Anxiety Disorders

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Matthew Macaluso, D.O. has conducted clinical trials research as principal investigator for the following pharmaceutical companies over the last twelve months:

1. Acadia
2. Allergan
3. Alkermes
4. AssureRx/Myriad
5. Eisai
6. Lundbeck
7. Liva Nova
8. Janssen
9. Neurim
10. Otsuka
11. SAGE pharmaceuticals
12. Suven

All clinical trial and study contracts were with and payments made to the either the University of Alabama at Birmingham Medical Center or the Kansas University Medical Center Research Institute.

From April 2019 to June of 2020, Dr Macaluso was a member of the speaker bureau for Janssen pharmaceuticals (Spravato/esketamine).

Dr Macaluso has also received royalties from Springer Nature for his work as co-editor of the textbook titled *Antidepressants: From Biogenic Amines to New Mechanisms of Action*. This book was published in May of 2019.

Generalized Anxiety Disorder
Panic Disorder

Generalized Anxiety Disorder

Question

True or False

Women have a higher lifetime prevalence of GAD as compared to men.

Question

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

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 5 GAD Diagnostic Criteria

- Excessive anxiety and worry
- 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

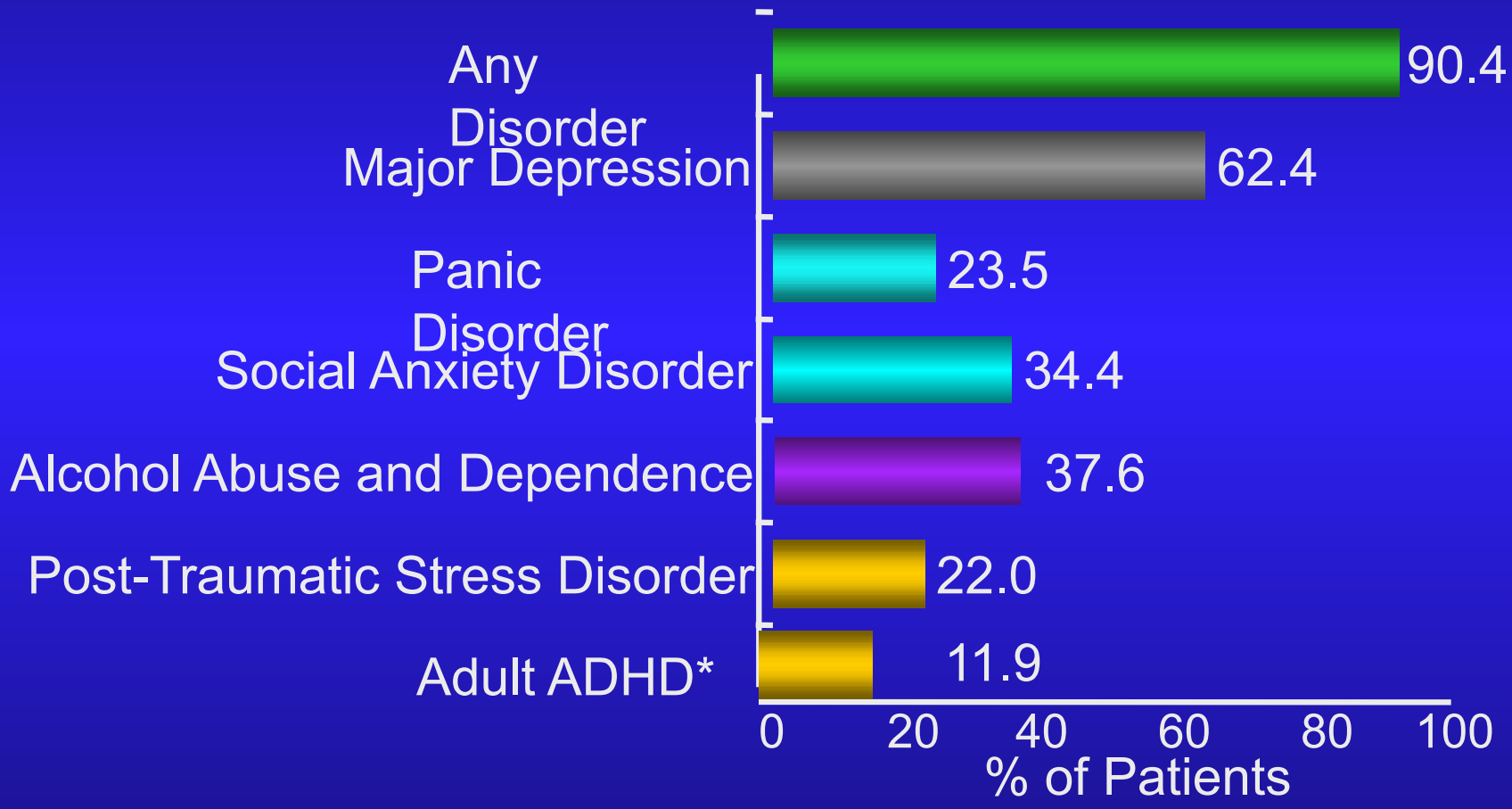
DSM 5. Washington, DC: American Psychiatric Association. 2013.
Kessler et al Psychol Med 2005; 35:1073-82*-see notes

DSM 5 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.

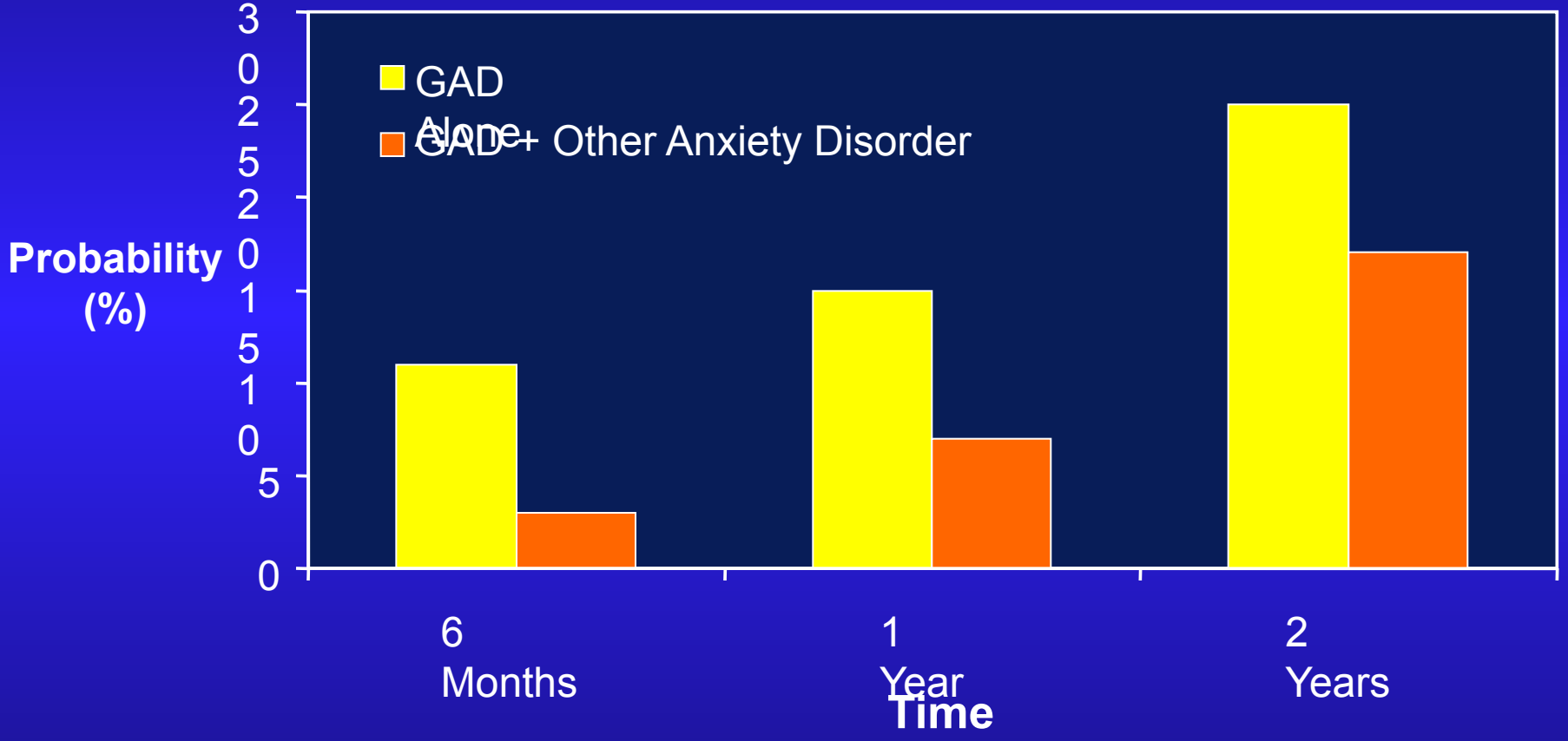
Lifetime Prevalence of Comorbid Disorders in Patients with GAD



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.*

Low Probability of Remission in GAD

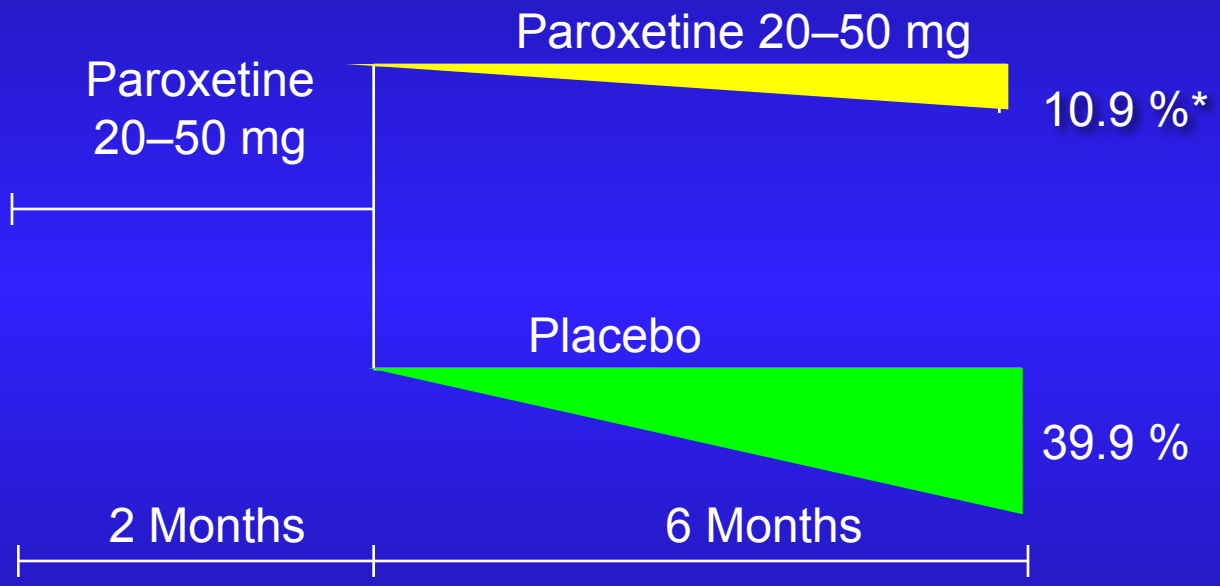
Patients in Harvard Anxiety Research Program



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

Paroxetine Long-Term GAD Treatment

Relapse Prevention



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

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

*

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

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

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

Classic 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)**

*

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**

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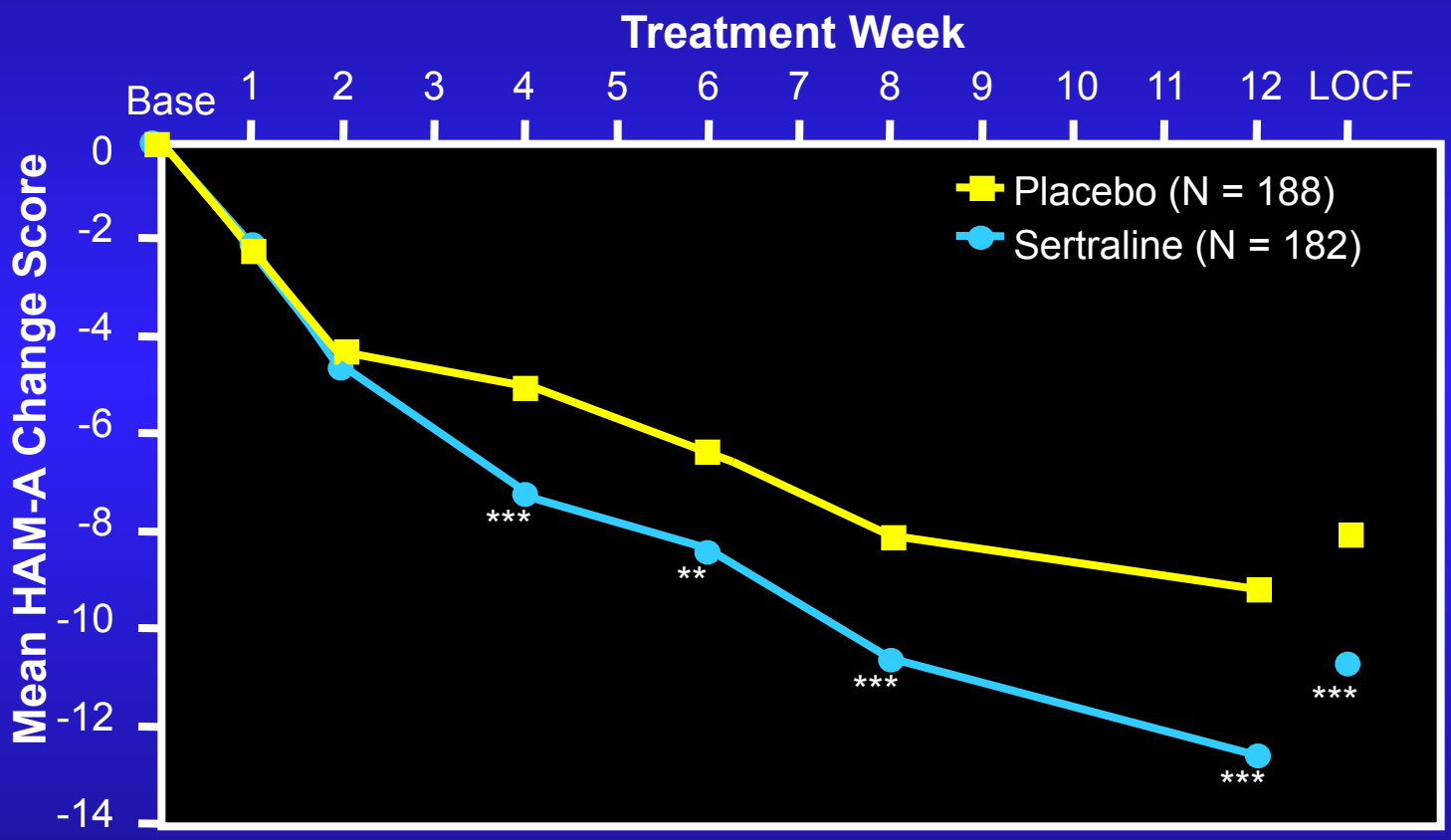
SSRIs for GAD: Sertraline vs Placebo

ITT sample



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

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

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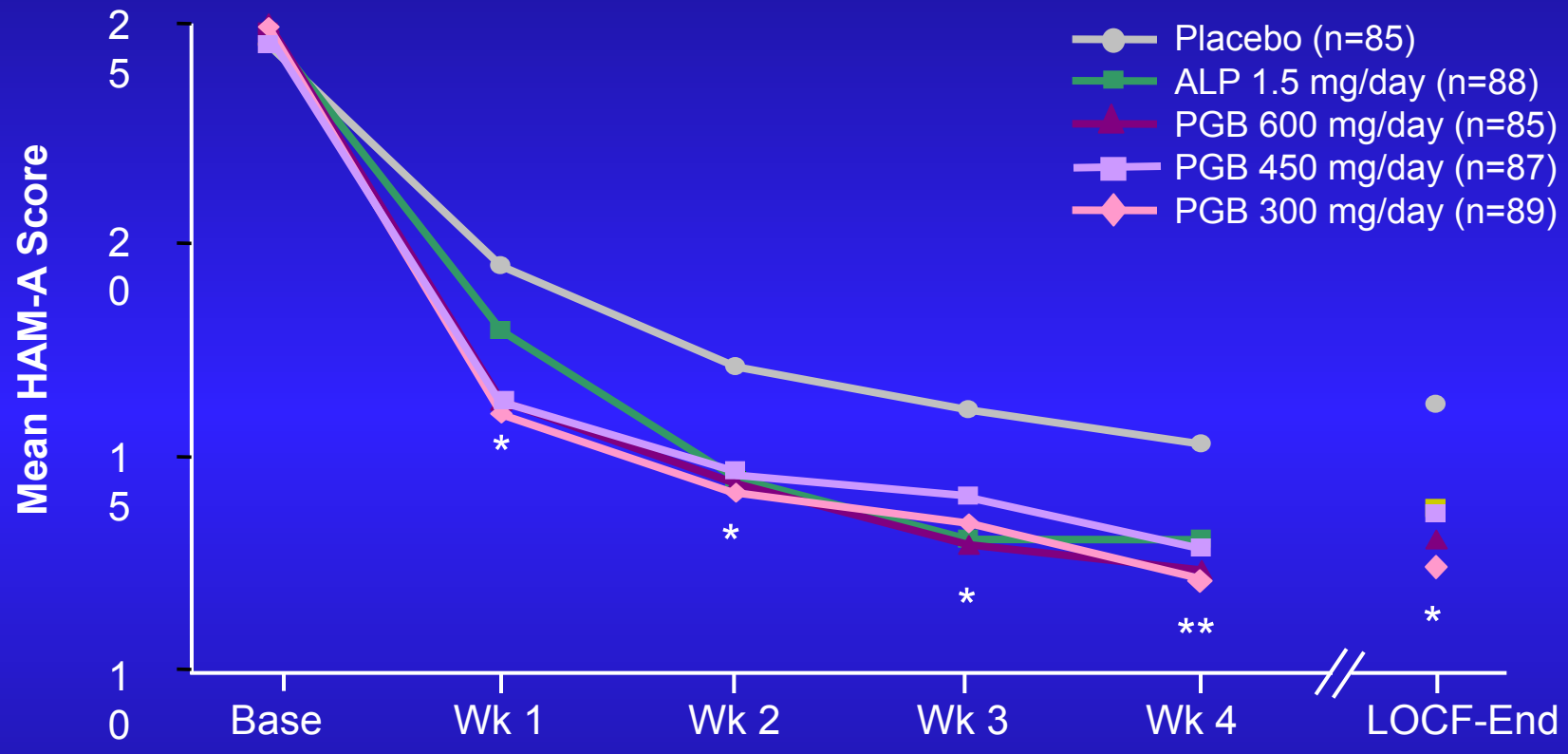
Antidepressants in Anxiety and Mood Disorders
FDA-Approved -X Effective ≥ 1 RCT -X

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	?	

*

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

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.

Panic Disorder

Question

True or False?

When panic disorder and major depression co-exist, the risk for suicide attempts increases.

Teaching Point #1

Choose an agent with efficacy against the disorders most frequently co-existing with PD, such as an SSRI or SNRI.

Teaching Point #2

Fear and avoidance is modulated by both cortical and sub-cortical areas in the fear circuit.

Important brain areas Include:

Prefrontal Cortex, Hippocampus, Amygdala, Locus Ceruleus

Teaching Point #3

The majority of patients with PD require long-term treatment.

DSM 5 Panic Disorder

- One or more unexpected panic attacks
- Followed by ≥ 1 month of worry or concern over the implications of the attacks
- With changes in
  - Cognition- Distorted: Catastrophic potentially serious medical illness
  - Behavior –Avoidance, health care consultations

DSM 5 Panic Attack Symptoms

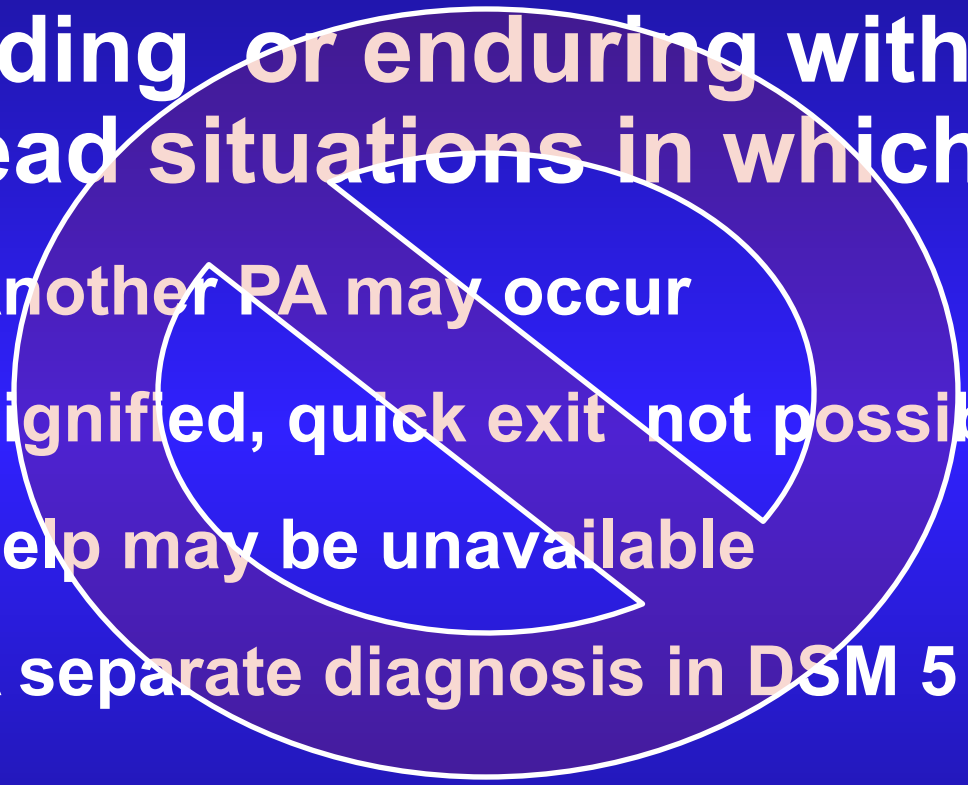
≥ 4 Sx, usually peak within 10-20 Minutes

1. Palpitations, pounding heart
2. Chest Pain or discomfort
3. Shortness of breath
4. Feeling of choking
5. Feeling of dizzy, unsteady, lightheaded or faint
6. Paresthesias (numbness or tingling sensations)
7. Chills or *hot flushes*
8. Trembling or shaking
9. Sweating
10. Nausea or abdominal stress
11. Derealization or depersonalization
12. Fear of losing control
13. Fear of dying

Agoraphobia

Avoiding or enduring with dread situations in which:

- Another PA may occur
- Dignified, quick exit not possible
- Help may be unavailable
- A separate diagnosis in DSM 5



Panic Attacks and Psychiatric Disorders Differential Diagnosis

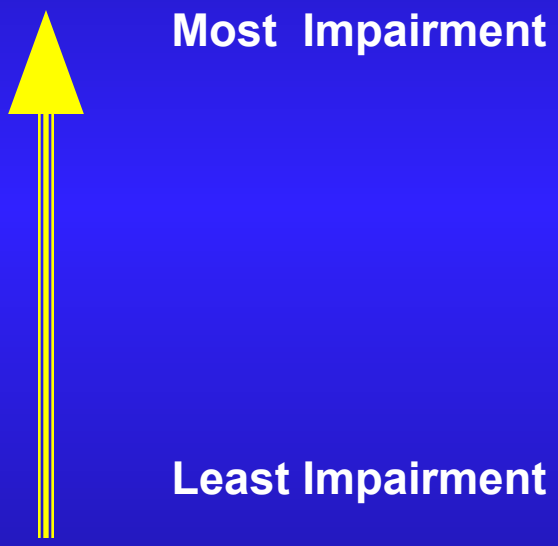
- PD: fear of *the attacks*
- Panic attacks also occur in
  - Social Anxiety-social cues
  - OCD reaction to obsessional cues
  - Specific phobia-specific cues (snakes, storms, etc)
  - PTSD-trauma related cues
  - Associated with MDD

Craske, MG et al. Panic disorder: a review of DSM-IV panic disorder and proposals for DSM-V. Depress Anxiety. 2010;27:93-112.

Avoidance Drives Impairment in PD

NCS Replication (n=9282)

- PD + Ag
- Ag + isolated PA
- PD without Ag
- Isolated PA



Kessler et al The epidemiology of panic attacks, panic disorder, and agoraphobia in the NCS Replication. AGP 2006;63: 415-24

Theoretical Pattern of Onset and Treatment Response in PD

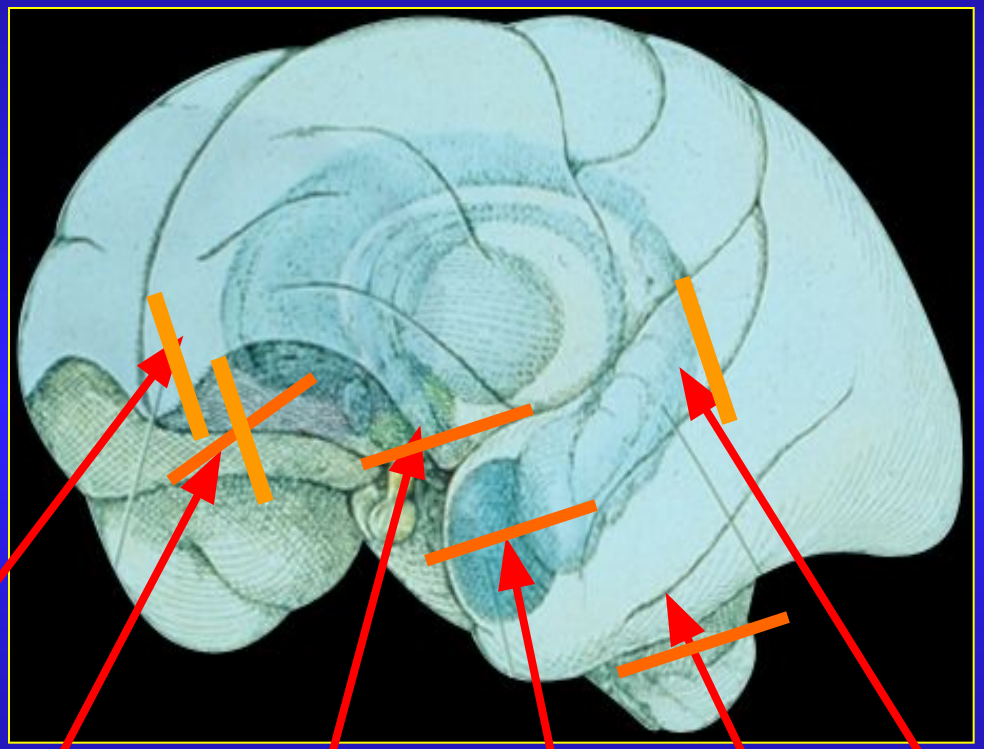
- Onset: Unexpected Panic -->anticipatory anxiety>--catastrophic thoughts -->agoraphobia

- With treatment: Symptom response pattern
  - 2-6 weeks-unexpected PA less frequent , severe
  - 8-12 weeks-Cued PA, anticipatory anxiety less severe
  - 8-?? Weeks-Agoraphobic avoidance decreases

* **Controversy exists re: order of appearance of agoraphobia and PA**

Model for Actions of Psychotropics and CBT

Fear Circuit Model explains both CBT and Drug Rx
reduce amygdala reactivity



CBT
Top-Down

Psychotropic Agents (Bottom-Up)

Prefrontal Cortex

Hippocampus

Hypothalamus

Amygdala

Cingulate Cortex

Brainstem
Locus Ceruleus, PAG, PBN,NTS, others

*

SSRIs/SNRIs First Line *

- Efficacy ~ 50-70% for each SSRI/SNRI
- Different patients may respond to different SSRIs
  - Try ≥ two SSRIs before switching class
- Initial dose = 1/4 to 1/2 initial antidepressant dose- (or less!)
  - Dissolve/crush fruit juice, water, applesauce to create small initial dose
- Final dose may be more than 2x antidepressant dose

*APA Treatment Guidelines for Patients with Panic Disorder APA, 2010

*

PD Medications That Don't Work

- Bupropion (Wellbutrin)
- Trazodone (Desyrel)
- Buspirone (Buspar)
- Neuroleptics*
  - Some evidence for atypical neuroleptics
- Beta-blockers

*

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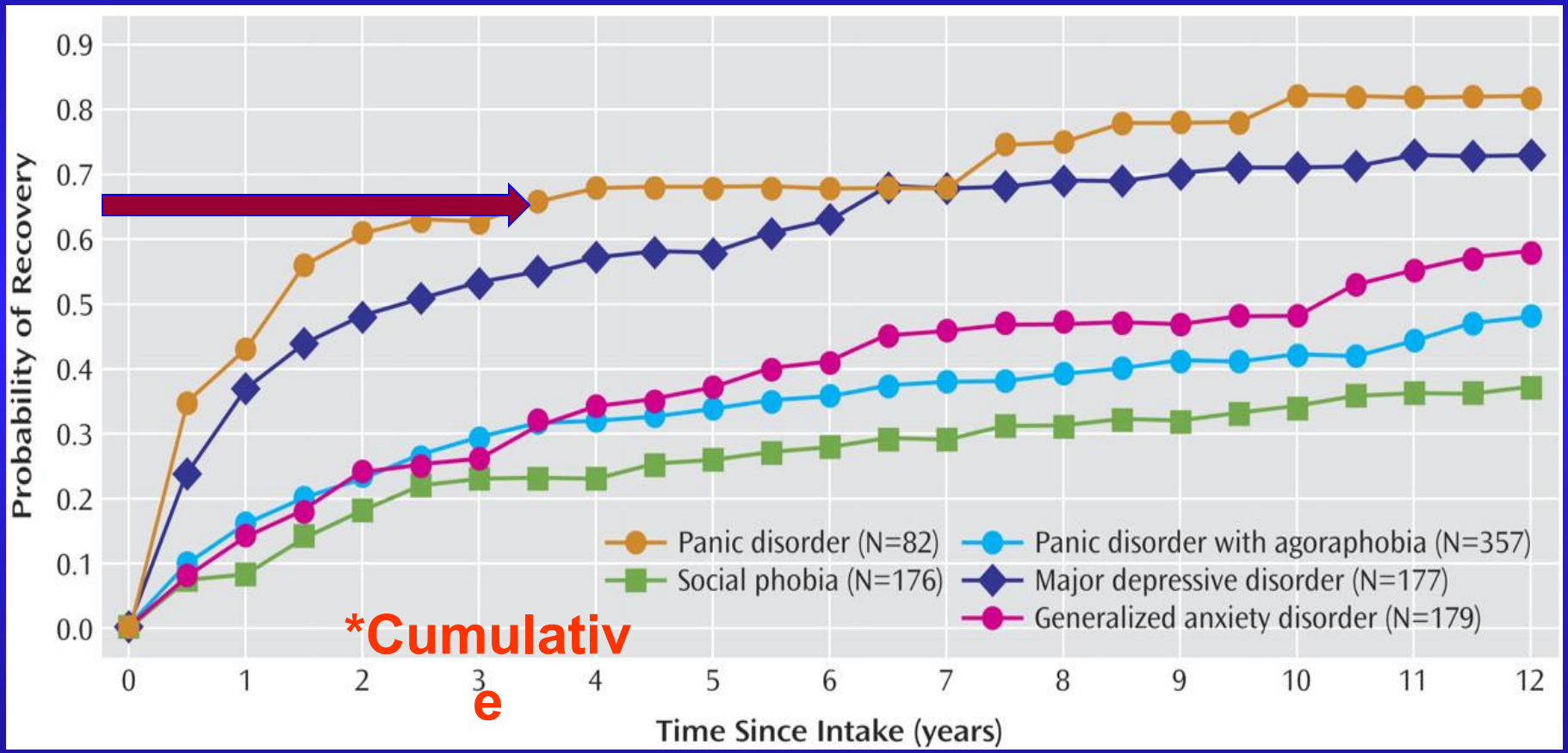
Panic Disorder - High recovery, high recurrence rate
* 12-Yr Probability of Remission



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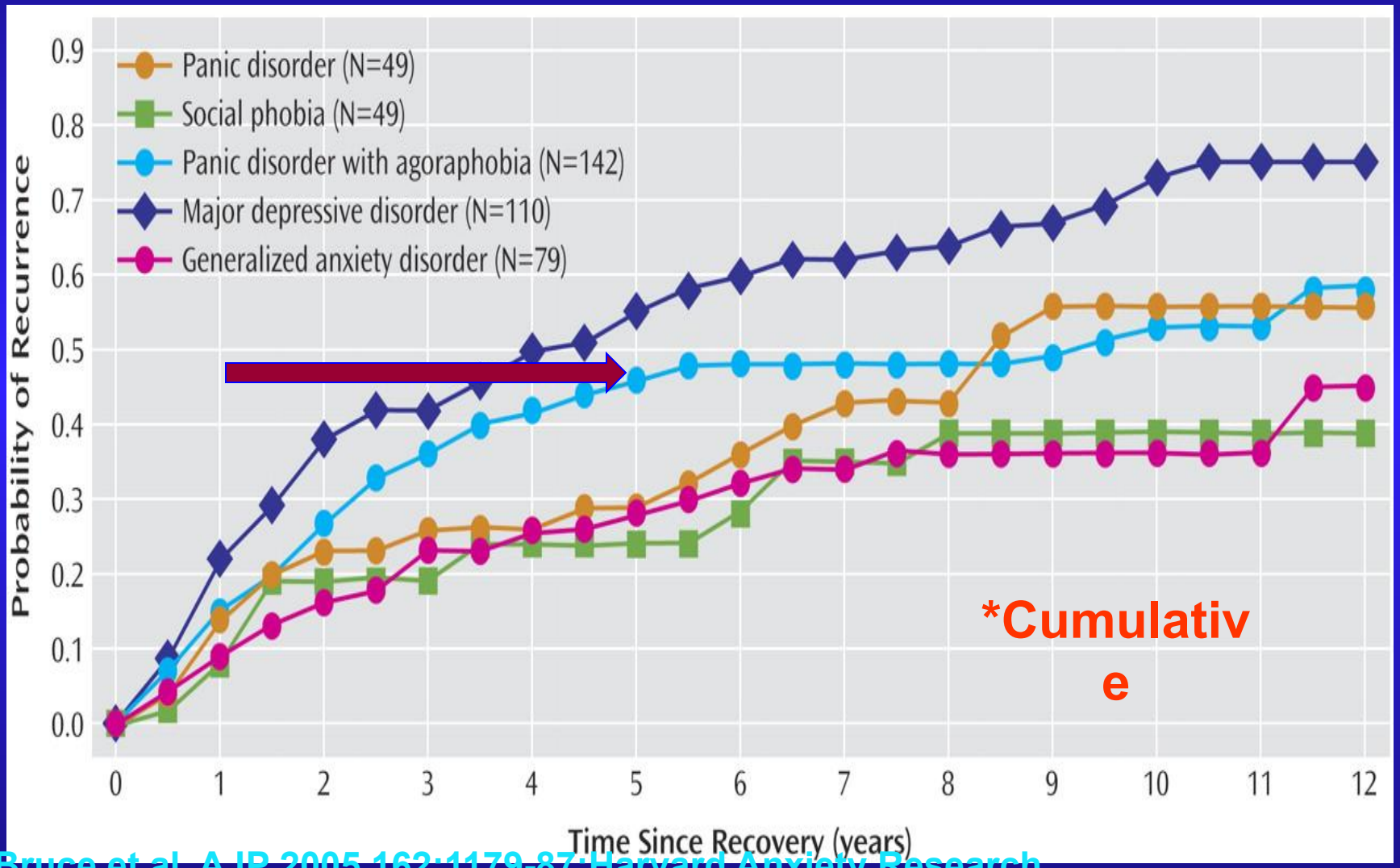
Bruce et al, AJP2005 162:1179-87 Harvard Anxiety Research Program

* 12-Yr Probability for PD Recurrence: High



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

Who needs Long-term Treatment?

- The majority of patients need long-term Rx
- Relapse rates after discontinuation of medication significant
  - -60% within 3-4 months after stopping meds*
  - CBT may assist in successful discontinuation
- Tapering medication should be very gradual and correlate with duration of treatment (2-6 months**)

*Relapse may be higher for BZ monotherapy

**Optimal taper may be longer after long-term BZ

*

Further Medical Evaluation Indicated

- Panic attacks clearly and consistently related in time to meals
- Loss of consciousness
- Seizures, amnestic episodes
- Symptoms similar to panic attacks but without the intense fear or sense of impending doom (non-fear panic attacks)
- Unresponsiveness to treatment
- True vertigo

Future Directions

Panic Disorder is a Generalized Inflammatory State

- Panic disorder (n= 20)
- Age, gender-matched controls
- Elevated levels of 18 of 20 cytokines/stress mediators assayed
- May be relevant to increased cardiovascular, other medical illness vs Normals

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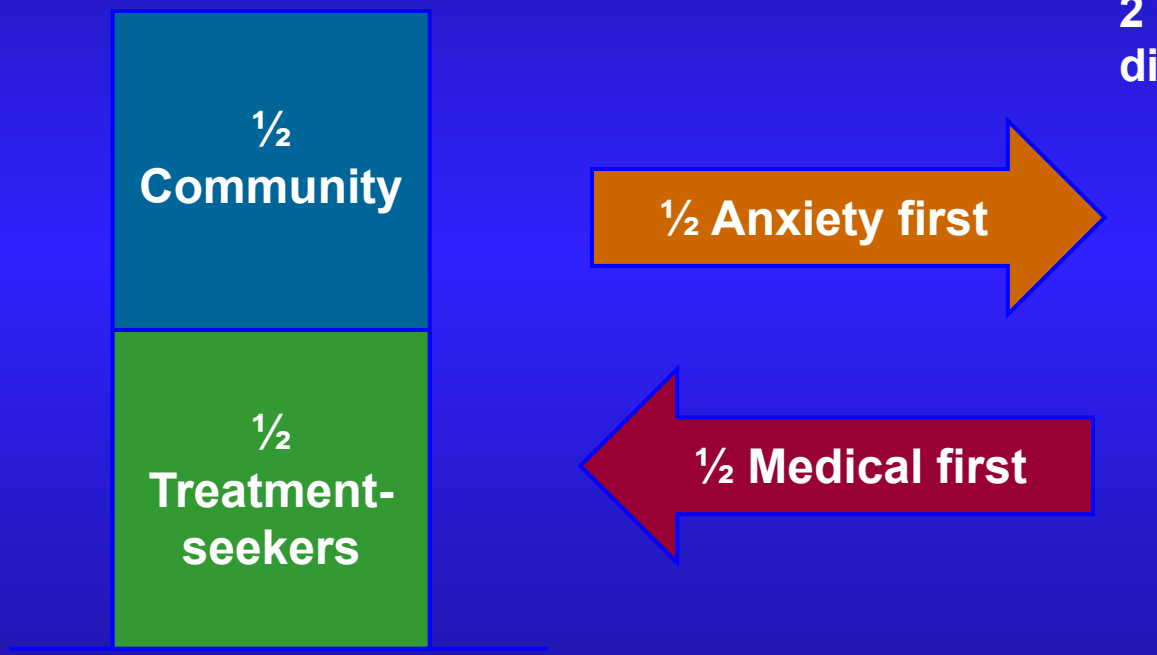
Hoge EA dt ql Depr Anx 2009; 26: 447-455

WORRIED SICK?

Health Problems with Anxiety Resemble Those Associated with Stress

≈300 Individuals With PD or GAD



2 to 6 times as many medical disorders vs. non-anxious*

- **Cardiovascular**
- **Respiratory**
- **Endocrine-metabolic**
- **Autoimmune 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.

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

Questions?
Comments?