence of GAD = 2.0
- Q2. d. Schizophrenia (prodromal) is not commonly comorbid with GAD
- Q3. c. Efficacy of atypical antipsychotics in GAD is not well supported by controlled trials
- Q4. c. 24-35% achieve a remission within 8 weeks.
- Q5. c. Unknown. No well-controlled trials have tested this hypothesis.