Generalized Anxiety Disorder

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Generalized Anxiety Disorder (GAD) Pharmacotherapy Lecture Outline

- Questions and Learning Points
- Diagnosis, DSM-V
- Epidemiology, Course of Illness
- Neurobiology
- Morbidity and Comorbidity
- 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 discontinuation of effective 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**
- **Concurrent medications and medical conditions should be Included in the differential diagnosis for GAD**

Teaching Point #3

- **SSRIs, SNRIs and benzodiazepines are effective for GAD**
- **Azapirones are effective, but**
  - **evidence suggests that their relative efficacy (vs. antidepressants and benzodiazepines) may be less robust**
  - **No long-term controlled studies to date**
- **Long term treatment often necessary**

DSM-IV GAD Diagnostic Criteria

- Excessive or difficult to control worry and anxiety

- More days than not for ≥6 months*
  - 6-month duration affects prevalence but not course or disability.
  - * Increasingly controversial

- Symptoms impair social,occupational, family role functioning and/or cause significant distress

DSM IV-TR. Washington, DC: American Psychiatric Association. 2000.
Kessler et al Psychol Med 2005; 35:1073-82*-see notes

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Kessler et al Psychol Med 2005; 35:1073-82*-see notes

DSM-IV Diagnostic Criteria for GAD, cont

- Associated with ≥ 3 of the following
  - restlessness/keyed-up
  - easily fatigued
  - difficulty concentrating
  - irritability
  - muscle tension
  - sleep disturbance
- Does not occur only when another Axis 1 disorder is present (such as MDD) or be due a substance or medical condition

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

DSM-V Changes for Criteria for GAD

- Duration more days than not ≥ 3 monhs
- Associated with ≥ 1 of the six GAD Sx
- Associated with≥1
- 1) avoidance of or
- 2) excessive preparation for situations where negative outcome possible
- 3) putting off decisions or
- 4) repeatedly seek assurance due to worries

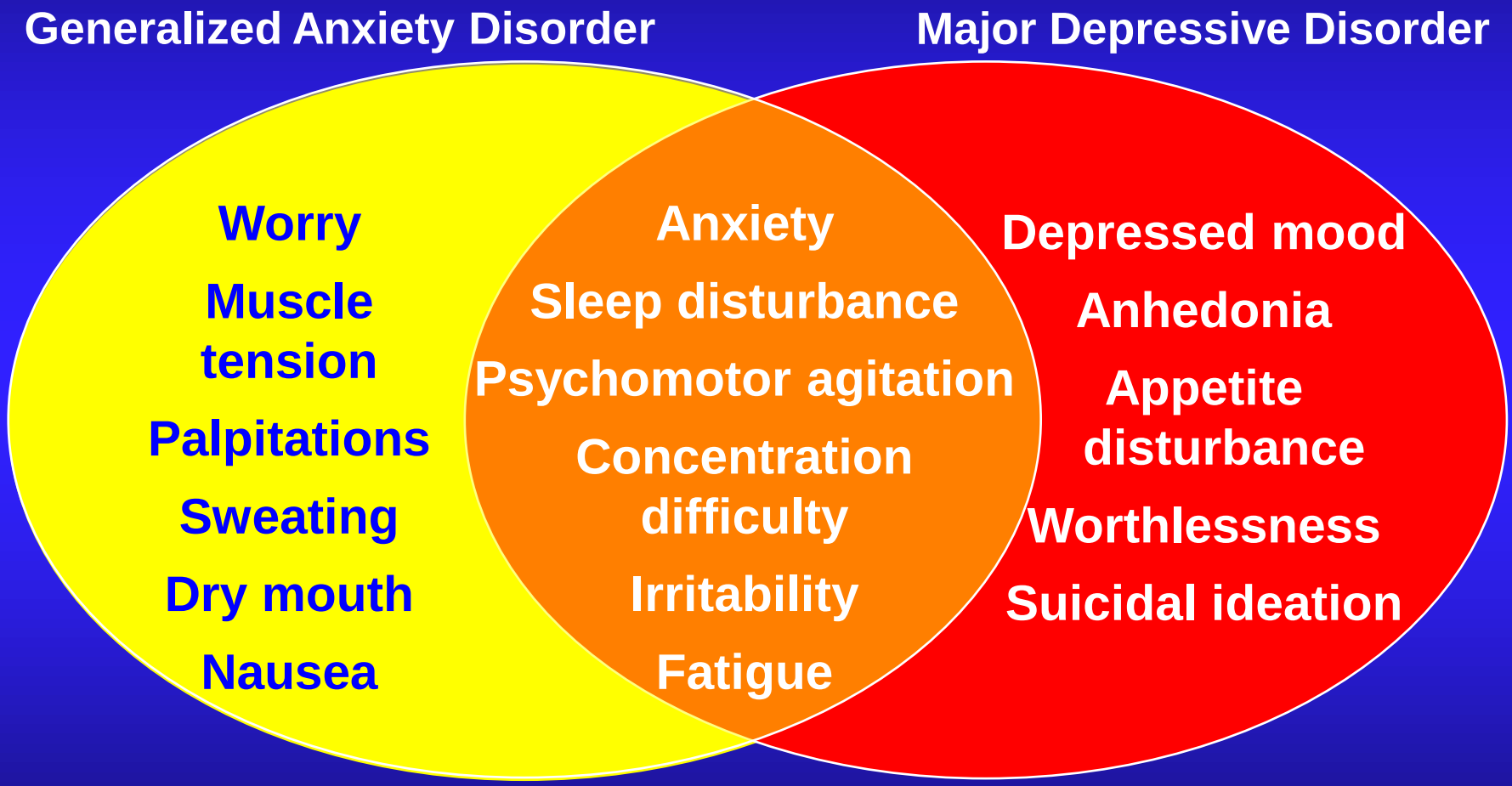
American Psychiatric Association. 2010.

Diagnostic and Associated 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 required diagnosis but often present (Schweizer E et al. J Clin Psychiatry. 1997;58(suppl 3):27-31.)

Overlapping Symptoms of MDD and GAD



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

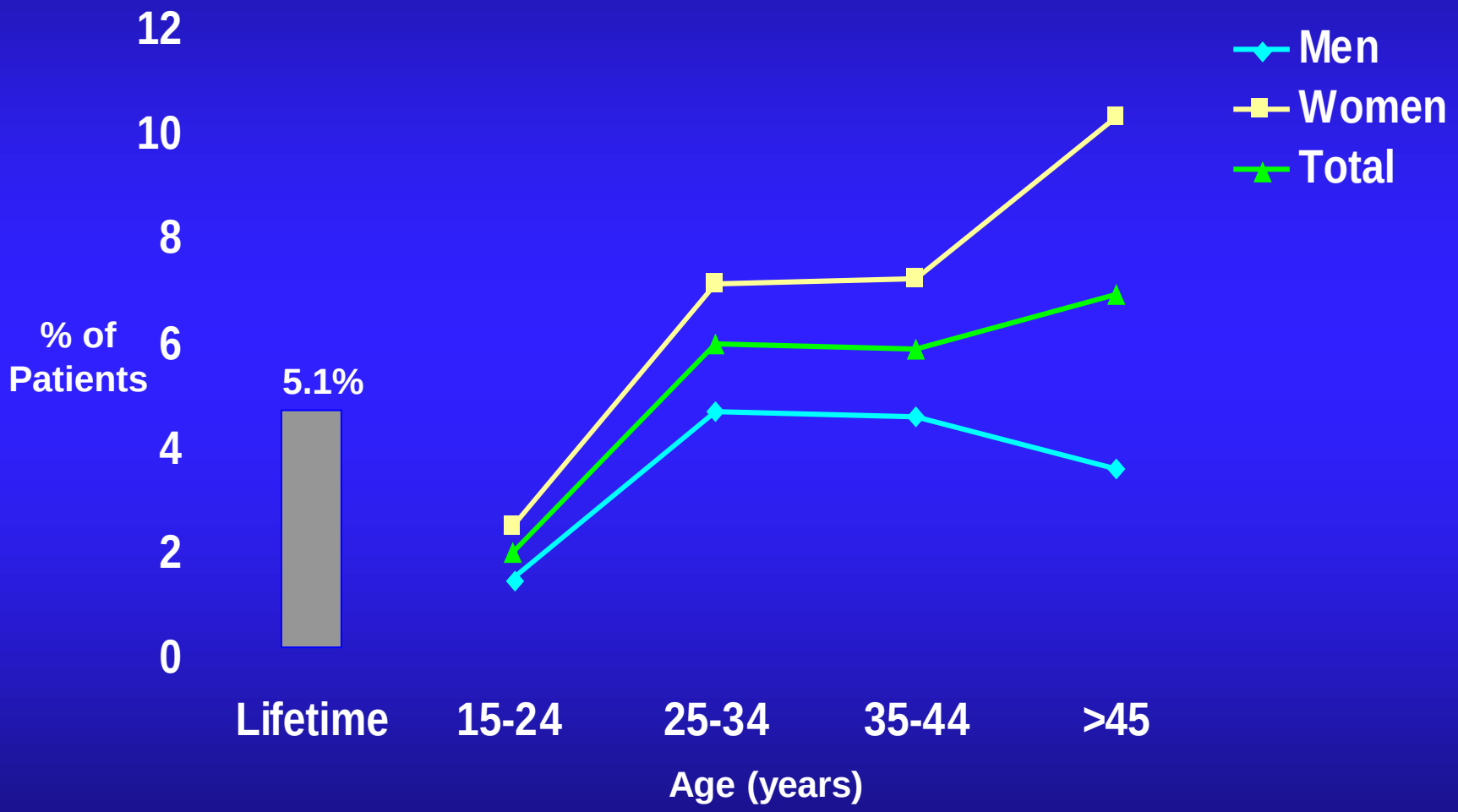
Epidemiology of GAD

- Lifetime prevalence ~ 5.1 %
- 12-month prevalence ~ 2-3%
- Women > men 2:1
- Median age of onset is 31yo.
  - 25% age 20; 50% between age 20 and 47.
- High comorbidity in clinical and community samples. : “Pure” GAD is rare.

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

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 -- > Chronic Treatment Indicated

- Overlap with MDD sbustantial
  - Both increase risk for the other
  - Literature differs on timing of onset
- Low rate of remission (25% at 2 yrs) in both psychiatric and primary care settings
- Remission 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, J Cin Psych 2002; 63 (suppl) :11-16;Yonkers KA et al. Br J Psychiatry. 2000;176:544-549 Yonkers et al, Depress Anxiety 2003 17:173-9. Rodriguez et al J Nerv Ment Dis 2006; 194:91-7; Keller and Lydiard , Psych CME Reports 2005; 1:1-7; Moffit et al, Arch Gen Psych 2007;64: 651-60

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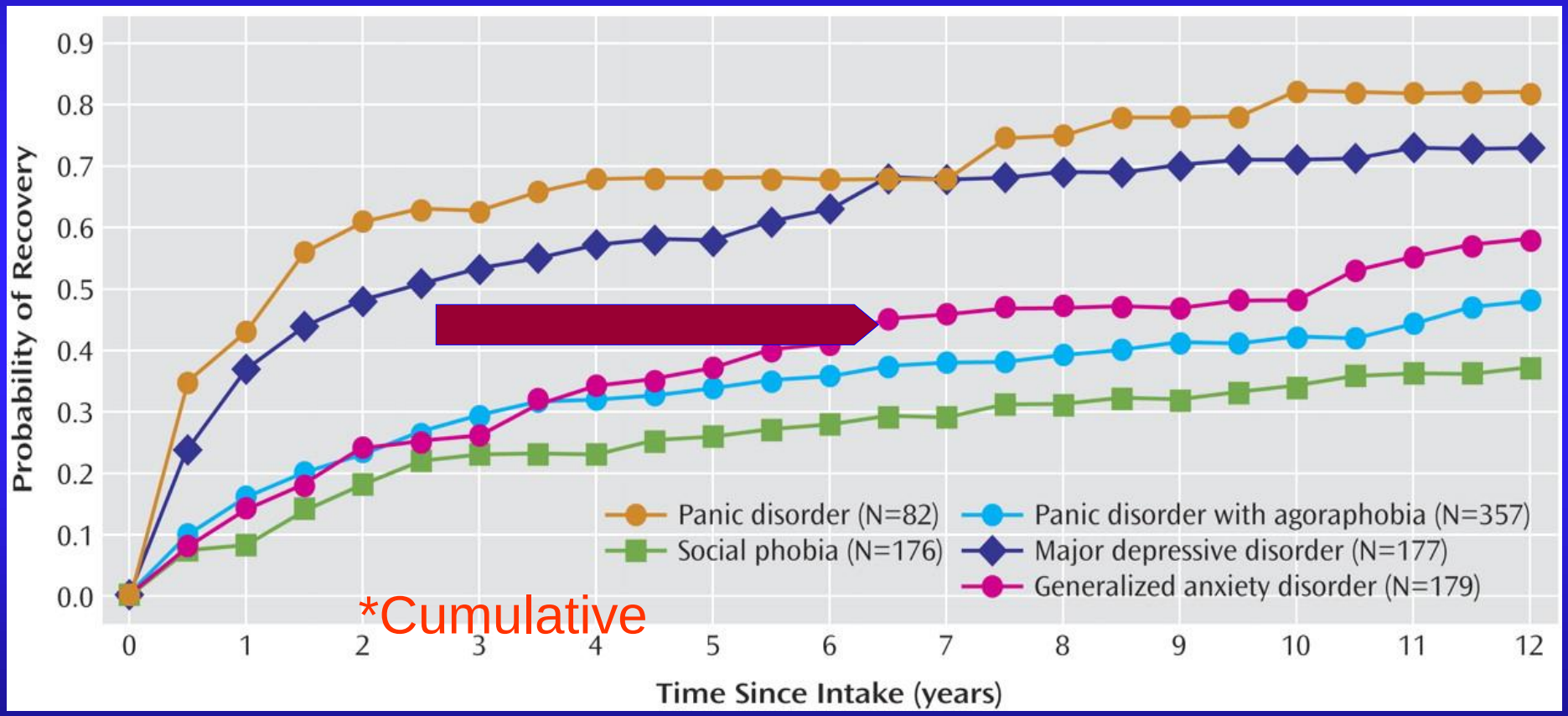
•12-Yr Probability of Remission in GAD

Low rate of recovery and recurrence (See notes)



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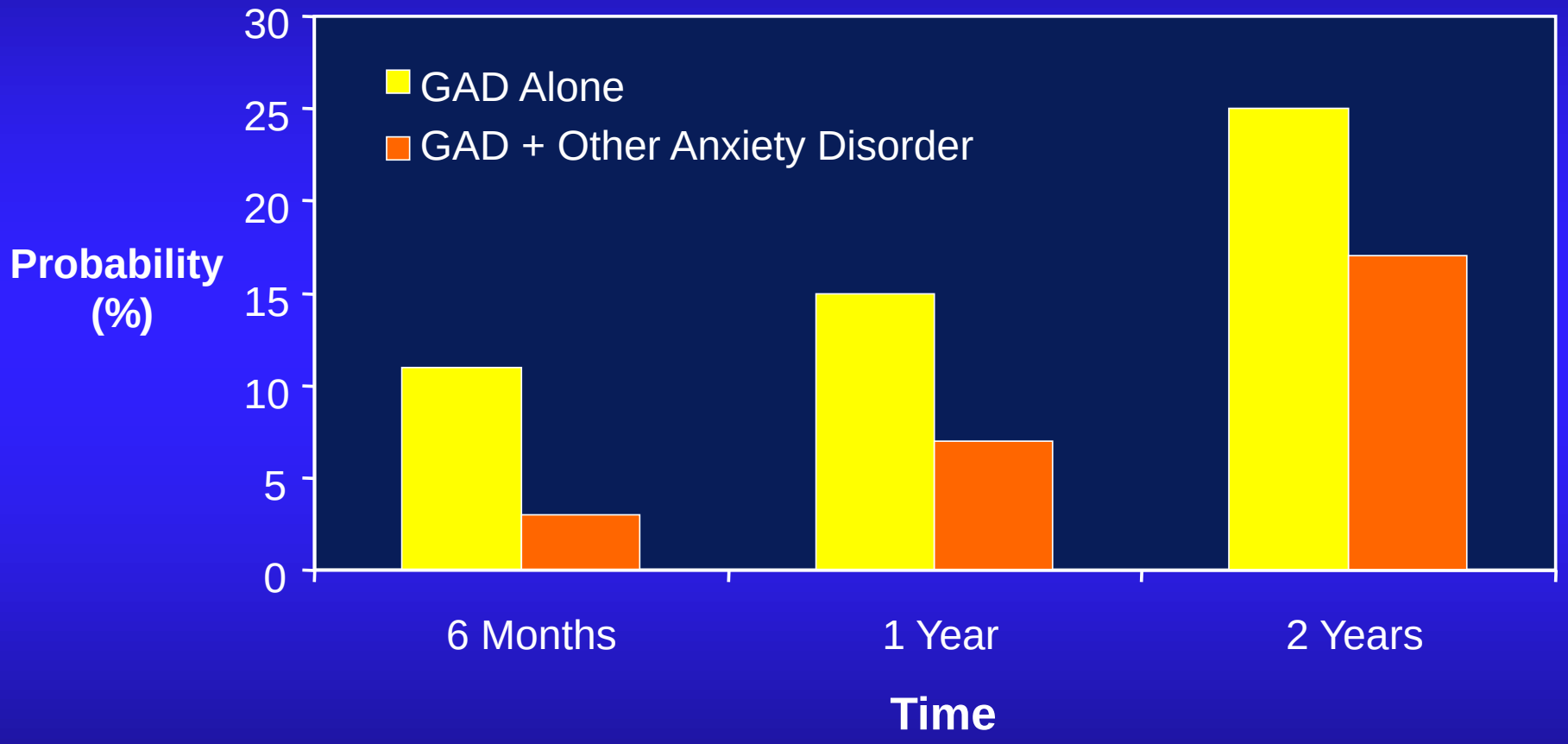
Bruce et al, AJP2005 162:1179-87 Harvard Anxiety Research Program

Low Probability of Remission in GAD

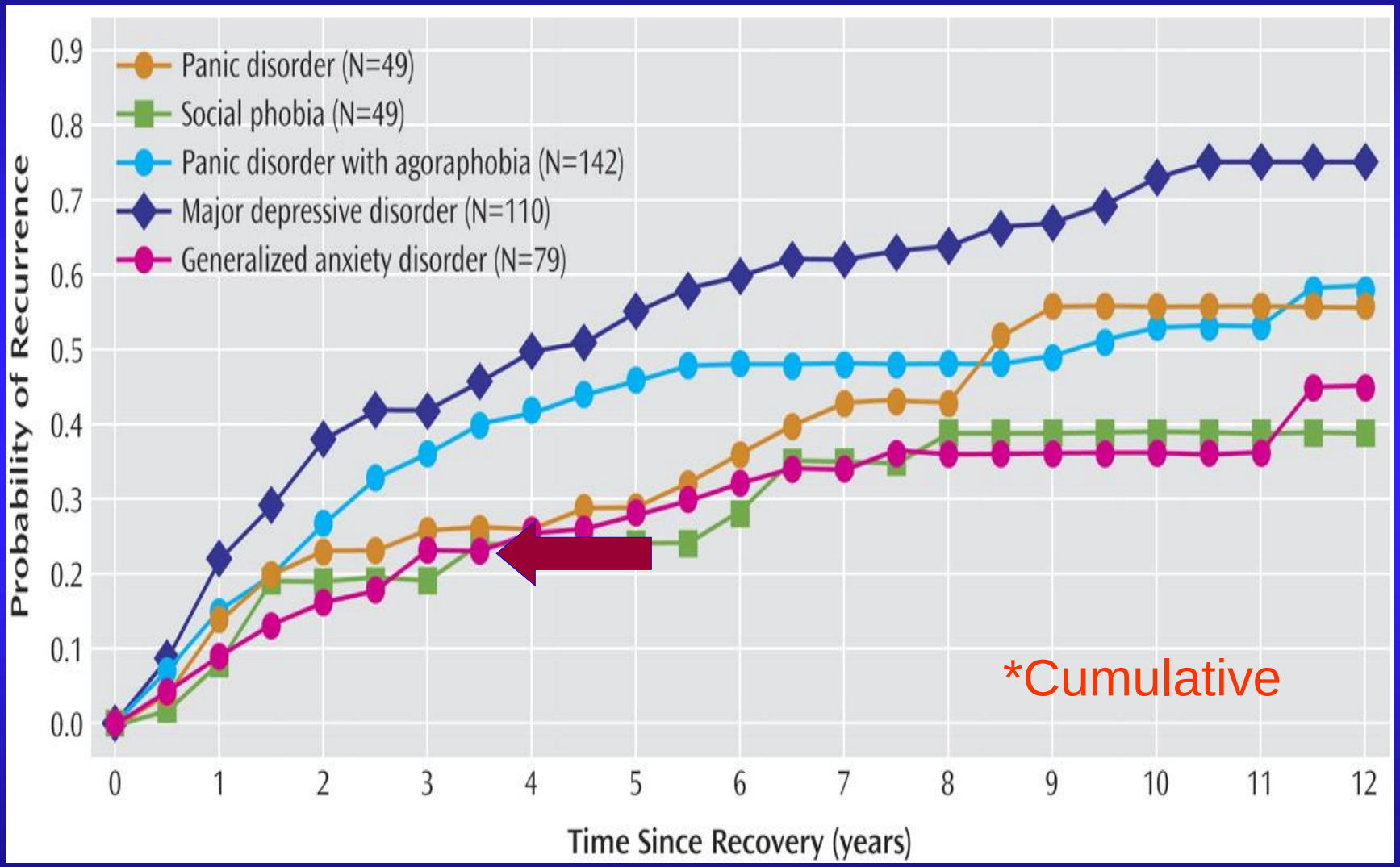
Patients in Harvard Anxiety Research Program
Strict criteria for remission



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

12-Yr Probability for Recurrence

Low rate of remission and low rate of recurrence after remission



Bruce et al, AJP 2005 162:1179-87;Harvard Anxiety Research Program

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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; Kessler et al Arch Gen Psych 2005;62:593Wittchen H-U et al. Arch Gen Psychiatry. 1994;51:355; W

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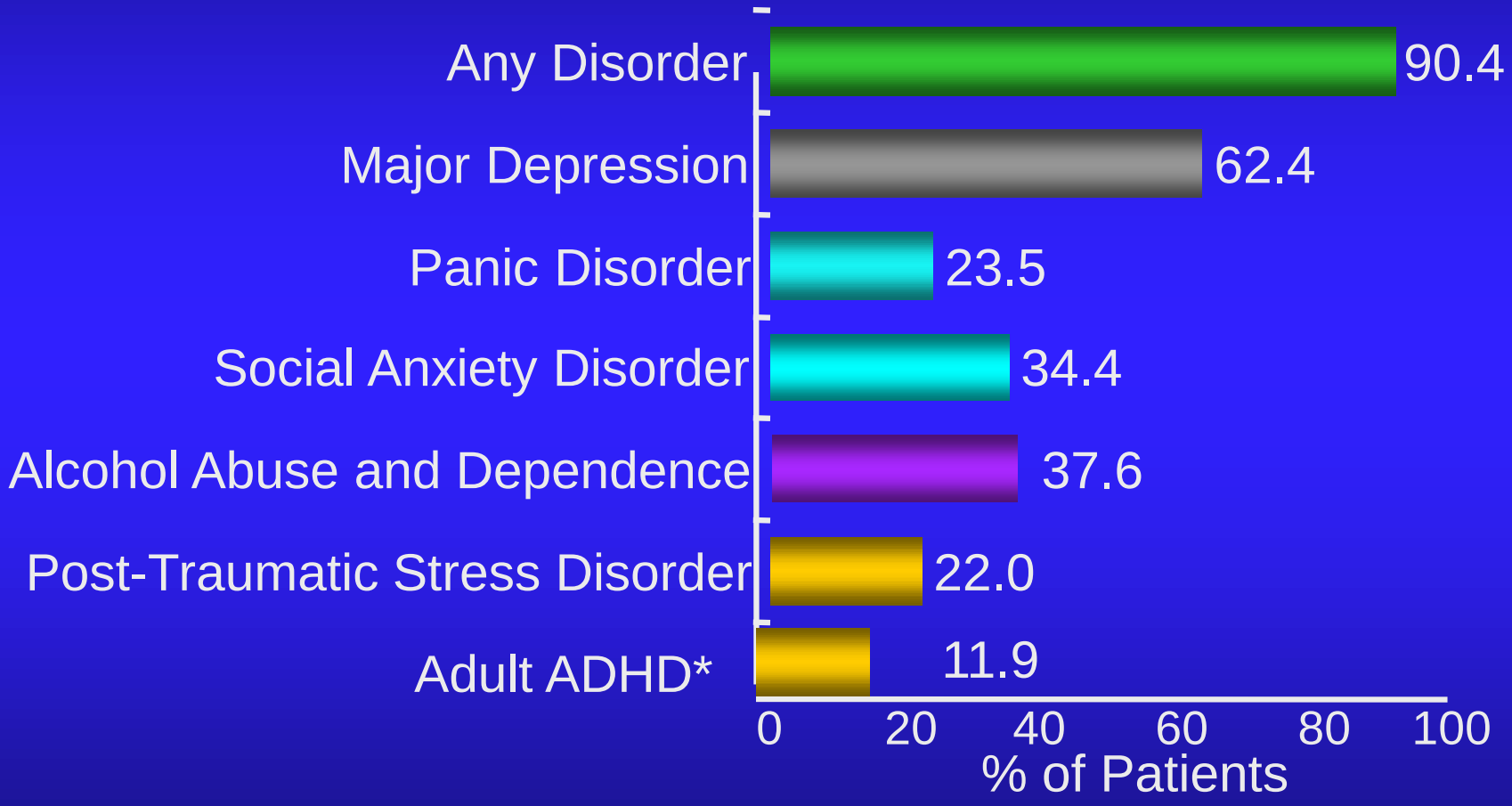
Lifetime Prevalence of Comorbid Disorders in Patients with GAD



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

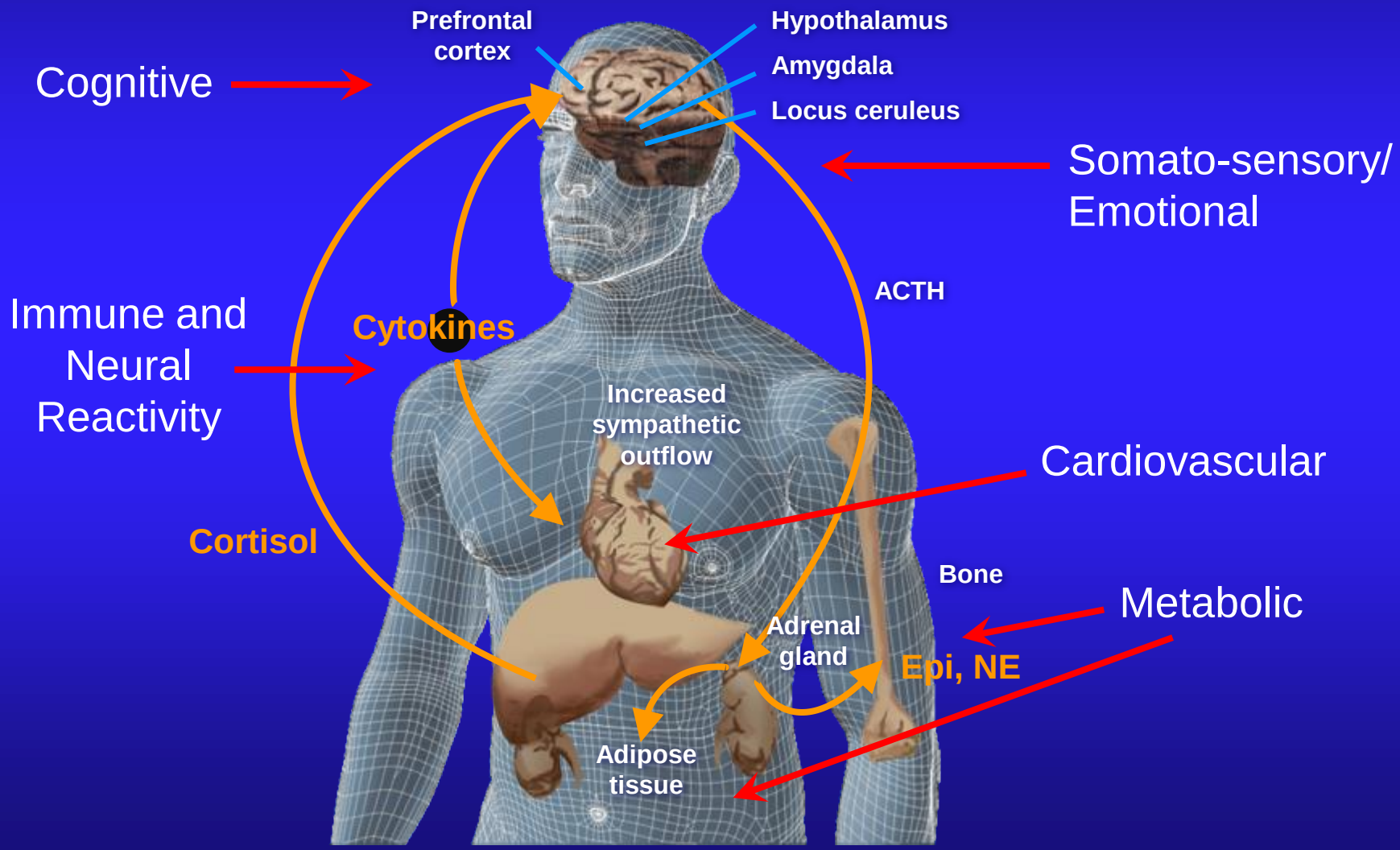
*

GAD with coexisting 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 states 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

Anxiety, Depression, and Stress: Brain and Body Affected



Consequences of Untreated Depression-Anxiety-Stress

- Metabolic Syndrome
  - Hypertension, CAD
  - Central obesity, Type 2 diabetes
  - Hyperlipidemia/hypercholesterolemia
- Immuno-dysregulation
- Neurodegenerative effects
  - (Reversible?)
  - Hippocampal, PFC, amygdala

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

Anxiety and Mood Disorders are Inflammatory Conditions

GAD Is an Independent Predictor of Heart Disease

- Community Survey
  - n=3032 ages 25-72
  - Controlled for MDD,smoking, BMI, recent Rx for cholesterol, DM, HTN
  - CIDI for DSM-III-R
- GAD independently predicted CHD
- May add to risk conferred by MDD

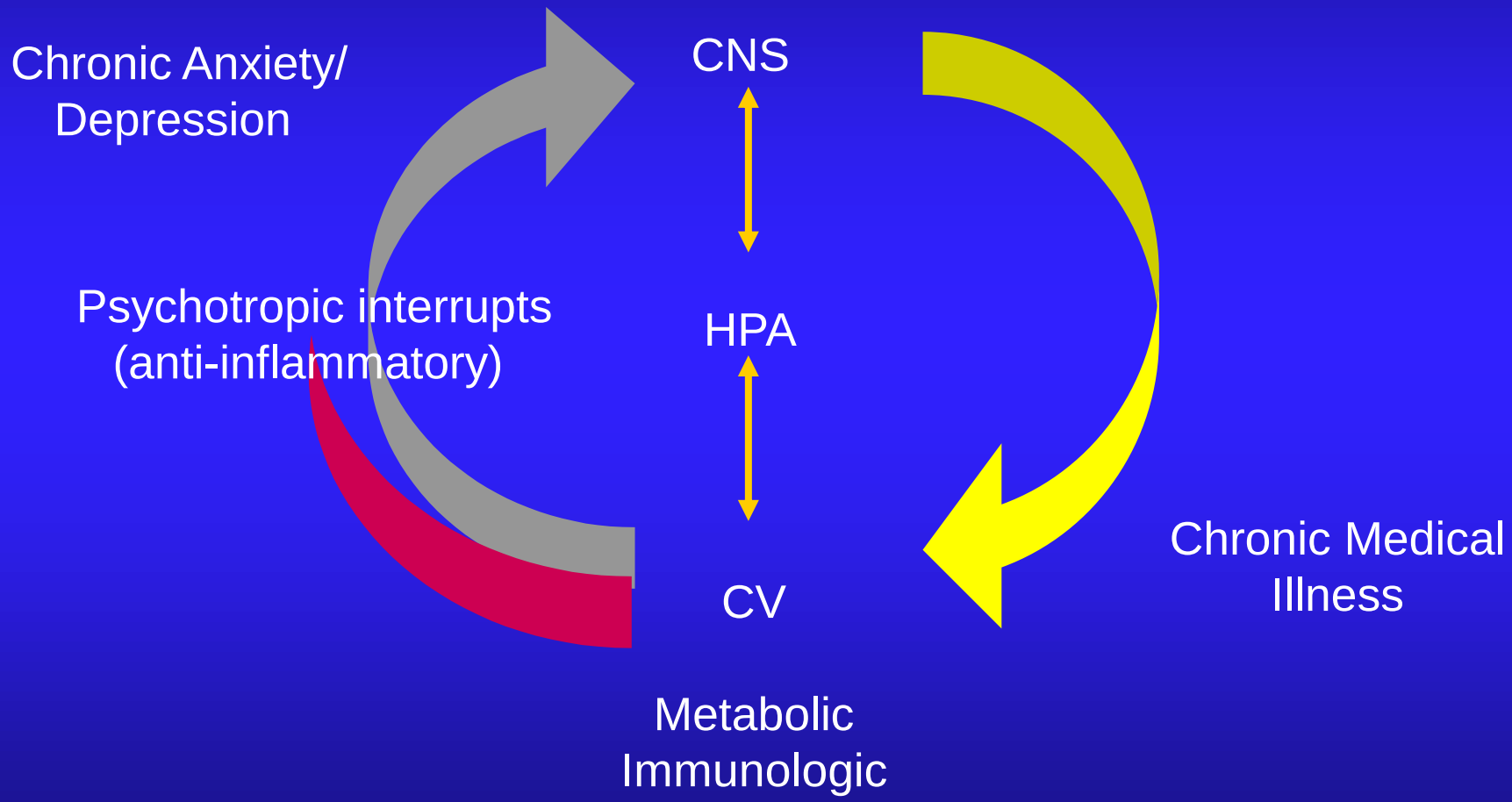
Barger SD, Sydeman SJ . *J Affect Disord*, 2005;88:87-91

Anxiety and Mood Disorders: Adverse Health Effects and Inflammation

- Anxiety/mood disorders ~allostatic load
- Independently confer negative prognosis for health outcome
  - Pain perception
  - Cardiovascular disease
  - Post-MI prognosis
  - Increased production of proinflammatory cytokines demonstrated in mood and anxiety disorders
- Association between inflammation and heart disease strong

Stover E, et al. *Biol Psychiatry.* 2004; 54:184-186; Culpepper J Clin Psych 2009; 70(suppl 2) 20-24)

Medical Illness ↔ Anxiety/Depression Proinflammatory Chronicity Cycle

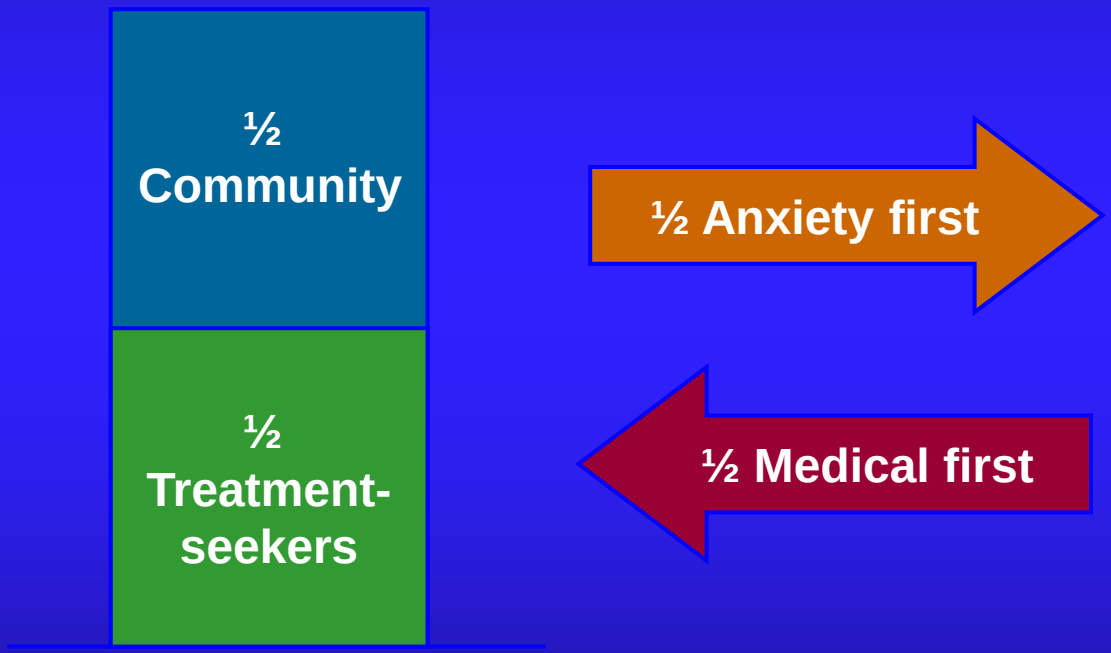


Kiecolt-Glaser JK, et al.. *Psychosom Med.* 2002;64:15-28
Kenis G, Maes M. *Int J Neuropsychopharmacol*. 2002;5:401-412

Anxiety: Worse Long-term Health

German Health Survey (n=4181)

~300 Individuals with GAD or Panic Disorder



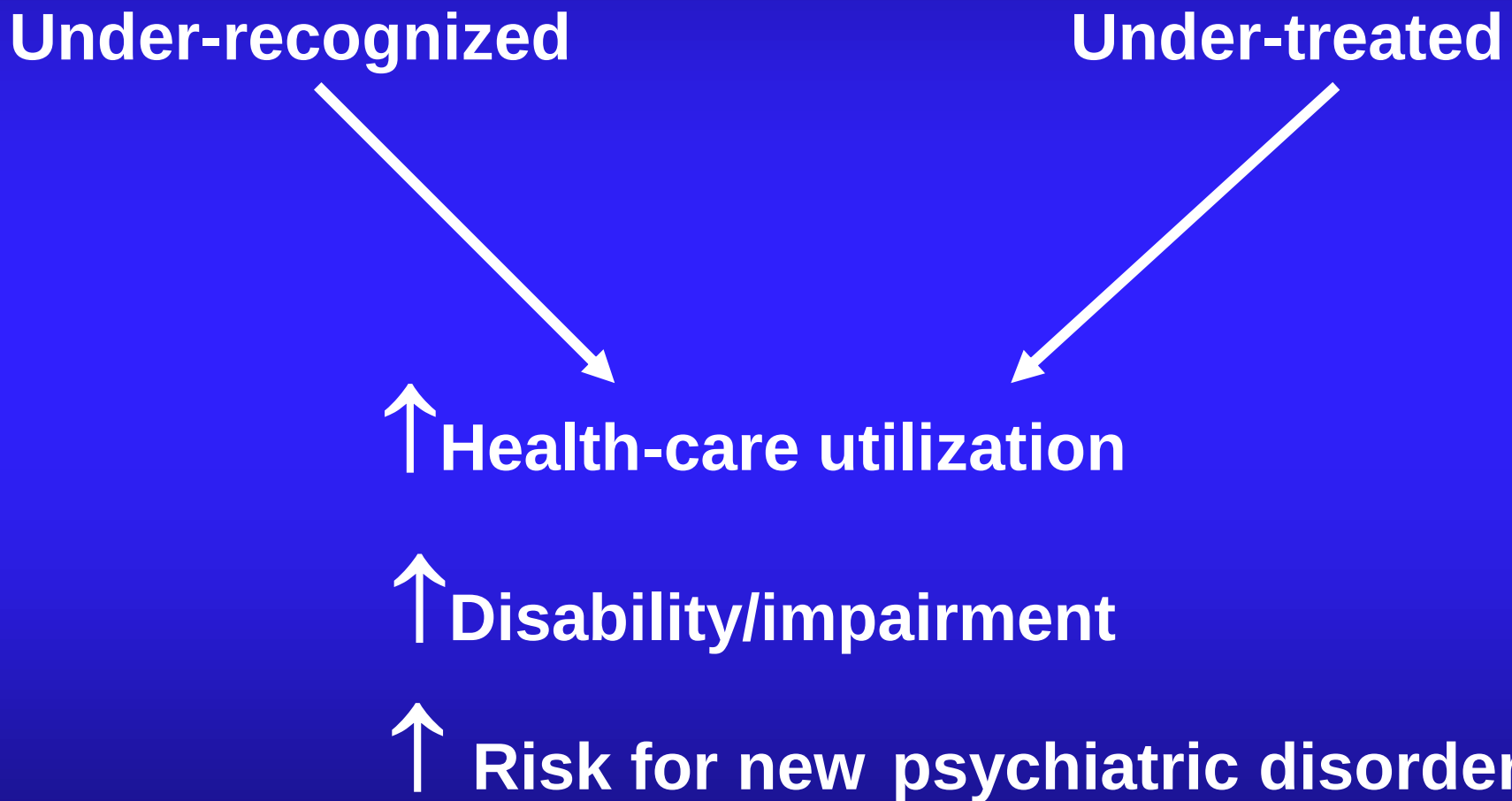
2 to 6 times as many medical disorders vs. controls*

- **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; data supported by McEwen BS. Biol Psychiatry. 2003;54:200-207; Sareen et al Arch Intern Med 2006; 166:2109-16

Generalized Anxiety Disorder (GAD)



GAD Neurobiology
Partial List

- Stress reactivity
- Genetic
  - Gender differences: risk for women 2x men
  - Familial inheritance pattern
  - Same gene, different environments?
  - Polymorphism
- Neurotransmitter differences
  - NE overactivity
  - BZ receptor differences
- Immune Dysfunction
  - Immunosuppression
  - Worry -->pro-inflammatory cytokine release
- Imaging
  - Lower BZ receptor density
  - Increase cCBF following worry

*

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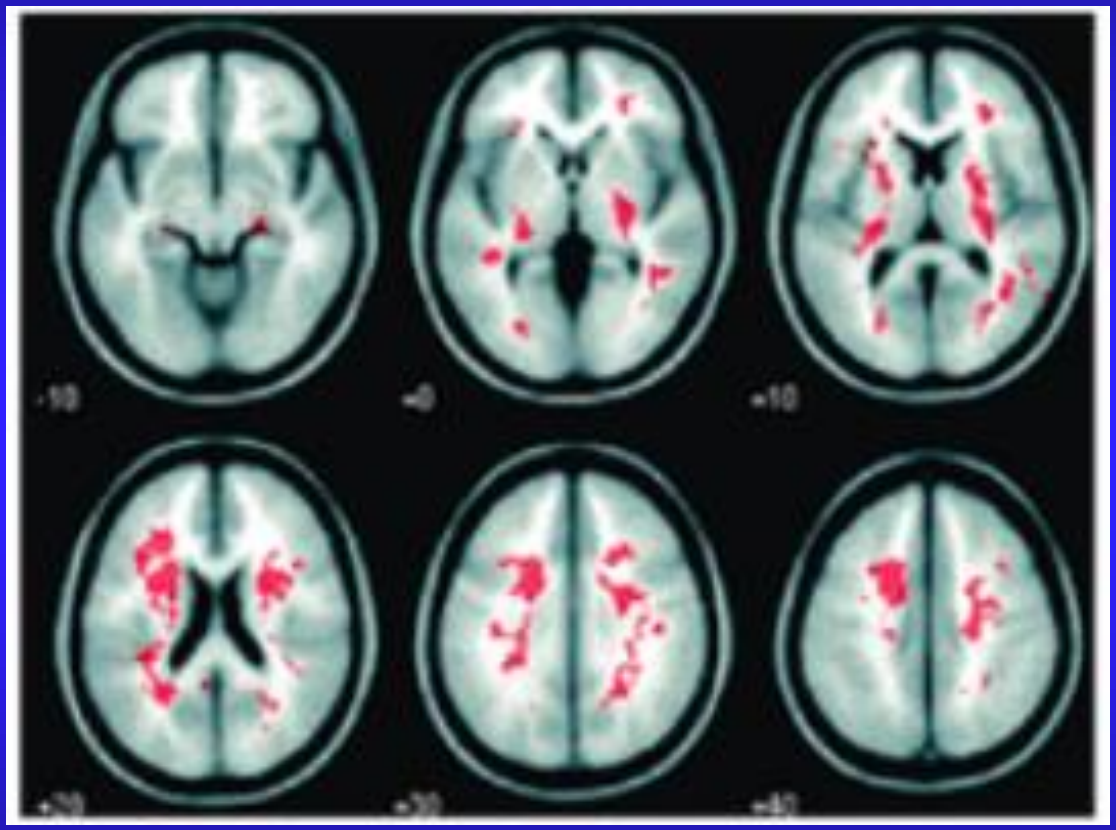
GAD: Increased rCBF in Response to Fear Cues and Worry: Reduced after Citalopram Rx



Abnormally increased activation :PFC, striatum, insula and paralimbic regions after citalopram treatment

Hoehn-Saric et al J Psych Res, 2004; 131: 11-21

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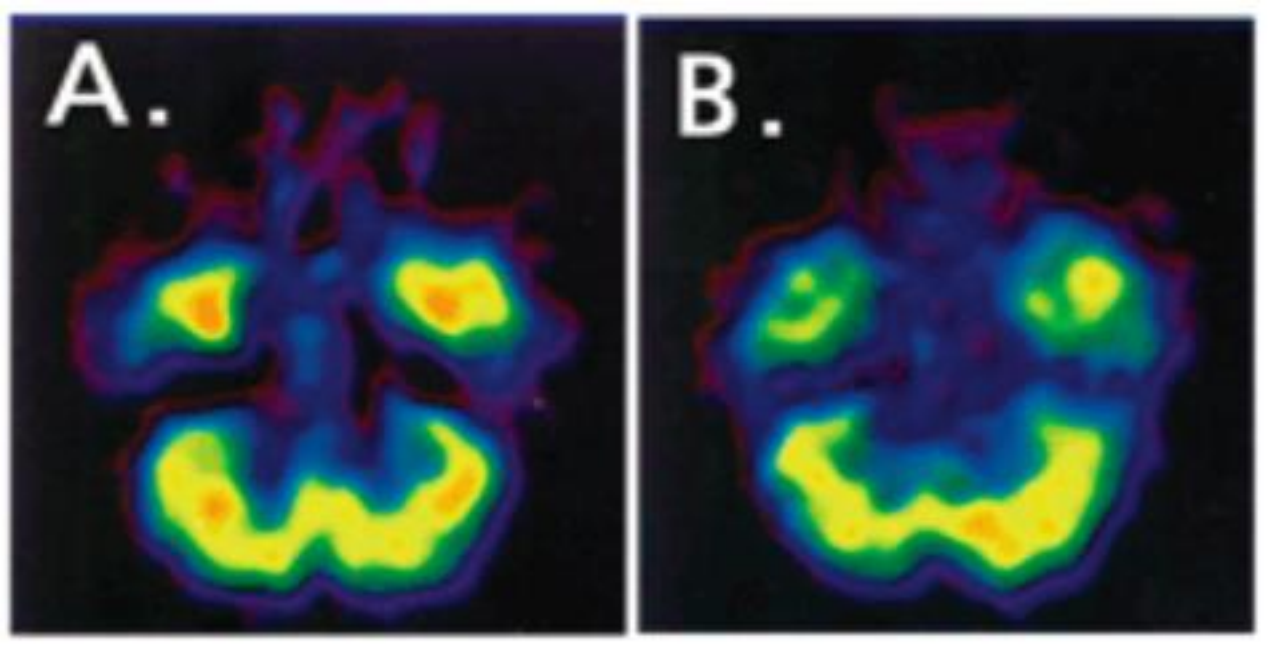
Reduced L Temporal BZ Receptor Density in GAD (A) vs Normals (B) via SPECT



Tilhonen et al, Mol Psych 1997;2:463-71

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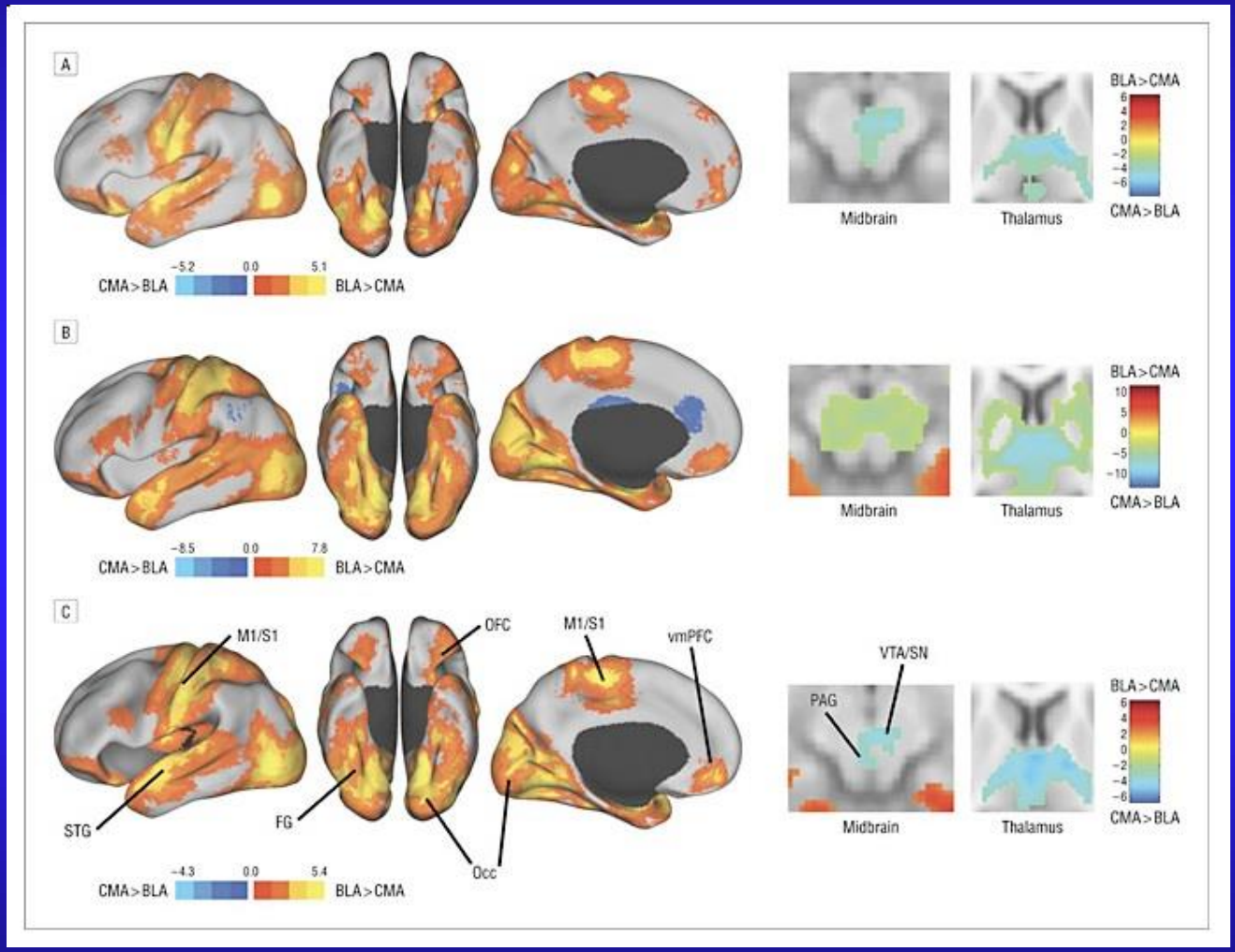
GAD: Different 'Wiring?'

Basolateral Amygda Direct to Cortical Structures



Etkin et al. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in GAD Arch Gen Psych 2009;66:1361-72.

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*

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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; Culpepper J Clin Psych 2009; 70(suppl 2) 20-24

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

Assessing GAD Treatment Effects

Response

≥ 50% decrease from baseline in HAM-A scores 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.

*

Interpreting the Literature

- Efficacy ≠ Effectiveness
- Improving functioning most important
- Short-term studies can't really examine this
  - Acute GAD-look for ≥ 10 point HAM-A decrease
  - Superior to placebo by ≥ 5 points HAM-A
  - Guideline only

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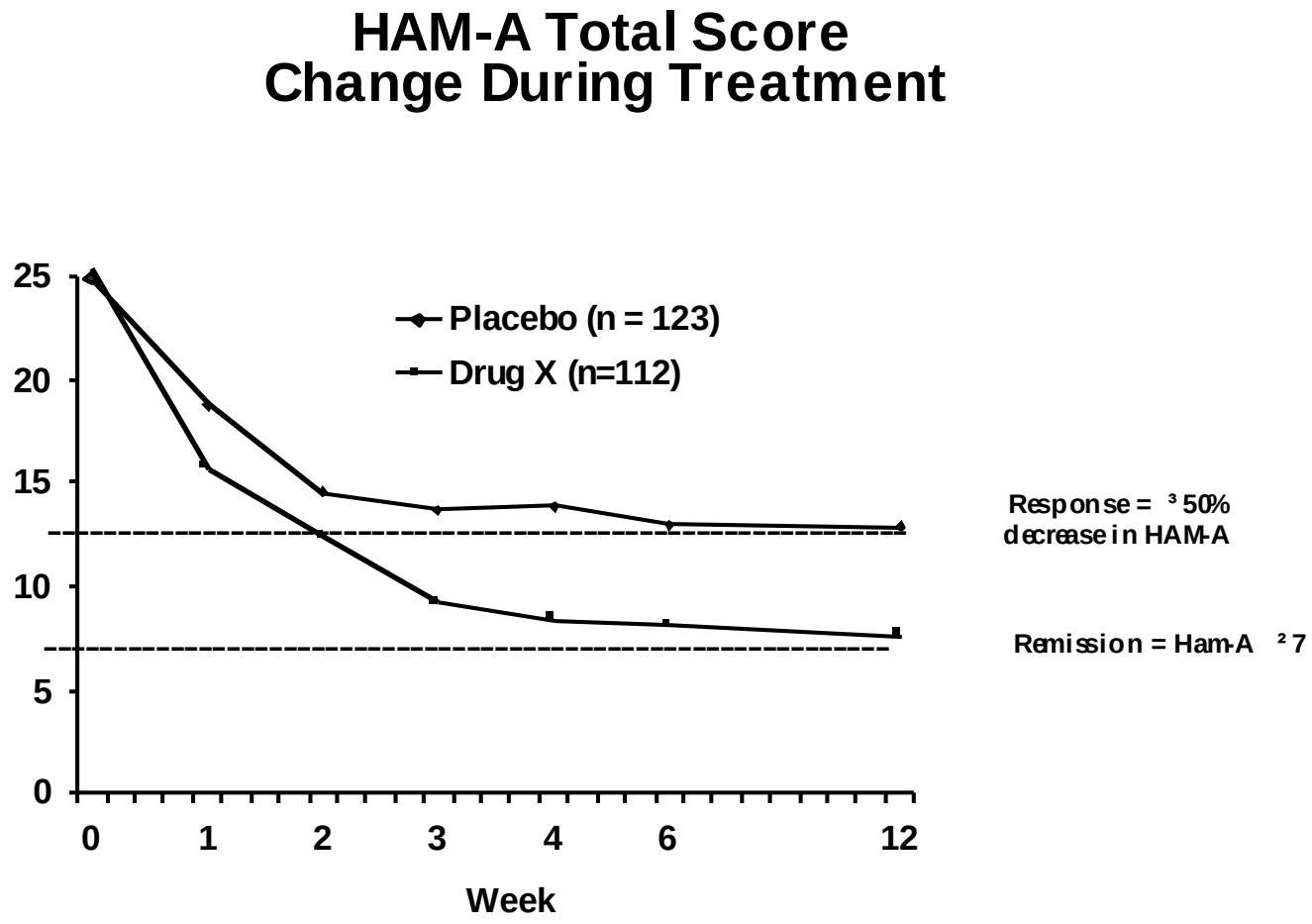
Response vs Remission



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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

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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

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Initiating therapy: treatment considerations

Ease of management

- Safety
- Concomitant meds
- Pregnancy
- Age
- Washout

- Compliance
- Ease of switching
- Ease of discontinuation

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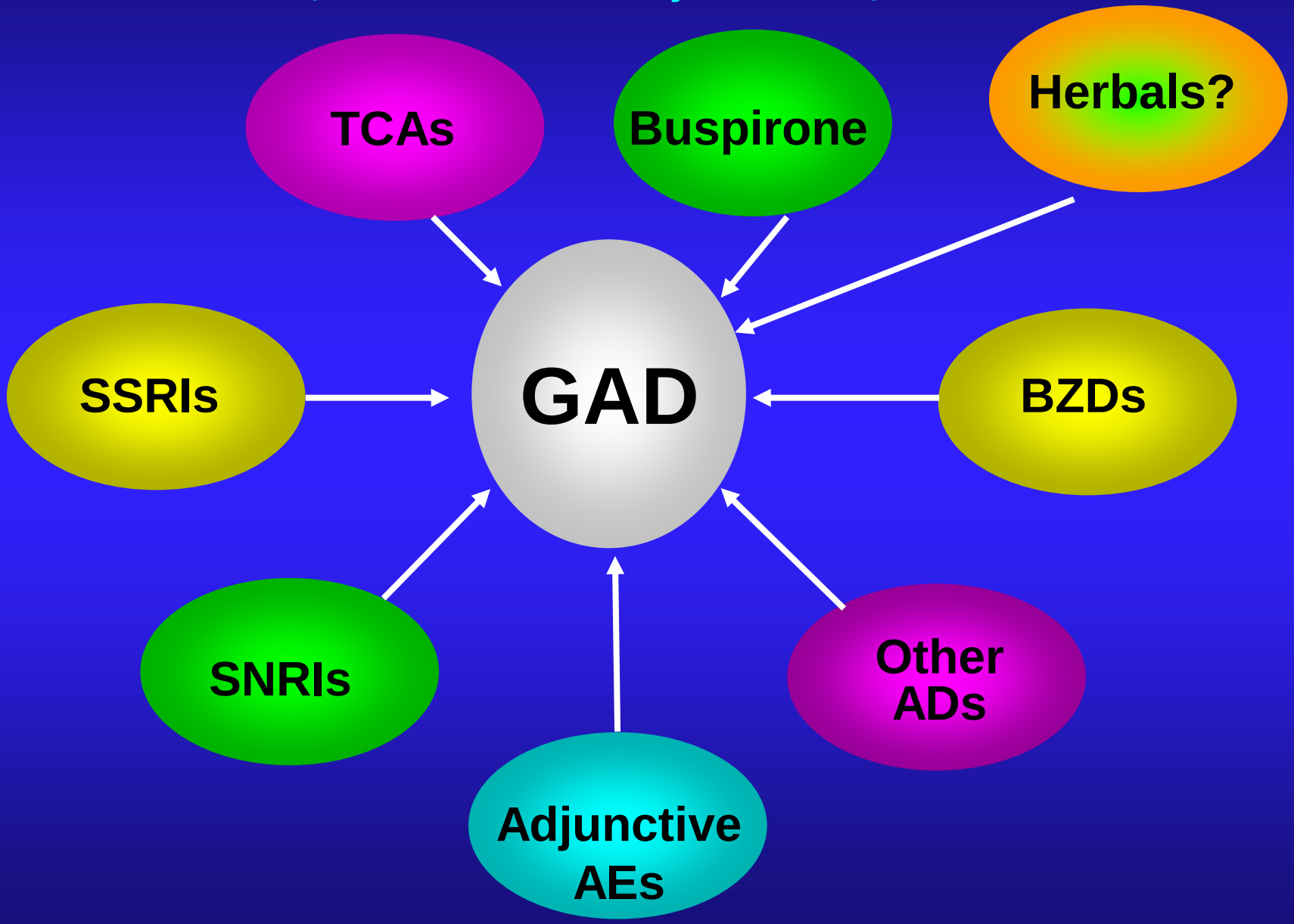
Pharmacotherapy for GAD

Ravindran LN, Stein MB. J Clin Psychiatr2010;71:839-54.



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Traditional Anxiolytics

Limitations

- **Poor tolerability (TCAs, MAOIs)**
  - ***SSRIs & SNRIs-Less than ideal***
  - ***Tolerance***
  - ***"Poopout"***
- **Limited breadth of efficacy**
  - **TCAs, BZDs, azapirones**
- **Lack of antidepressant efficacy**
  - **(buspirone, BZDs)**
- **Safety (TCAs, MAOIs)**

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GAD Treatments
SSRIs and SNRIs

Advantages

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

Disadvantages

- **Delayed onset of action**
- **Early anxiogenic effects**
- **Sexual side-effects**
- **Dose titration (often)**
- **Discontinuation Sx**

*

Antidepressants in Anxiety and Mood Disorders
FDA-Approved -X Effective ≥ 1 RCT -X

SSRIs	MDD	PD	SAD	PTSD	GAD	OCD	PMDD
Citalopram	X	X	X	X	X	X	X
Escitalopram	X	X	X	X	X	X	X
Fluoxetine	X	X	X	X	X	X	X
Fluvoxamine	X	X	X	X	X	X	X
Paroxetine	X	X	X	X	X	X	X
Sertraline	X	X	X	X		X	X
SNRIs							
Venlafaxine	X	X	X	X	X	?	X
Duloxetine	X	?	?	?	X	?	

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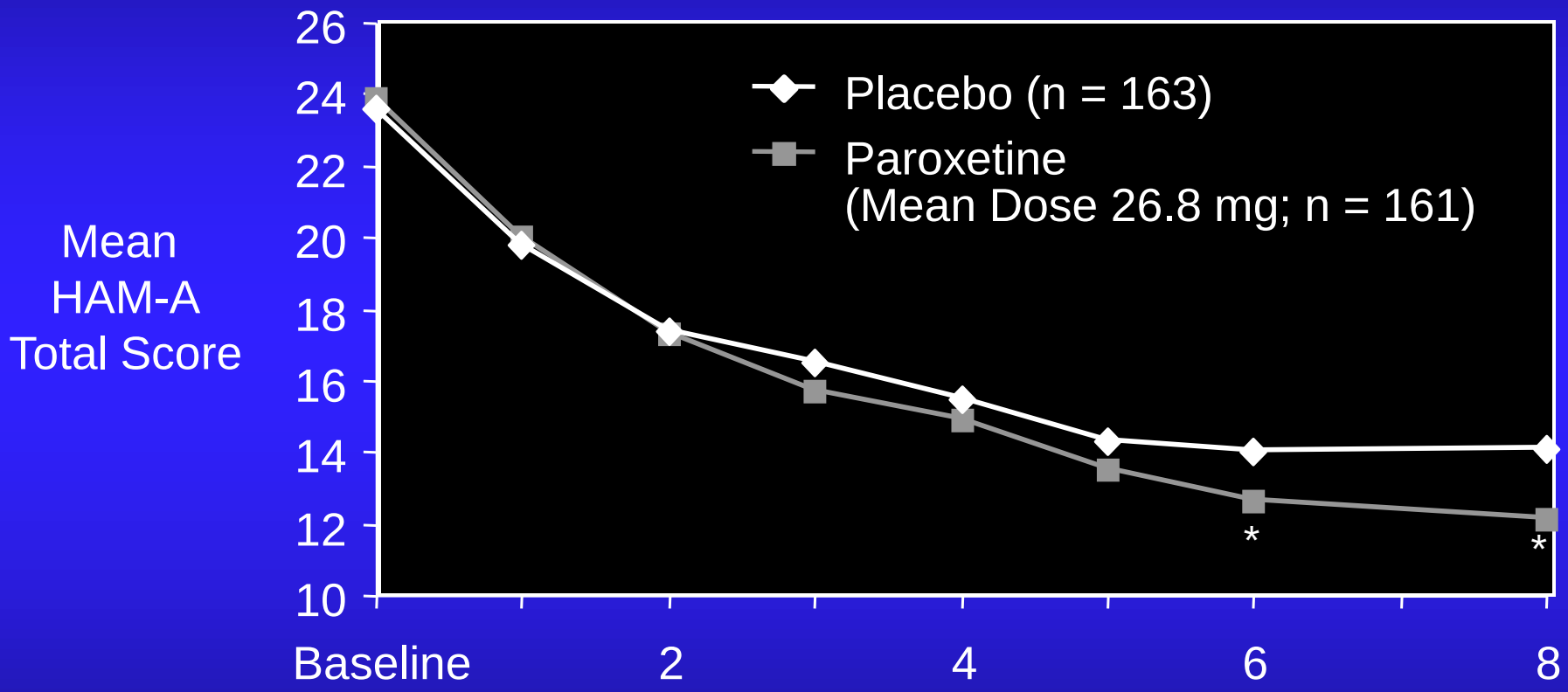
Jefferson , JW Current Psychiatry 2007; 6: 35-6 and Literature Available prior to Nov 2007

SSRIs: Paroxetine for GAD

Flexible Dosing



LOCF dataset.

*$P < .05$ vs placebo.

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

*

Paroxetine: The Best or the Most?

- 1800 outpatients with DSM-IV GAD
  - Placebo-controlled RCTs
    - 3 eight-week studies
    - 6-month relapse prevention
    - Solid design and sample size
- BUT the majority of comparative studies indicate no significant differences among SSRIs in GAD
- Paroxetine is most studied but not superior to other SSRIs or the SNRIs

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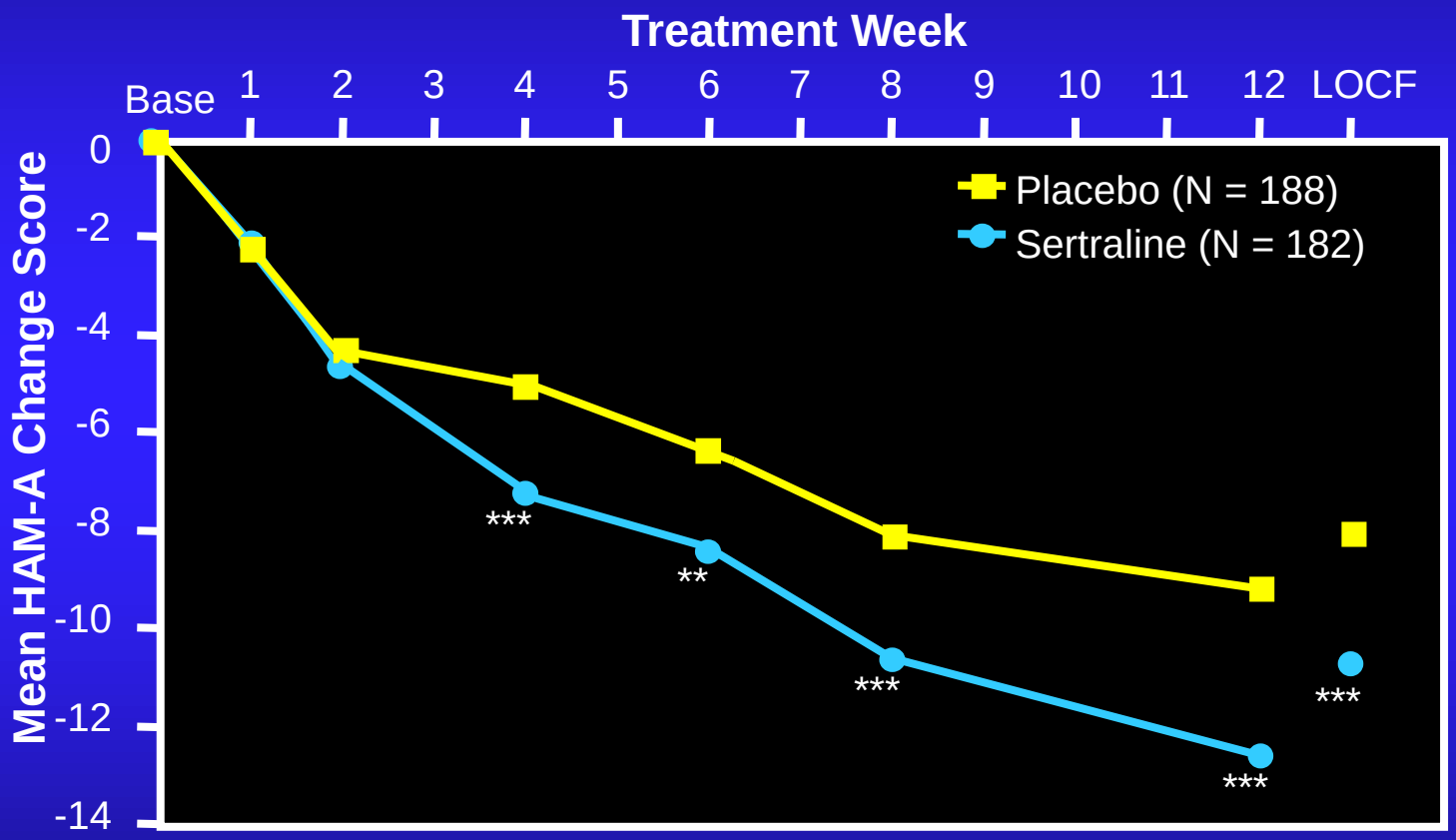
SSRIs for GAD: Sertraline vs Placebo

ITT sample



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

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

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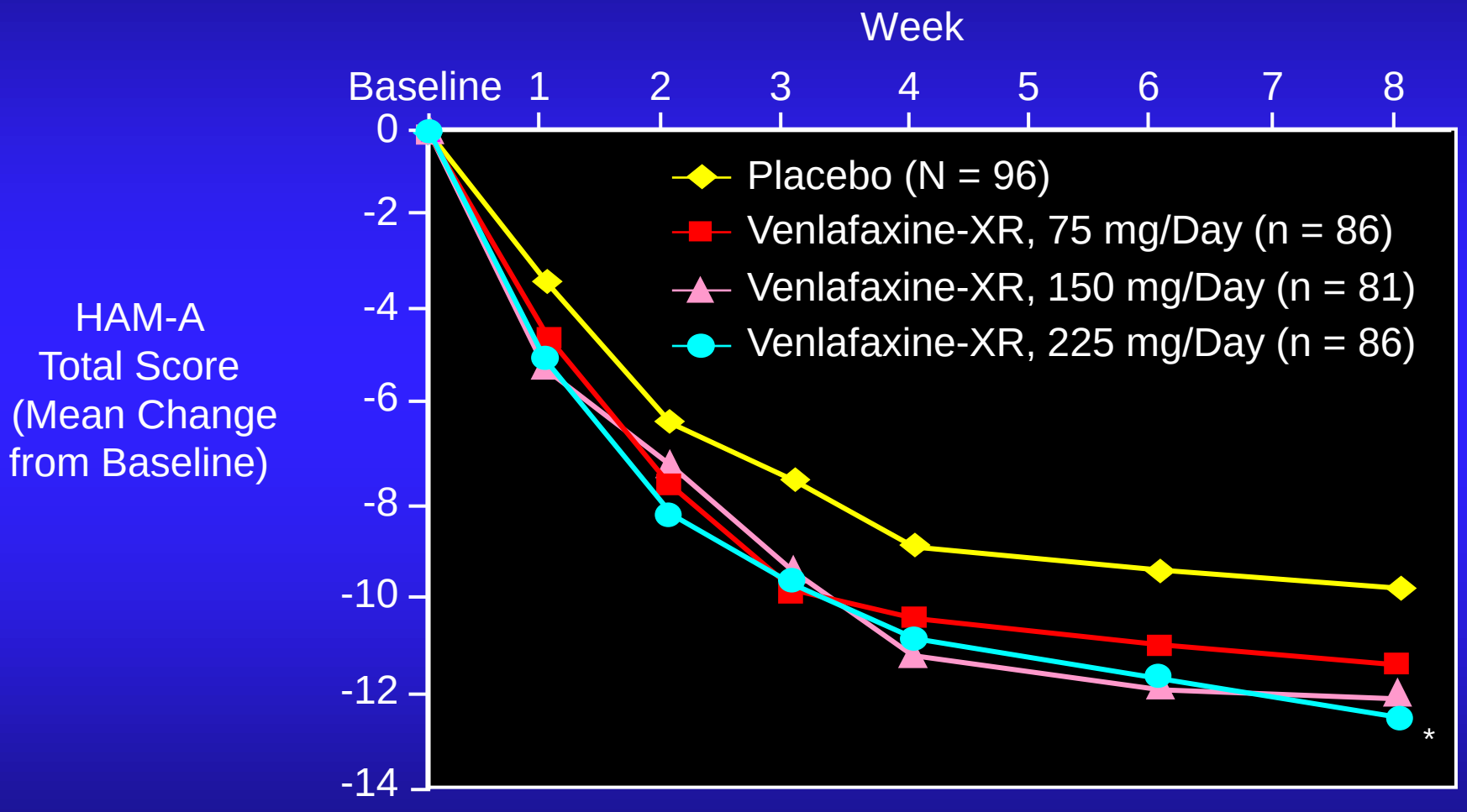
Venlafaxine Treatment of GAD

Fixed-dose Study



*P = .03.

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

Venlafaxine in Childhood GAD

- 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 wks
- Study 1 Significant on primary & some secondary outcome measures
- Study 2 Significant on some secondary, not primary
- Pooled sample-Significant primary outcome overall
  - See notes

*

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

Duloxetine

- **SNRI: binds with high affinity to serotonin and norepinephrine transporters**
  - **More potent than fluoxetine as inhibitor of serotonin reuptake**
- **3 RCTs with placebo completed, 9-10 weeks (see notes)**
  - **60-120 mg daily**
  - **one fixed dose 60 and 120 vs PbO**
  - **2 flexible dosing 60-120 vs PbO**
  - **Improved anxiety, reduced disability and increased quality of life**
- **Effective in preventing relapse of GAD**
- **FDA-approved for MDD, GAD and fibromyalgia**

Karpa KD. *CNS Drug Rev.* 2002;8:361-376; Endicott et al, J Clin Psychiatry 200768: 518-24;

*

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 except clonzepam**
- **Abuse potential in patients w/ Hx drug abuse**
- **Antidepressant effect unreliable**

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

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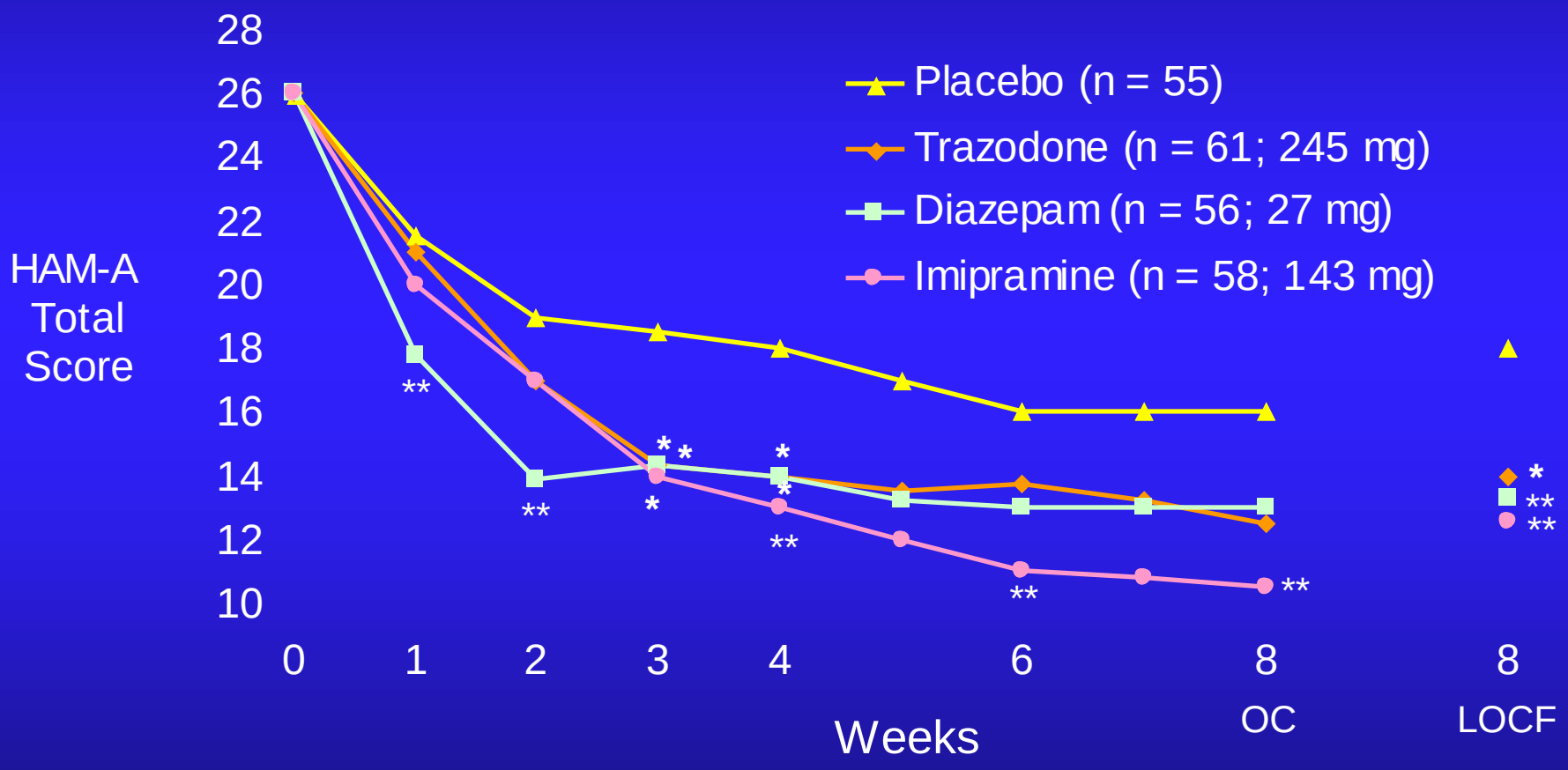
GAD Treatment
Benzodiazepines

Agent	Daily Dosage
Benzodiazepines	**Range (mg)**
Alprazolam	0.75-6
Clonazepam*	1-3
Lorazepam	4-10
Diazepam*	15-20

*Slow elimination, longer to steady-state

*

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

*

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

*

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

*

Other Agents Dosing for GAD

	Agent	Daily Dose, mg
Ca++ Channel mod.	Pregabalin	150-600 (450 for most)
Antihistamine	Hhydroxyzine	50-100
Azapirones	Buspirone	15-60

Long-Term Treatment of GAD

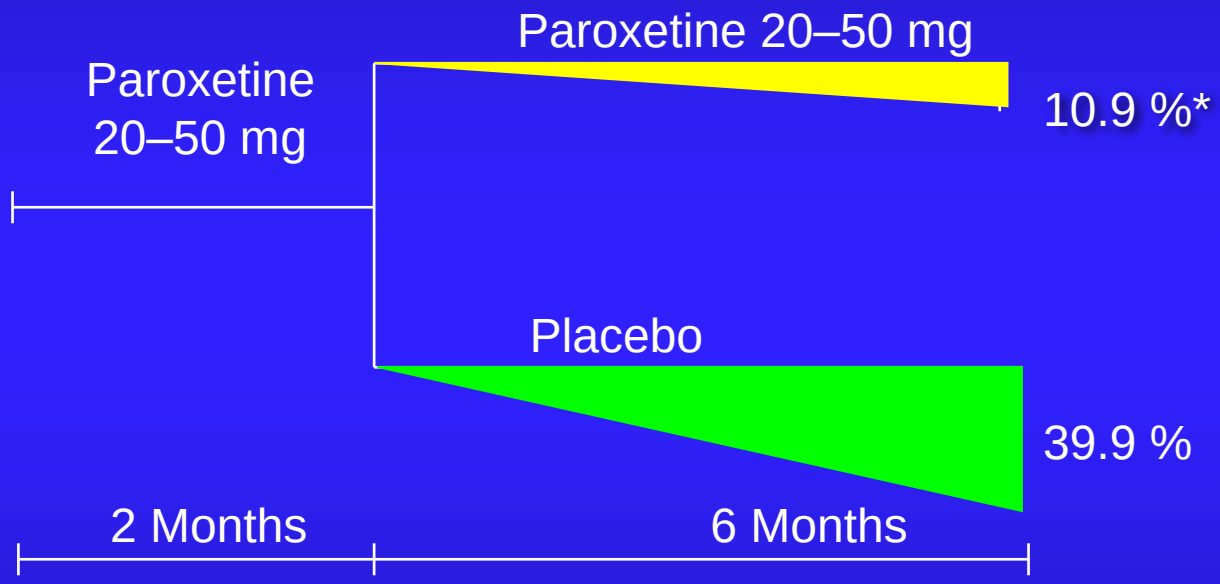
- **Need to treat for long term**
- **Full relapse in approximately 25% of patients 1 month after stopping treatment**
- **60%-80% relapse within 1st year after stopping treatment**
- **Most favorable response to SSRI in RCT maintenance than other anxiety disorders**

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
Donavan et al, **Journal of Affective Disorders 123 (2010) 9–16**.

*

Paroxetine Long-Term GAD Treatment

Relapse Prevention



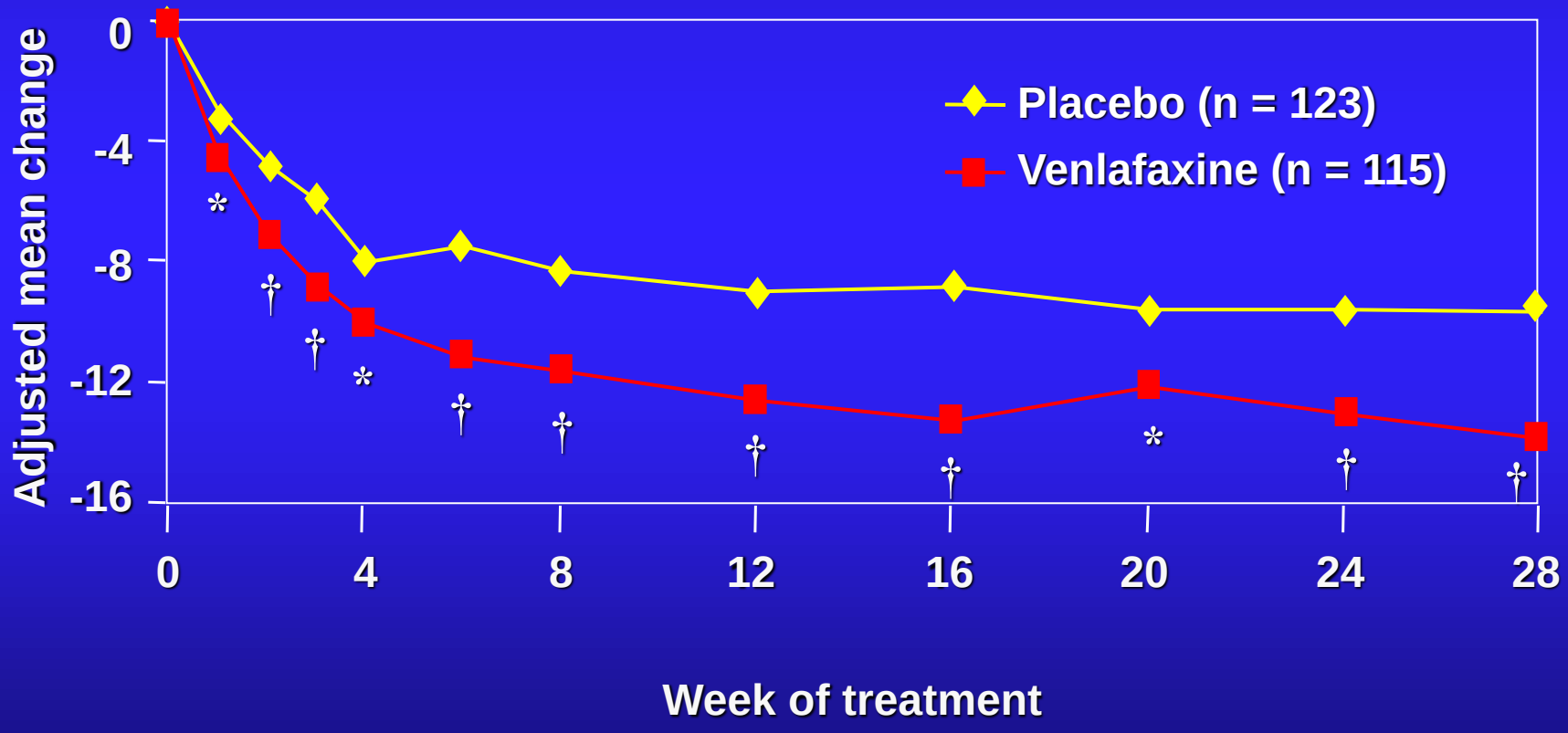
***P* <.001; N = 286/274; LOCF**

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

*

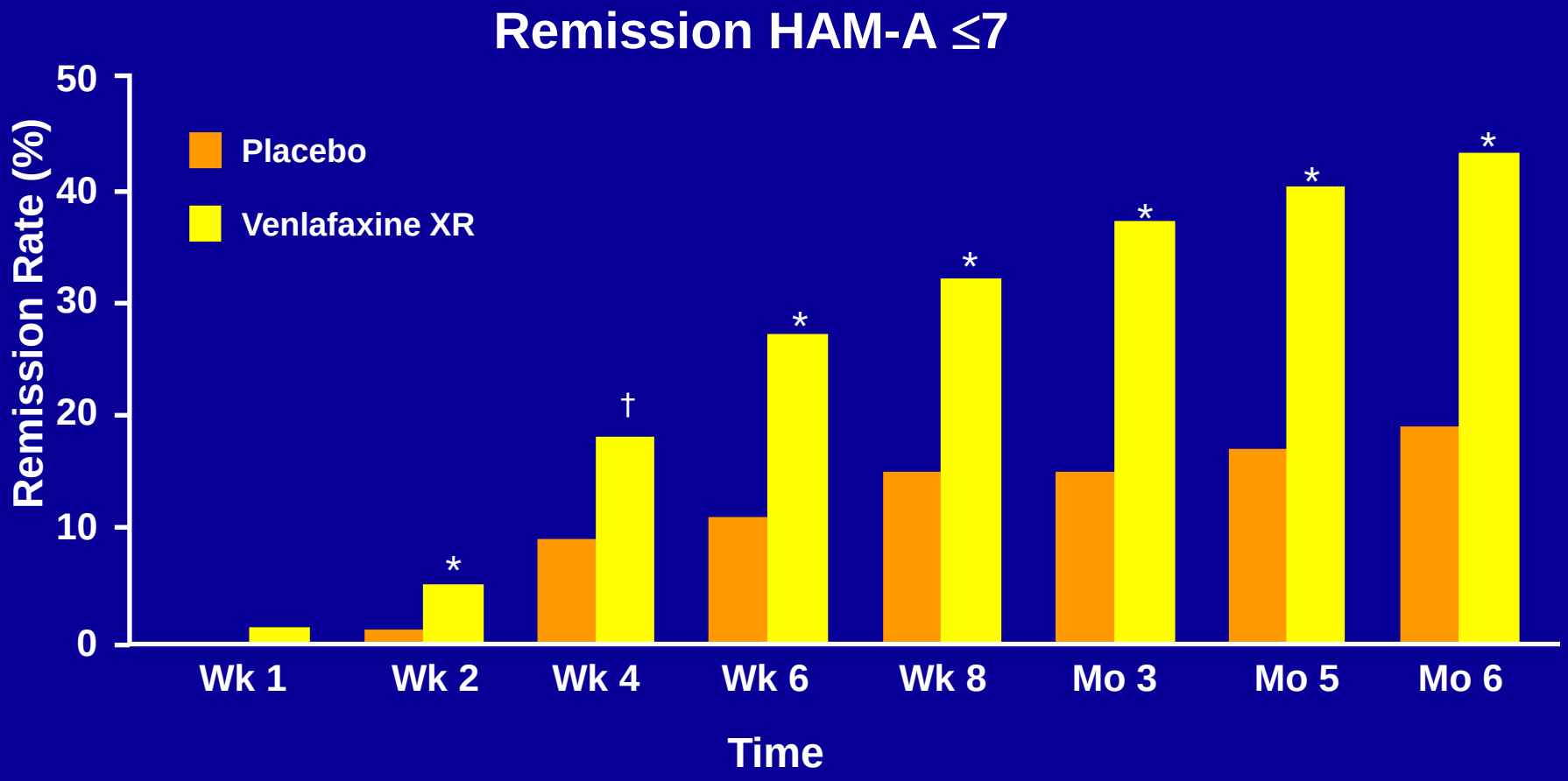
6-Month, Placebo-Controlled Trial of Venlafaxine XR in GAD

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

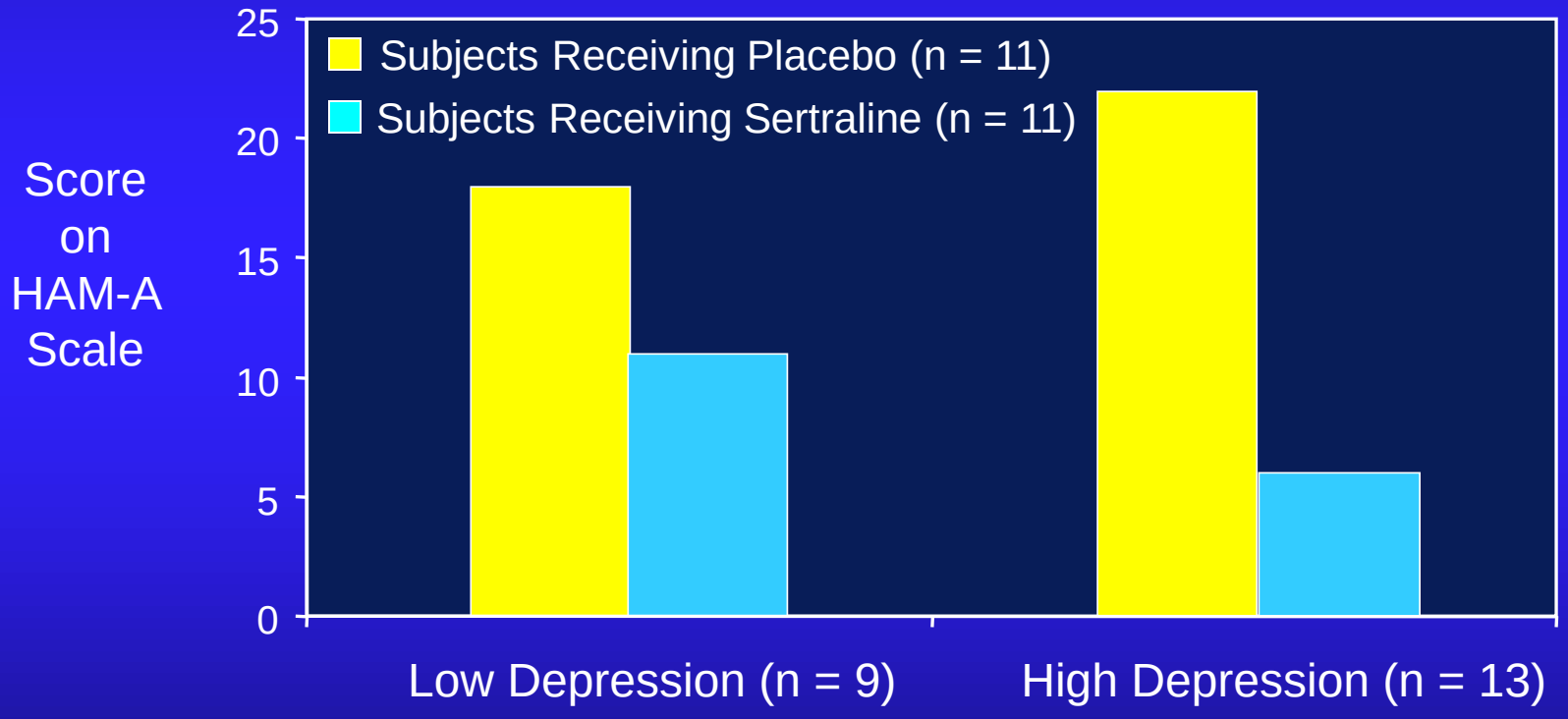
- N = 22
- 2-3 week run-in, 9 weeks of double-blind treatment with sertraline or placebo
- Primary diagnosis of GAD; excluded MDD, OCD, MR, ADD
- Ages 5-17 years (mean 11.7 ± 3.9 years)
- Sertraline dose: 25 mg/d for week 1; 50 mg/day weeks 2-9

*

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.

*

Pregabalin

- Randomized RCT shows 450mg daily (n=170) > Pbo (n=168) for preventing relapse in responders for 24 weeks

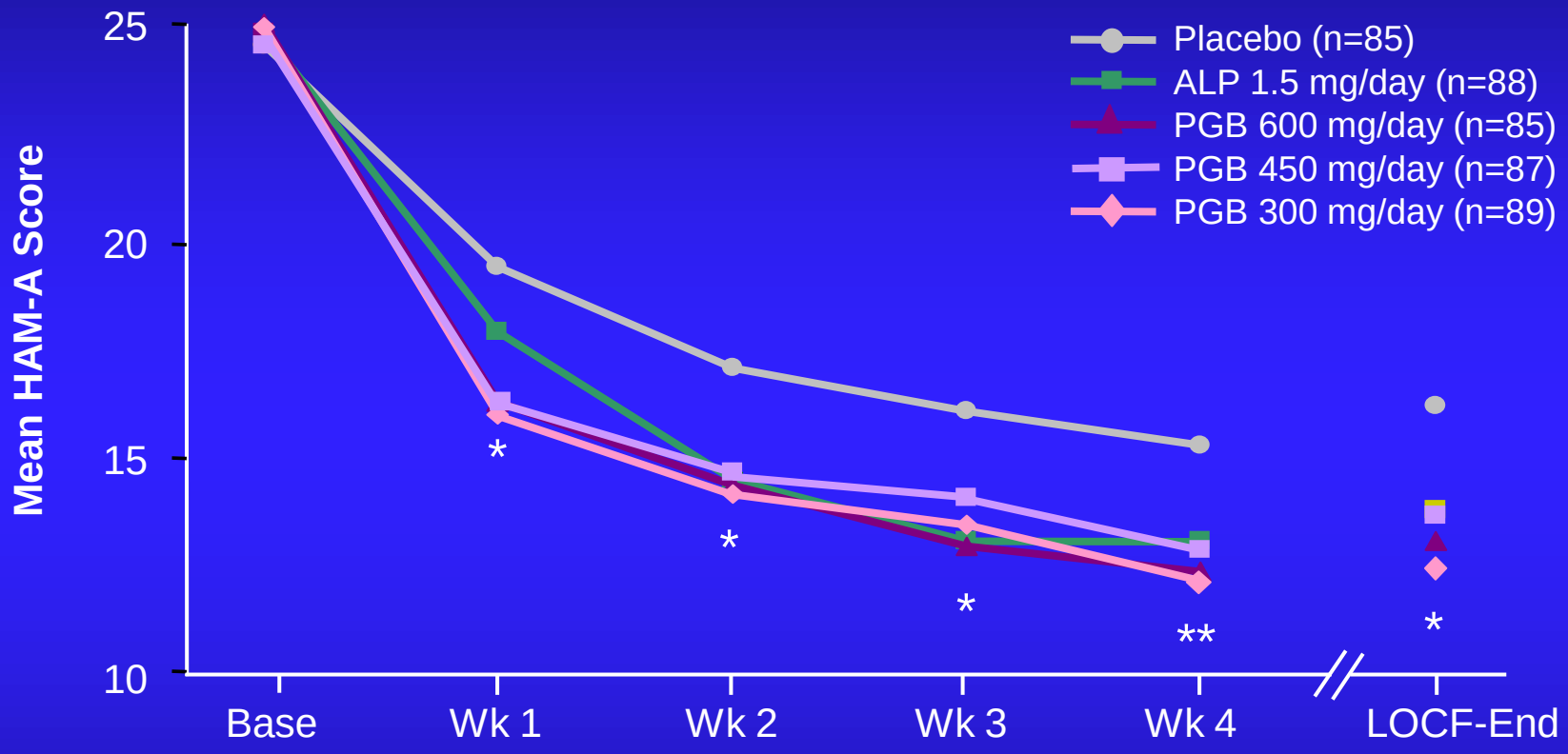
- PGB target
  - Binds to $\alpha_2\delta$ subunit of widely distributed voltage-dependent calcium channels

  - Like gabapentin, reduces calcium influx through trans-membrane ion channel, thus decreasing firing rate of neurons which are firing excessively

- Downstream effect
  - Inhibition (especially under excitatory conditions) of release of rapid excitatory neurotransmitters
    - glutamate, aspartate, NE, DPN, 5-HT, substance P, others

Festner et al In Clin Psychopharmacol,2008; 23:18-28

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



All medications dosed tid.
*$P \leq .05$ vs placebo (ANCOVA) for all medications.
**$P \leq .05$ vs placebo (ANCOVA) for PGB 300 mg/day and PGB 600 mg/day only (OC).

Rickels et al. APA 2002.

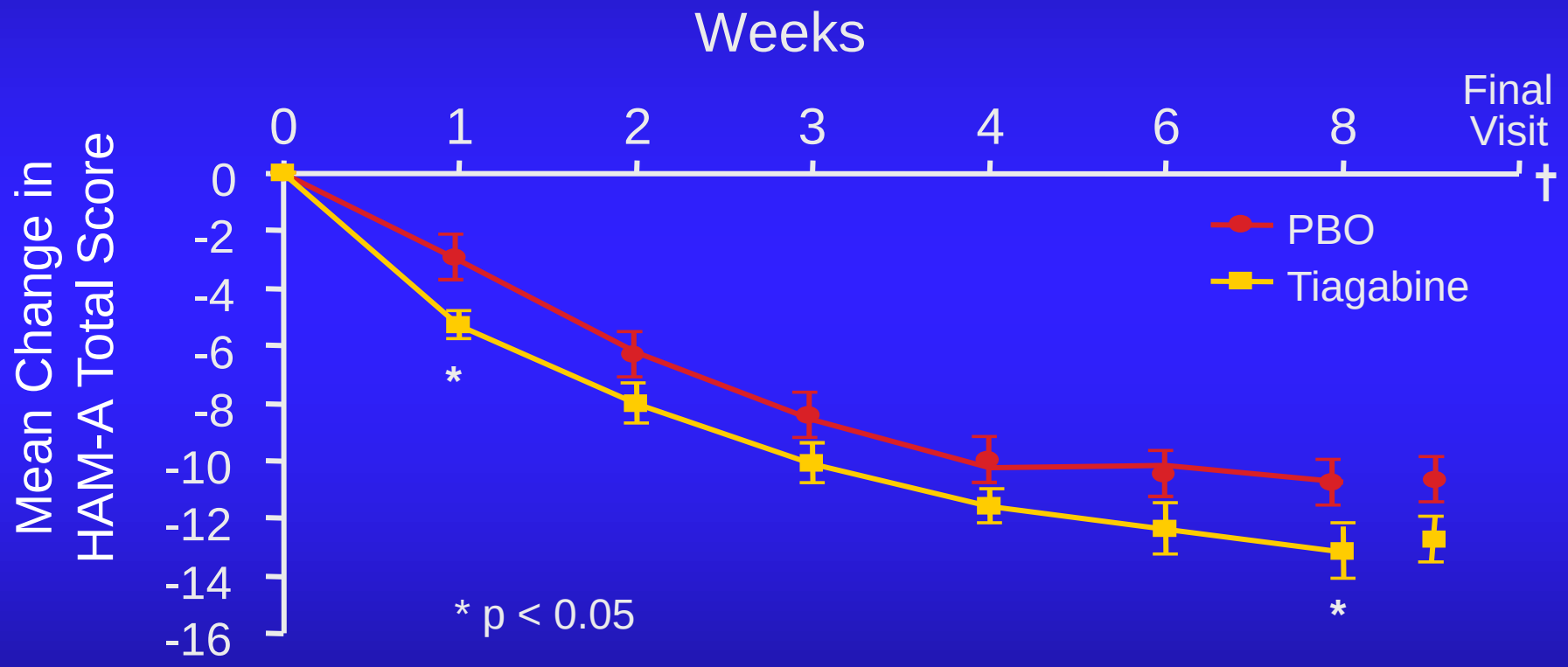
Pregabalin vs. Venlafaxine in GAD

- DSM-IV GAD outpatients(n = 421), 6 wks
- Primary care and psychiatry settings (Europe)
  - PGB 400 or 600 mg/d
  - Venlafaxine 75 mg/day
  - placebo
- Both PGB dosages > PbO by wk 1
- Venlafaxine > PbO by week 2
- 75 mg venlafaxine approved for GAD in Europe
  - Lower doses venlafaxine may be sufficient
  - Discontinuation for side effects ven -20.4%,PGB 400 - 6.2%; PGB 600 - 13.6%; placebo- 9.9%.

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

Selective GABA Reuptake Inhibitor Tiagabine for GAD :

Not diferent than placebo Abandoned development



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

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

Kava (Piper methysticum) 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 possible**
  - **See notes**

Connor KM, Payne V, Davidson JR Int Clin Psychopharmacol 2006; 21:249-53

*

Ginko Biloba (Egb 761) in GAD

- DSM-IIIR GAD (n=82) or DSM-IIIR adjustment disorder with anxious mood (n=25)
- 4 wk placebo controlled RCT (Germany)
- Both 480 mg-Egb(14.3), 240 mg Egb(12.1) > PbO-7.8 on HAM-A
- High dose superior all measures
  - Possible dose-response effect
- May be effective in elderly with cognitive decline
- Well-tolerated
  - Comparable to SSRIs, SNRIs, BZs even with small samples
  - May not have been as ill as pts in US RCTs
  - Downside-formulation may be unreliable at usual sources
  - See notes

Woelk et al, J Psych Res 2006

*

Strategies for Refractory GAD

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

* Most suggestions from clinical experience and Coplan et al JCP 154 (supp) 63-74,1993; Pollack et al, Biol Psychiatry 2006;59:211-215; Stein DJ CNS Spectrums, 2005 (Dec); Snyderman et al J Clin Psychopharmacol 2005; 25:497-499

Quetiapine Monotherapy for Anxiety

- FDA did not approve indication for quetiapine monotherapy for GAD and MDD (4/09)
  - Despite positive short-term studies
- Risk for continuous exposure did not warrant approval
  - Sudden death
    - Dose-related for both atypicals and typicals
    - Samples of >40,000 each group
    - Former users -- no increased risk
  - Metabolic consequences
    - Illness being treated long-term may contribute

Sudden Death Ray et al NEJM 2009; 360:225-35

FDA http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4424b2-01-FDA.pdf

CBT for GAD

- Cochrane Review, 2007
  - 25 studies, total n =1305
- CBT vs.
  - Treatment as usual (TAU) /waiting list (WL) (13 studies)
  - Other psychological therapy (12 studies)
- CBT superior to TAU or waitlist
  - CBT " very effective" in for secondary symptoms
  - Group CBT Rx , elderly : higher dropout rate
- CBT vs. other psychological treatments -unclear
- None were long-term
- Comparative studies with medication not yet done
  - See notes

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

*

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.

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?

Answer #1

TRUE!

Answer #2

Major Depressive Disorder

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.

Answer #4

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

Answer #5

60-80%