Treatment of Panic Disorder

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Panic Disorder Presentation Outline

- Pre-lecture Questions
- Main Teaching Points
- Illness Characteristics
- Morbidity and Comorbidity
- Diagnostic and Assessment Issues
- Treatment Options
- Summary
- Post-lecture questions

Question #1

True or False?

In the U.S., the lifetime prevalence of panic disorder in men is twice as high as in women.

Question #2

True or False?

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

Question #3

Panic disorder is associated with increased risk for other psychiatric disorders : GAD, OCD, social anxiety disorder, major depression

Which disorder usually precedes panic disorder?

Question #4

What is the APA recommendation for first-line pharmacotherapy for panic disorder?

Question #5

Which sub-cortical structure is the critical brain nucleus for fear conditioning?

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-IV 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 pr potentially serious medical illness
  - Behavior –Avoidance, health care consultations

DSM-IV Panic Attack Symptoms

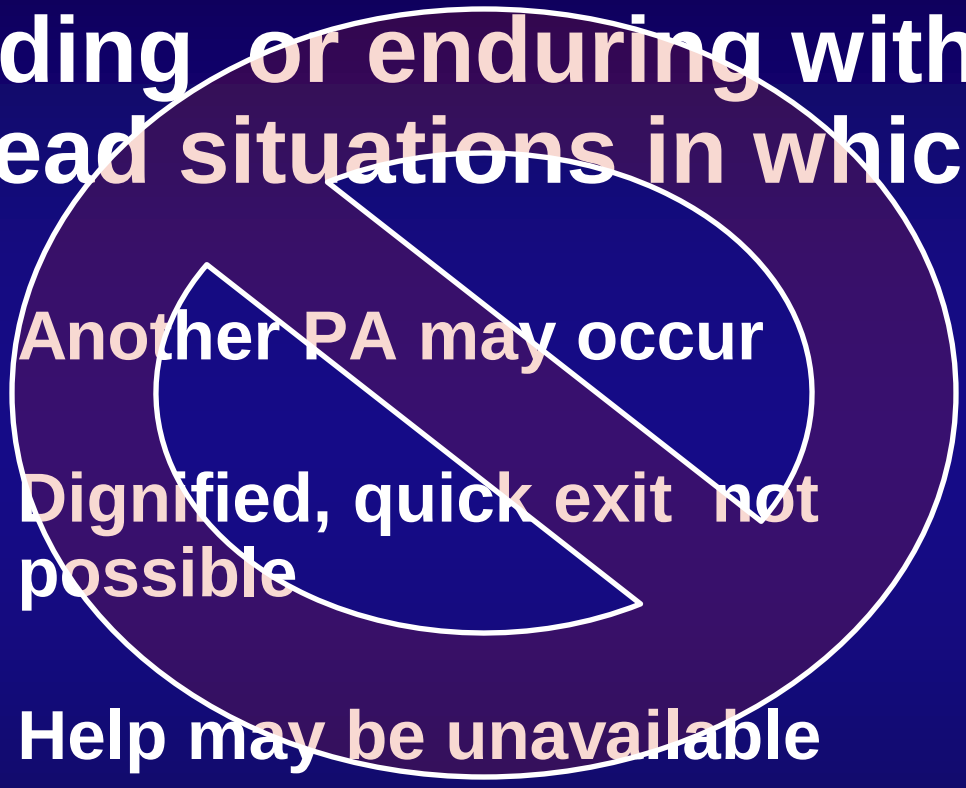
≥ 4 Sx, usually peak within 10-20 Minutes

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--→ 'heat sensations' for DSM-V*
8. Trembling or shaking
9. Sweating
10. Nausea or abdominal stress
11. Derealization (unreality) or depersonalization (detached)
12. Fear of losing control or going crazy
13. Fear of dying

DSM-IV Agoraphobia

Avoiding or enduring with dread situations in which:

- **Another PA may occur**
- **Dignified, quick exit not possible**
- **Help may be unavailable**



Agoraphobia proposed as separate diagnosis for DSM-V

Limited DSM-V Changes Proposed

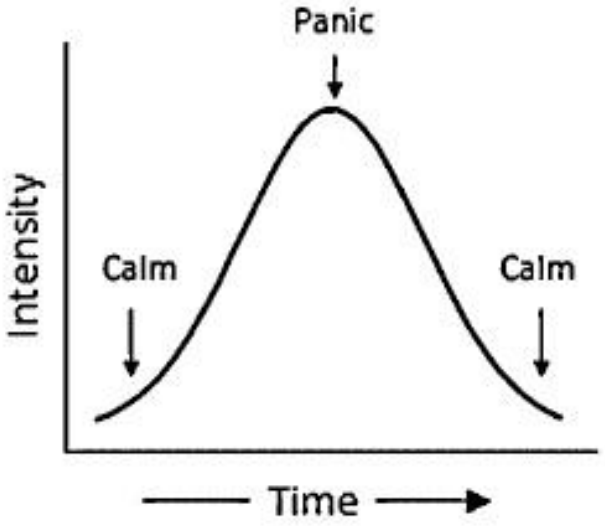
Panic Attack : An abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four or more of the following symptoms occur. The abrupt surge can occur from a calm state or an anxious state' (see picture)

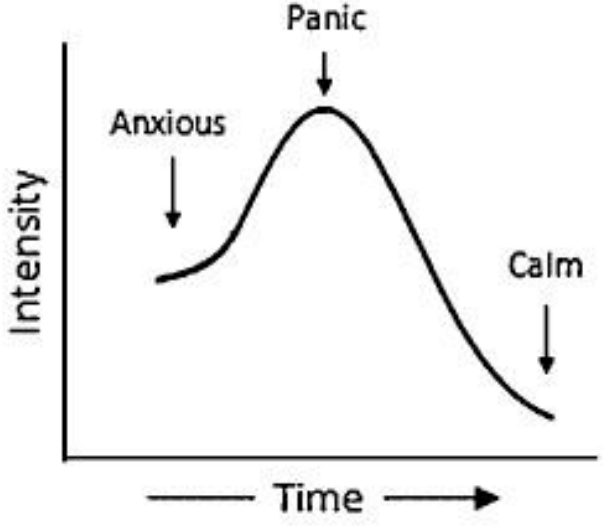
And is associated with

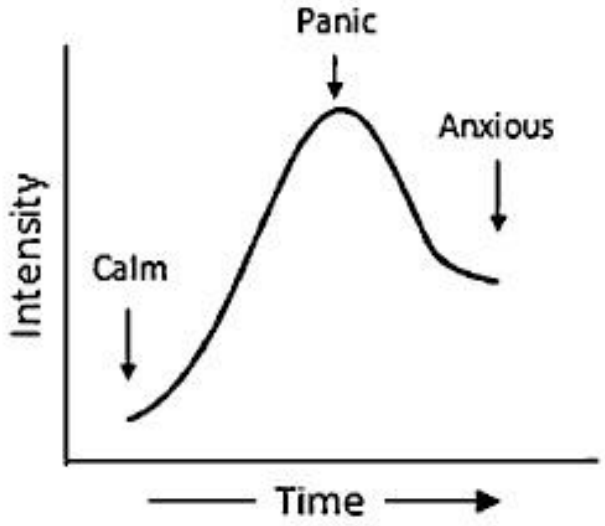
''significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having the PAs), which may include agoraphobia avoidance''

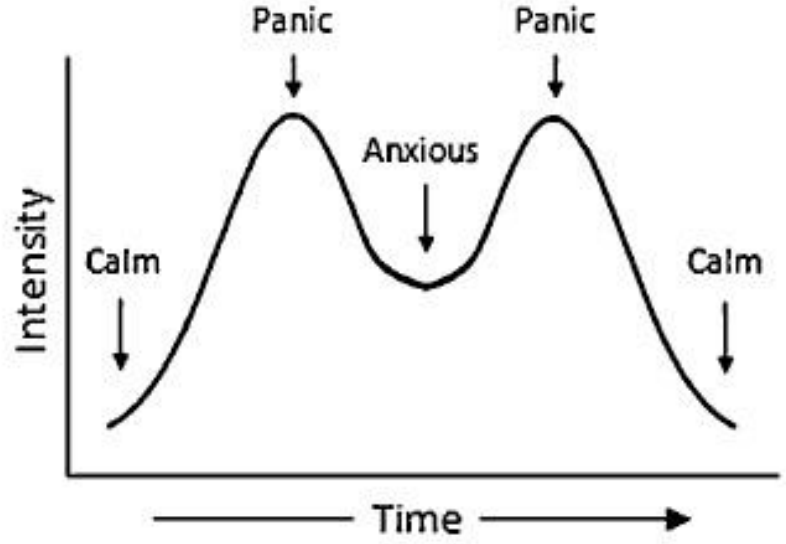
Craske MG et al. Panic disorder: a review of DSM-IV panic disorder and proposals for DSM-V. Depress Anxiety. 2010;27:93-112.

Visual Aid Proposed to Help Patients to Describe Their PA Pattern









Panic Attacks and Psychiatric Disorders Differential Diagnosis

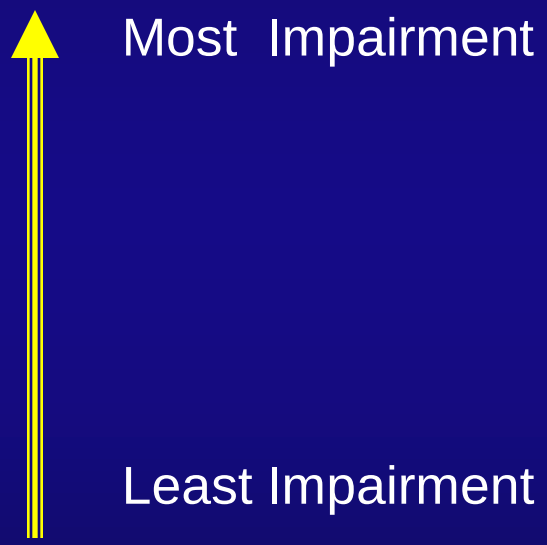
- **PD: fear of *the attacks***
- **Panic attacks also occur in**
  - **Social Anxiety-social cues**
  - **OCD reaction to obsessional cues**
  - **Specific phobia-specific cues (snakes, storms, etc)**
  - **PTSD-trauma related cues**
  - **Associated with MDD**

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



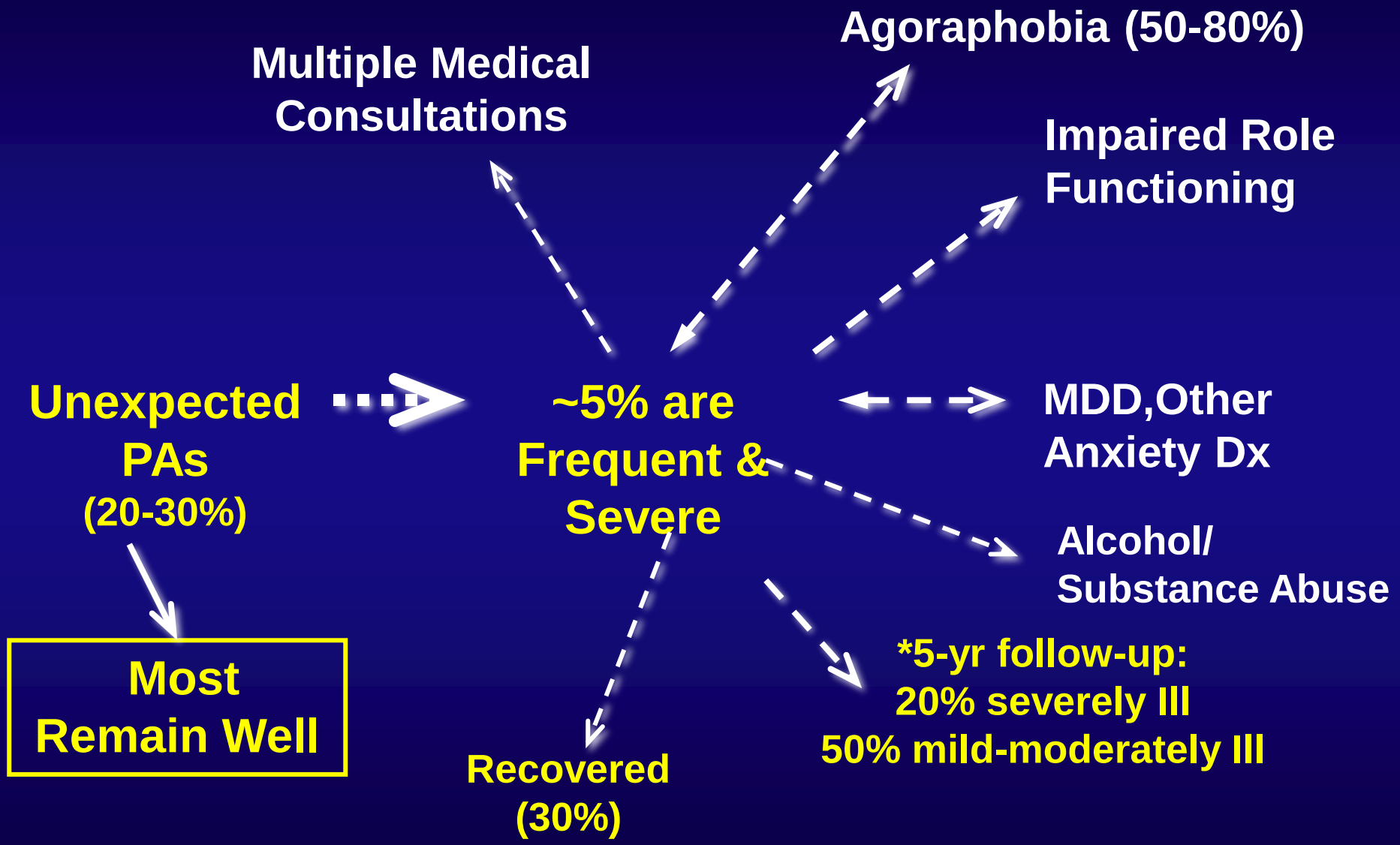
Kessler et al_The epidemiology of panic attacks, panic disorder, and agoraphobia in the NCS Replication. AGP 2006;63: 415-24

Theoretical Pattern of Onset and Treatment Response in PD

- Onset: Unexpected Panic -->anticipatory anxiety>--catastrophic thoughts -->agoraphobia
  - Reverse of order of onset
- 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

PD 5-yr Course After Initial Treatment



***423 PD patients treated ; 323 re-interviewed;** Katschnig, H. et al Long-term follow-up after a drug trial for panic disorder. Br Psychiatry 1995;167:487-94

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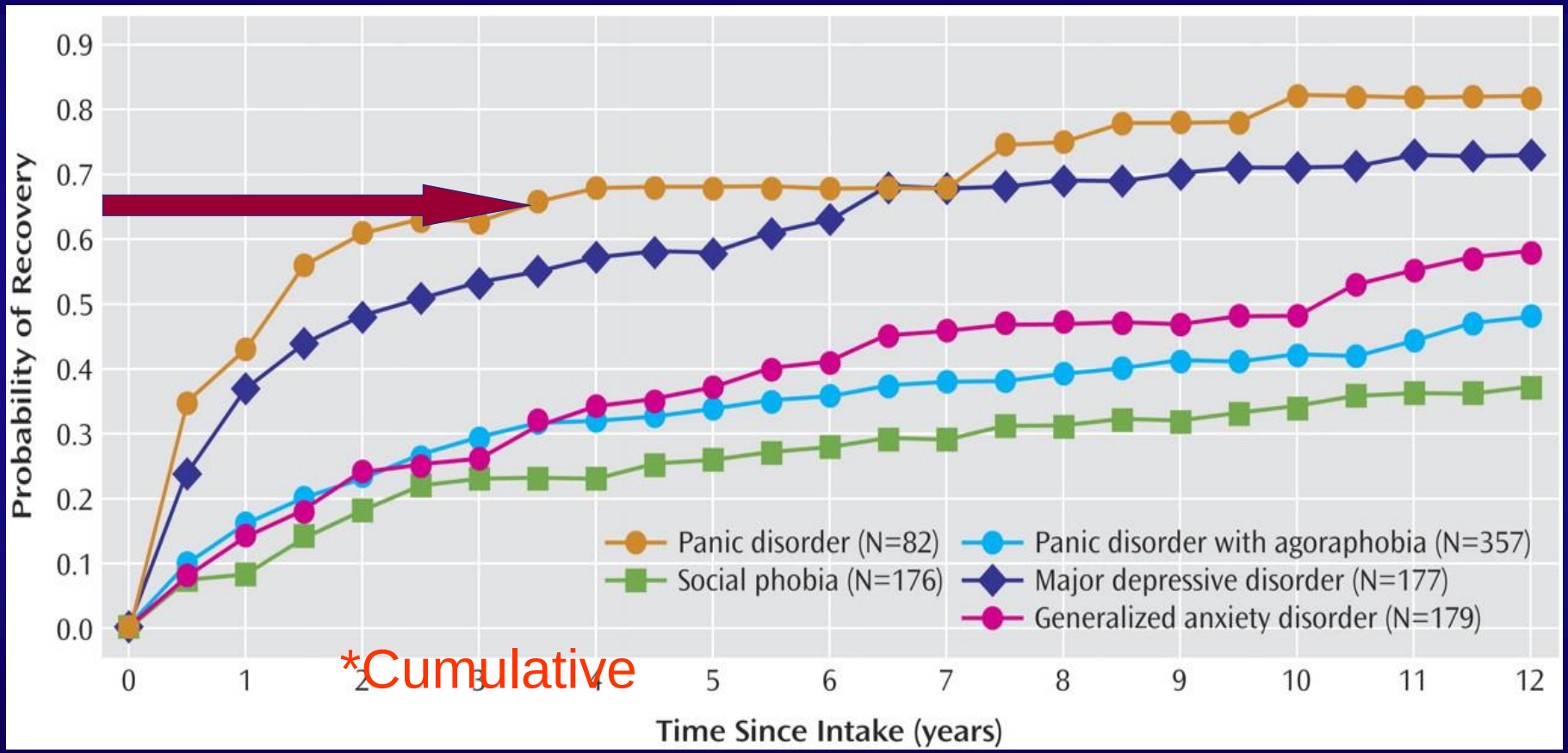
Panic Disorder - High recovery, high recurrence rate
* 12-Yr Probability of Remission



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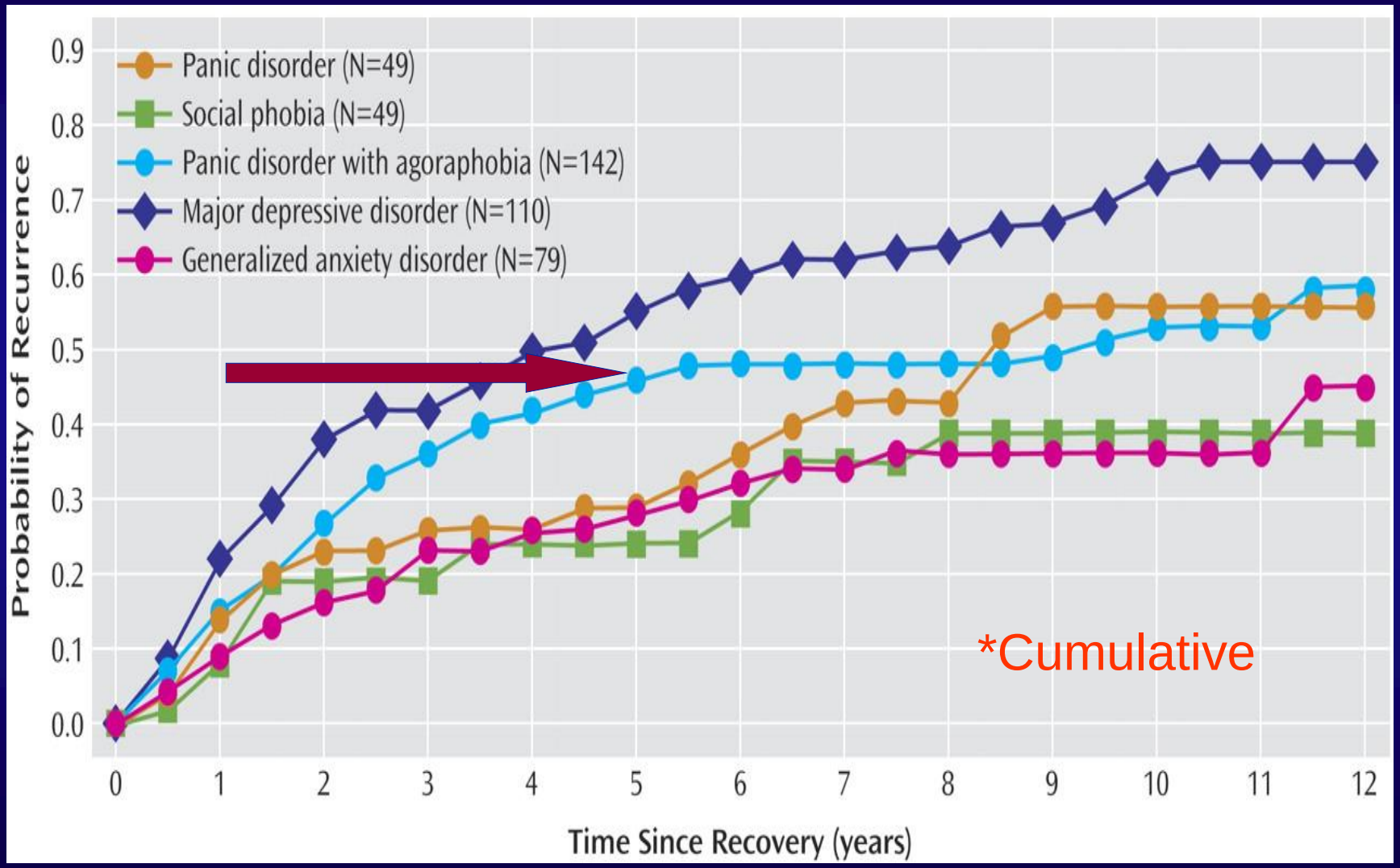
Bruce et al, AJP2005 162:1179-87 Harvard Anxiety Research Program

* 12-Yr Probability for PD Recurrence: High



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

Panic Disorder Neurobiology

- **Fear Circuit Dysfunction**
- **Women:men = 2:1**
- **Inherited risk-polymorphism**
  - **Lower brain serotonin transporter Meron et al, Psych Res 2004;132:939-45**
  - **Reduced brain 5HT1a receptor binding Nash et al Br J Psychiatry 2008; 193:229-34**
- **Non-random comorbidity**
- **Challenge studies**

The Fear Circuit Model

- Explanation for both CBT and Pharmacotherapy

*

Brain Circuits in Anxiety Disorders

- Neurocircuits:
  - **Interconnected , interactive brain regions**
- Amygdala:
  - **Subcortical structure serving as the “central hub” in fear processing.**
- Cortico-Striatal-Thalamic-Cortical (CSTC) Pathways:
  - **Closed loops originating in the frontal cortex which sequentially process specific types of information about emotion, cognition or behavior.**

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The Fear Circuit Model:

Critical Components Inter-modulate

- **Amygdala Central Nucleus = "alarm button"** filters input- 'watchdog' function, fear conditioning
- **Hippocampus**: Storage and retrieval of contextual and declarative memory
- **Prefrontal Cortex--Executive Function** :Coping and problem solving, probability estimation , Fear extinction , Inhibitory influence over lower structures
- **Lateral Nucleus of Hypothalamus- Brainstem:** Sympathetic activation **,** Locus ceruleus, nucleus solitarius, PAG, parabrachial nuceus, etc.
- **Anterior Cingulate Cortex**: Monitors likelihood for potential errors

ALL Shown to function abnormally in PD

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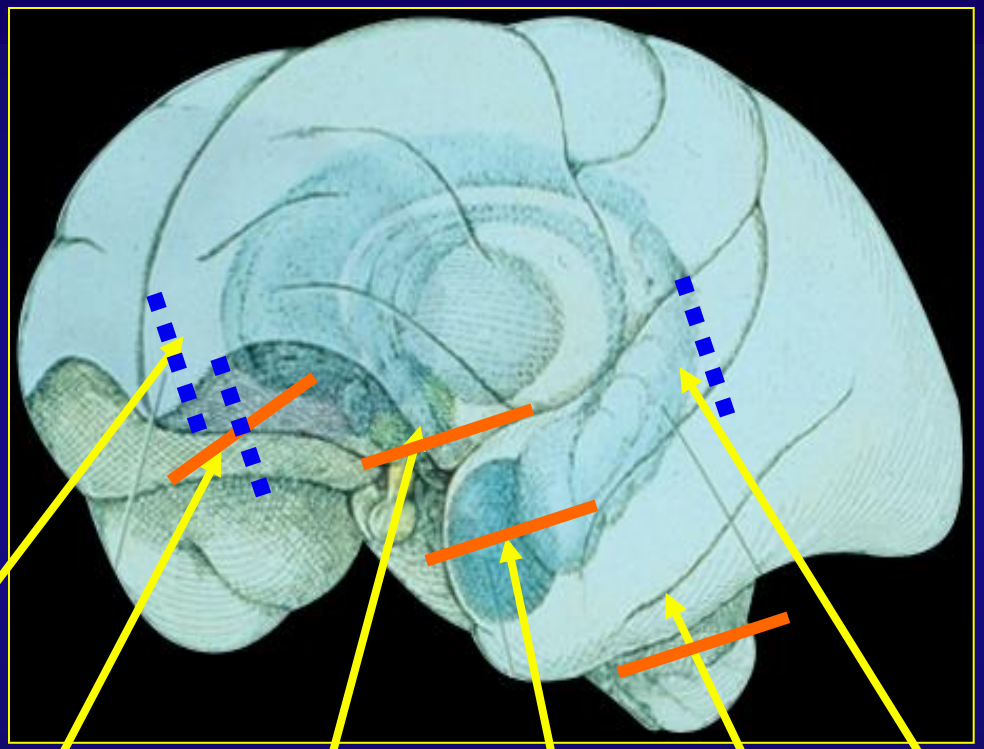
Model for Actions of Psychotropics and CBT

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

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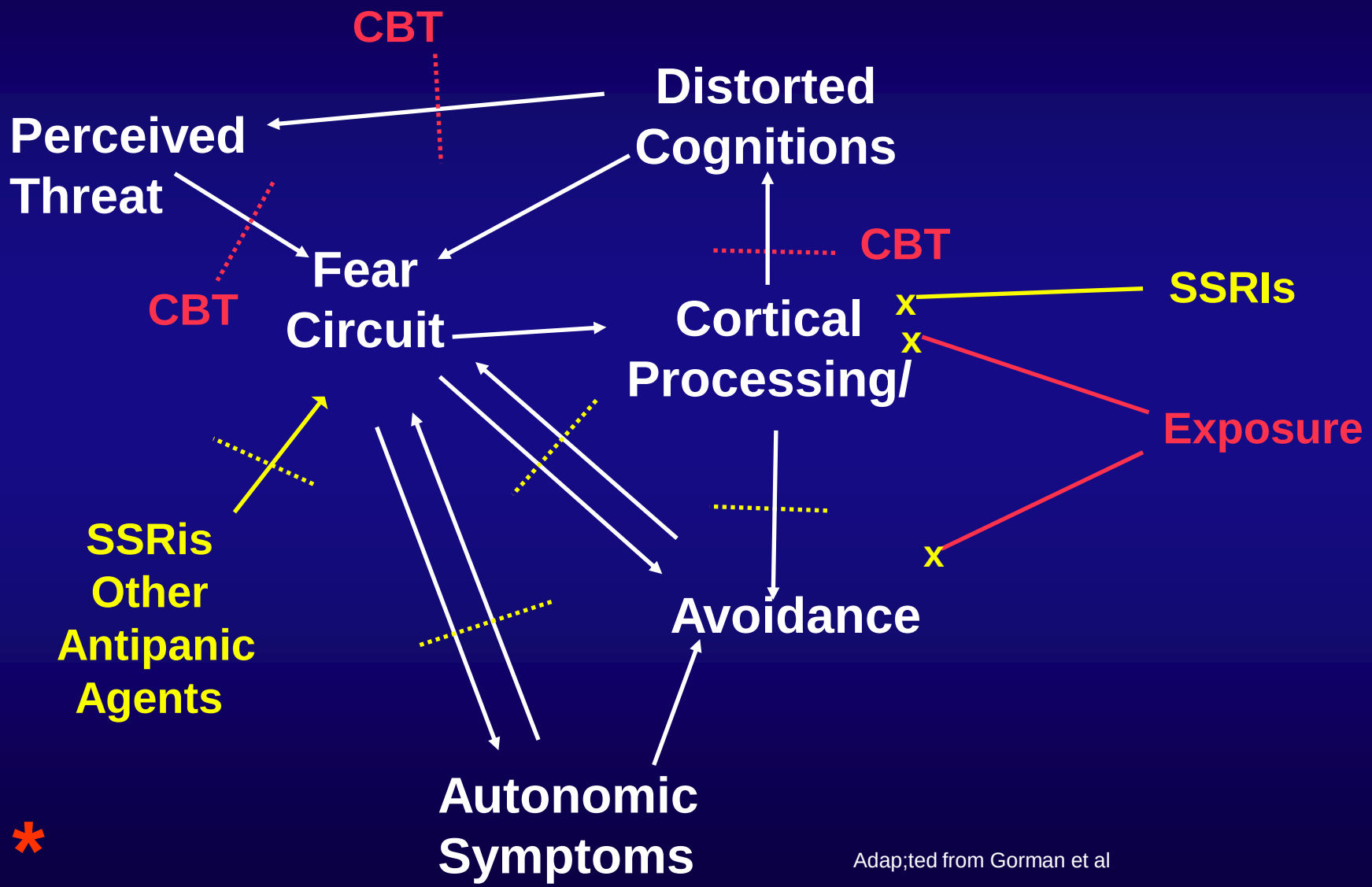
Theoretical Sites of Action of Antipanic-Antiphobic Treatment(s)



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Adap;ted from Gorman et al

Challenge Studies in PD

- PD sufferers susceptible to challenge with Lactate, CO_2 ,Yohimbine. Caffeine, Isoproterenol, others
- Multiple abnormalities but not clear which is central to PD

Abnormal GABA and BZ Receptors in PD

Altered Distribution, Sensitivity and GABA concentrations

- **Reduced sensitivity to i.v.diazepam**
  - Roy-Byrne et al *Am J Psychiatry.* 1996;153:1444-1449
- **Flumazenil anxiogenic in PD**
  - *Woods et al Psychiatry Res.* 1991;36:115-127
- **Reduced [GABA] in occiptal cortex; attenuated response to BZs**
  - Goddard et al, AGP 2001; 58:556-61;AJP 2004 161: 2186
- **Reduced GABA-A binding insular cortex**
  - Cameron et al, AGP 2007;64:793-800;Haasler G et al. Arch Gen Psych 2008;65:1166-75

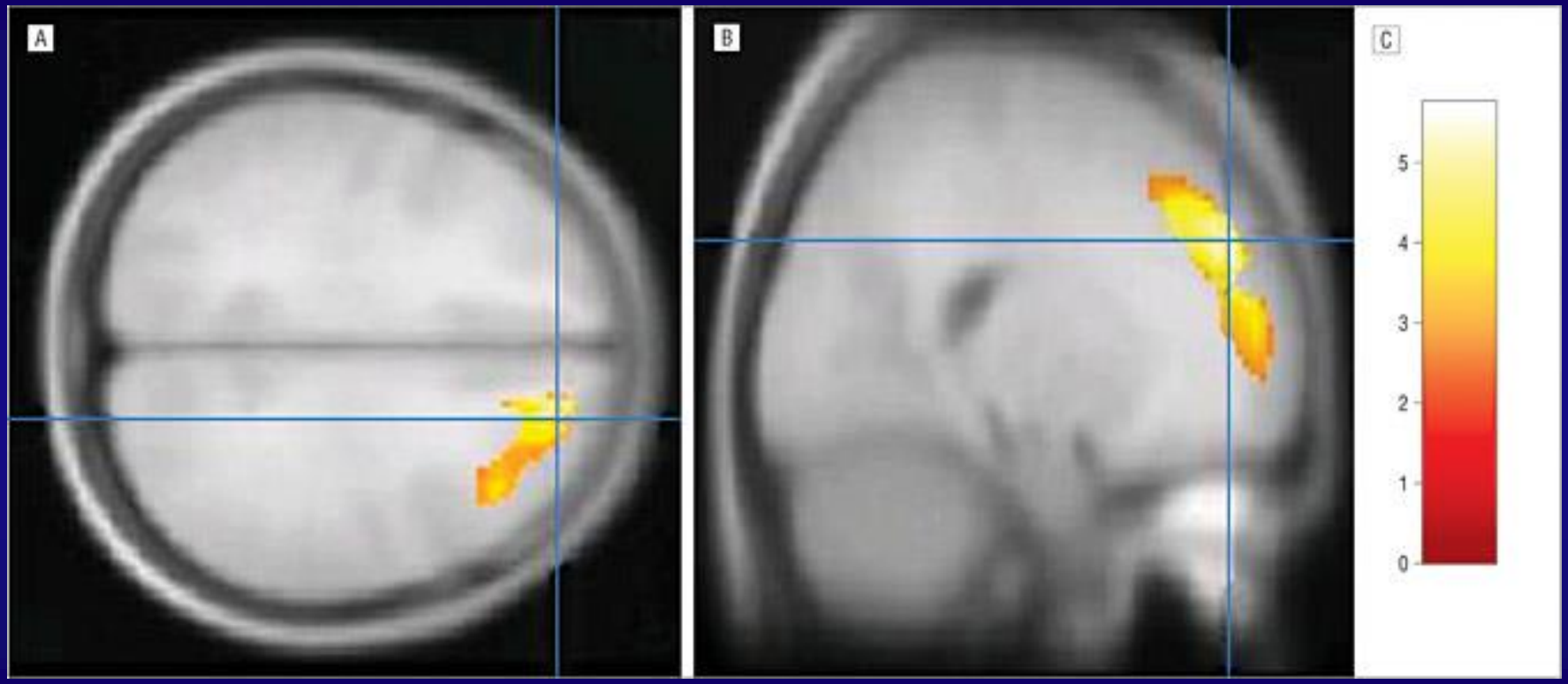
PD: Imaging Studies

- Reduced 5HT post synaptic receptors in untreated PD
- Reductions in volume and function in mPFC and Anterior Cingulate Cortex
- Imaging studies reveal over-reactive amygdala following presentation of fear stimuli.
- Prefrontal instability to emotional cues remains after remission post-treatment

Chechko N, et al PLoS One. 2009;4(5):e5537; Sobanski T, et al Psychol Med. 2010;40(:1879-86.

Regional Differences

Right Dorsal Anterolateral PFC: Decreased BZ Binding in PD

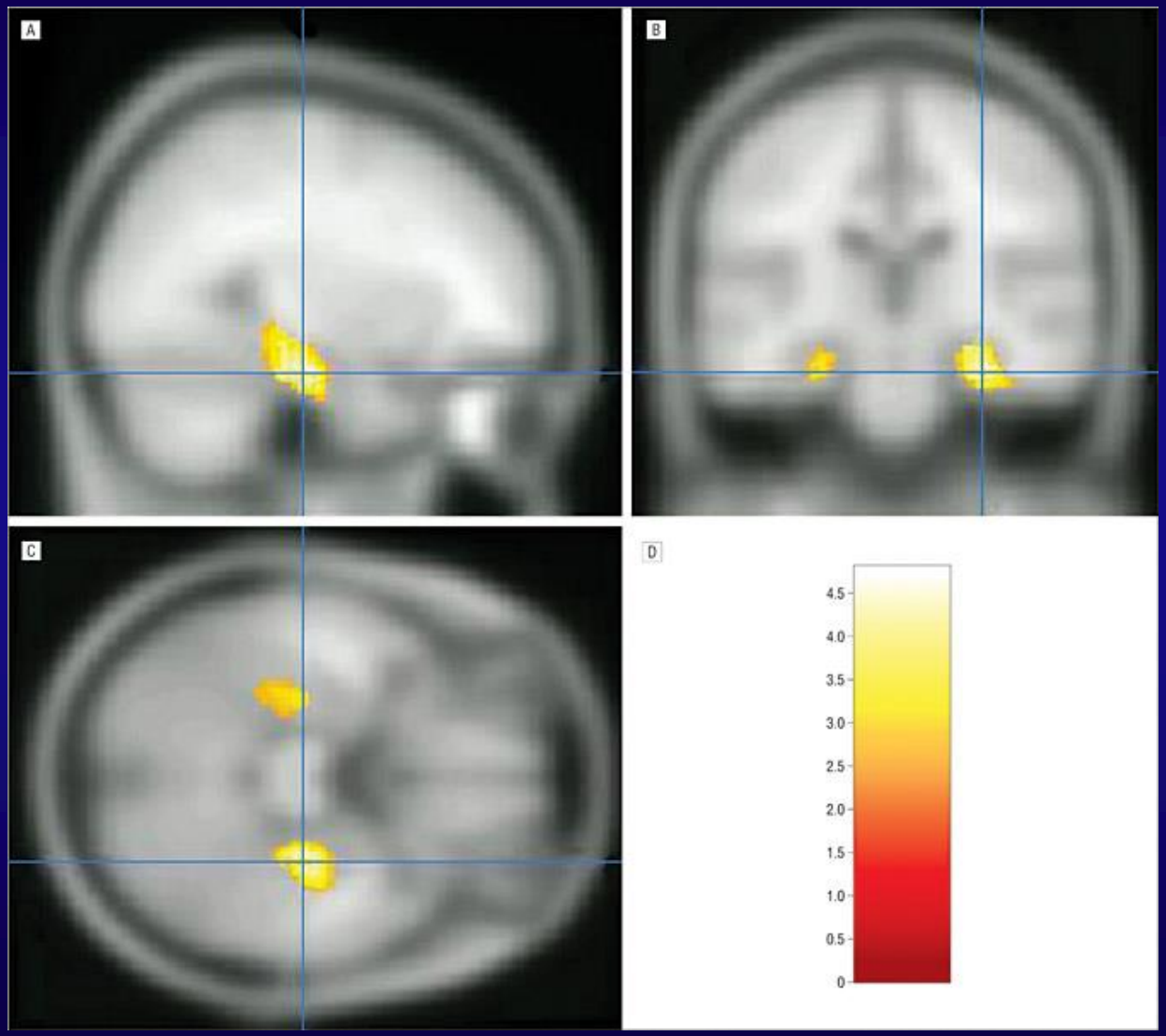


r, G. et al. Arch Gen Psychiatry 2008;65:1166-1175.

Regional Differences

Hippocampus and Parahippocampal Region

BZ Receptor Binding Increased in PD



Hasler, G. et al. Arch Gen Psychiatry 2008;65:1166-1175.

Morbidity of PD:
Epidemiological Catchment Area (ECA) Survey

Depression

Social impairment

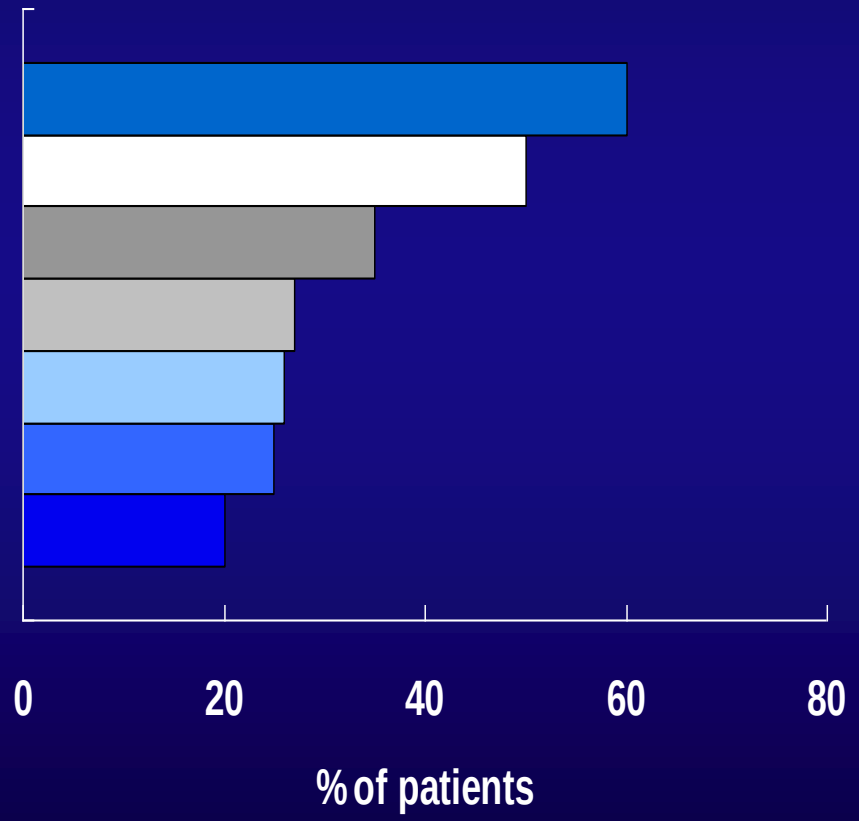
Poor health perception

Financial dependence

Emergency room visits

Alcohol abuse

Suicide attempts



Johnson J et al Arch Gen Psych 1990

Increased Medical Utilization in PD
Top 10% of Users

Odds ratio of ≥ 5 MD visits

	Males	Female
• MDE	1.5	3.4
• Panic disorder	8.2	5.2
• Phobic disorder	2.7	1.6

Simon and Von Korff, 1991

Panic Disorder : worsened by stress *and acts as a* stressor

- Panic disorder resembles unpredictable stress
- *Criteria for stressor:
  - Perceived threat or challenge
  - Perceived inability to control it
- Elevated plasma pro-inflammatory cytokines/stress mediators

*Schulkin J, et al. *Neurosci Biohbehav* Rev. 1994;18:385-396. McKewen BS. *N Engl J Med.* 1998;338:171-179; Hoge et al, Depression and Anxiety 2009 26 : 447–455

Panic Disorder is a Generalized Inflammatory State

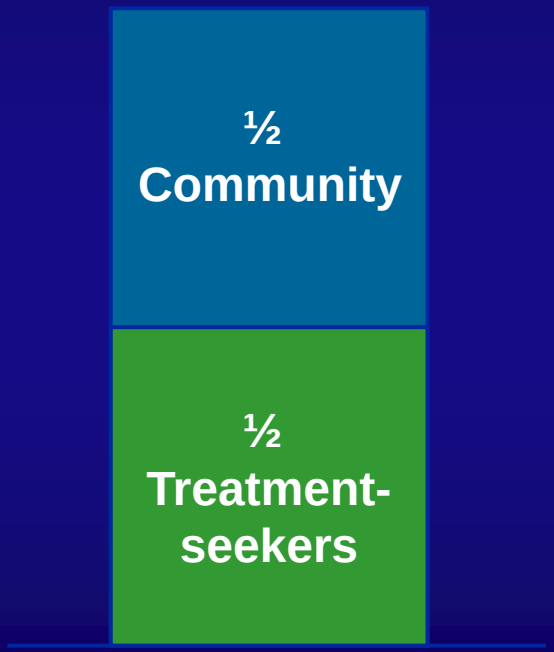
- Panic disorder (n= 20)
- Age, gender-matched controls
- Elevated levels of 18 of 20 cytokines/stress mediators assayed
- May be relevant to increased cardiovascular, other medical illness vs Normals

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.

Comorbidity

Comorbid Conditions Provide Important Clues

- Clinical characteristics and severity
- Course and outcome
- Treatment response

PD - Major Depression Comorbidity Worsens Prognosis

- Over 50% have melancholia
- More Severe Anxiety
- More Severe Depression
- More Severe Phobic Avoidance
- Longer Course of Illness
- Suicide risk twice vs. either disorder alone

Roy-Byrne et al Br J Psychiat 2000;176:229-35

Family History

- Panic and other anxiety disorders
- Depression
- Alcoholism
- Suicide
- Treatment and outcome results if known

Panic Disorder

Evaluation

The Diagnosis?

- Assess panic attacks
  - Unexpected vs. “cued” (stimulus-bound)
  - How frequent and severe ?
- Cognitive distortion or behavior change ?
  - Fear of consequences or implications of PAs?
  - Are there lifestyle / behavioral changes?
- Avoidance or dread due to fear of another panic attack?

Panic Disorder Differential Diagnosis

- **Different *or* Comorbid Anxiety disorder with Pas**
- **Depression-Other comorbid disorders**
- **Substance Abuse**
- **Medical Condition**
- **Iatrogenic**
- **Other**

Bruce et al. *Arch Gen Psychiatry*. 1992;49:867; ; Roy-Byrne and Uhde. *J Clin Psychiatry.* 1988;49:56 Strohle et al. *Acta Psychiatr Scand.* 1998;98:254; **Lydiard RB. In: *Textbook of Anxiety Disorders*. Washington, DC: American Psychiatric Press, Inc; 2002:348-361**

Other Relevant History

- Psychosocial stressors
- Developmental history
- Occupational, social, family role Impairment

Medical Evaluation of PD

History

- Complete description of physical symptoms
- Medical history
- Family medical history
- Drug treatment, CBT, and medication history
- Dietary history, esp caffeine from all sources (include Mountain Dew, colas, iced tea, etc)

Medical Evaluation of PD

- Physical Examination
- EKG
- Laboratory
  - CBC
  - Electrolytes, BUN, Creatinine, Glucose
  - Urinalysis
  - T_4 and TSH

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

PD: Patient Approach

- **Positive diagnosis is critical**
  - **Many told there is nothing wrong.**
- **Relieve the patient of perceived failure to overcome alone**
  - **Discuss inherited risk**
  - **"It's not your fault--anyone would feel like you do if they had panic attacks."**
  - **"You have had a normal human response to terrifying symptoms. They are frightening but not dangerous."**

[1]Hirshfeld DR et al. Panic disorder and its treatment., New York:Marcel Dekker,1998:93-152; Lydiard RB: Assessment and Management of Treatment Resistance in Panic Disorder Focus 2011;9:253-63

PD: Patient Approach

- Patient Education
- Disease management is the goal like diabetes or asthma
- Immediately and repeatedly re-frame attacks as ‘Distressing but not medically dangerous.’
- Include significant other or family to educate about PD
- Warn about about limiting caffeine intake

PD: Patient Approach *(cont.)*

- **Be patient**
  - Repeat as needed
- **Be thorough, credible and realistic**
  - Outline a plan and pattern of improvement expected
  - Same as order of symptom onset relief (panic attack→phobia)
  - Time frame for getting better vs. back to normal are not the same

PD: Patient Approach *(cont.)*

- Address medication treatment duration as soon as it presents
  - Doctor, how long will I need to take the medicine?
- Re-frame treatment as a way to be independent, not dependent
- Eyeglasses example:
  - Do you expect that your eyes ‘learn’ to see after a few months?
  - Are you worried that you will become addicted to them?

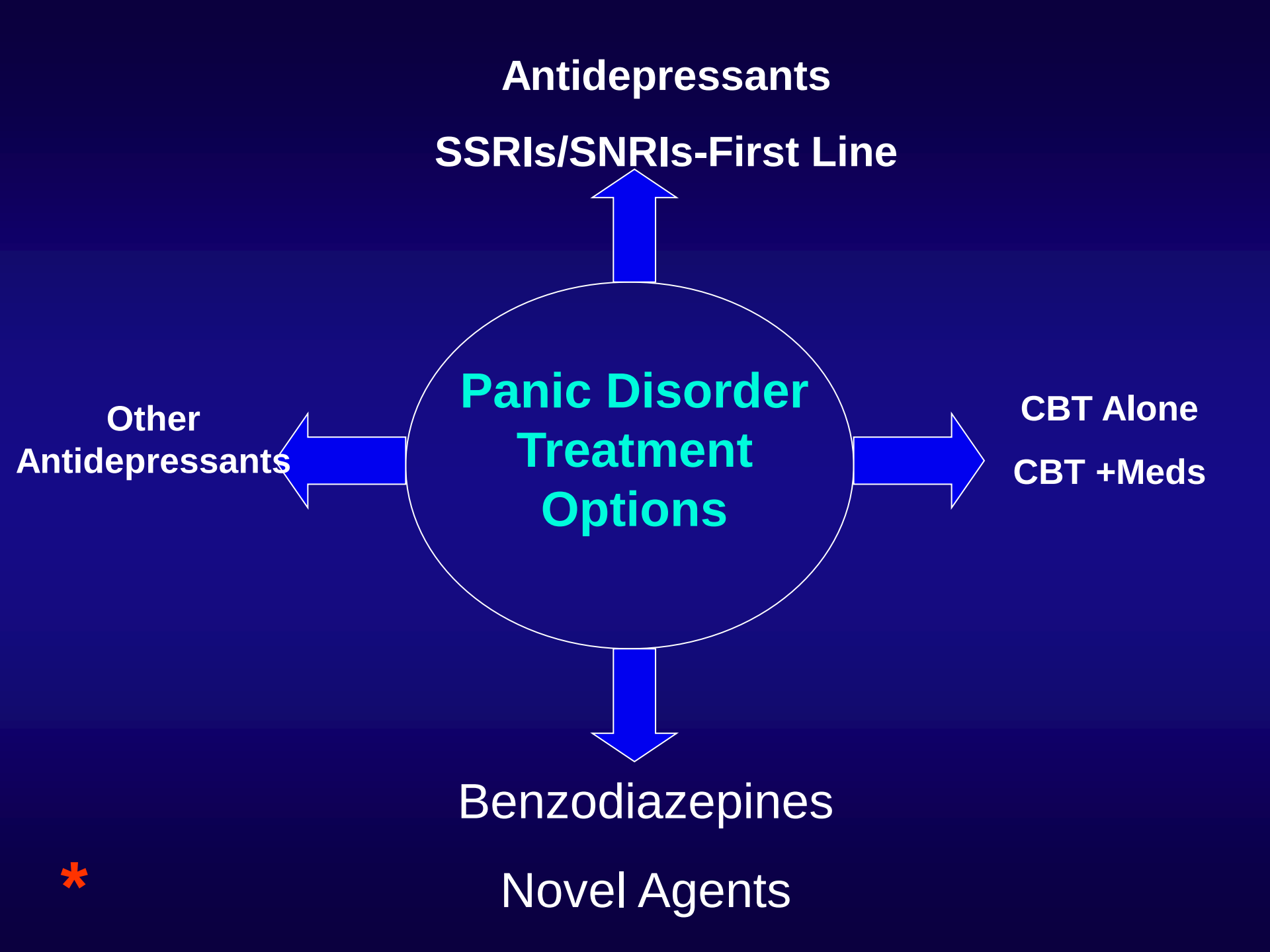
PD: Patient Approach *(cont.)*

- Collaborative approach promotes less perceived threat and lack of control
- Map out "the plan", document treatment
  - usual dose needed, necessary duration, how you will deal with possible adverse effects
- Give the patient some control
  - You: "I will help you steer the car, but you will control the gas pedal as we drive toward our goal. We will get there eventually."

[1]Hirshfeld DR et al. Panic disorder and its treatment., New York:Marcel Dekker,1998:93-152; Lydiard RB. In Textbook of Anxiety Disorders. Washington, DC: American Psychiatric Press, Inc; 2002:348-361.

PD: Patient Approach *(cont.)*

- **Initial Goals to Outline**
  - Reduce and stop unexpected attacks (unexpected)
  - Situation-bound attacks
  - Fearful anticipation
  - Fearful (phobic) avoidance
  - Distorted, catastrophic cognitions


Antidepressants
SSRIs/SNRIs-First Line
Other Antidepressants
Panic Disorder Treatment Options
CBT Alone
CBT +Meds
Benzodiazepines
Novel Agents
*

PD Outcome Assessment

- ***Functional status is key issue !!***
- **Panic attacks alone-- least useful measure**
  - **Poor correlation with other domains**
- **PDSS-Gold Standard Assesses Multiple Domains**
  - **Phobic avoidance**
  - **Cognitive distortion**
  - **Depression**
  - **Somatic symptoms**

* Shear et al Panic Disorder Severity Scale. Am J Psychiatry 1997; 154:1571-1575 panic frequency, severity, phobia, impairment

CBT: Pros and Cons

- Advantages
  - 70%–85% efficacy
  - May have low relapse rate when discontinued
  - Most people like it
  - Time-limited
  - Overall low price
  - Few adverse effects
- Disadvantages
  - Harder to administer than medication
  - Limited availability
  - More effort than taking medication
  - Lack of third-party coverage
  - Not all patients willing or able
    - Cognitively impaired
    - Severe disorders

American Psychiatric Association. *Practice Guideline for the Treatment of Panic Disorder*. 1998; Ballenger. *Biol Psychiatry.* 1999;46:1579; Fava et al. *Br J Psychiatry.* 1995;166:87.

CBT for PD

- Targets fear of bodily sensations
  - Breathing retraining
  - Cognitive restructuring
  - Interoceptive exposure to physical symptoms
  - Exposure to feared situations
    - Technique-Hierarchy least to most feared, in that order

PD Drug Treatment: General Principles

- **SSRIs or *SNRI First Line**
  - **Other ADs work**
  - **MAOIs**
  - **Benzodiazepines**
    - **Not reliably antidepressant, useful adjunct**
  - **Beta-blockers**
    - **Not adequate as monotherapy, may help reduce physiologic arousal symptoms**

Stein MB et al. Pharmacologic treatment of panic disorder. Curr Top Behav Neurosci. 2010;2:469-85.

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Efficacy of PD Pharmacotherapy

Agents/ Classes with Proven Efficacy*

PD	GAD	SAD	PTSD
SSRIs	SSRIs / SNRIs	SSRIs	SSRIs
BZD	BZD	Venlafaxine	MAOIs
TCAs	TCAs	BZD*	TCAs
MAOIs	Buspirone	MAOIs	Mirtazapine
Venlafaxine	Trazodone	Clomipramine	Nefazodone
		Gabapentin*	

•Not reliably antidepressant or insufficient information

*Consideration includes comorbid disorders

Not all agents in all classes approved by FDA but all empirically supported in RCTs; duloxetine not yet studied

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Adapted from: Lydiard RB. *Textbook of Anxiety Disorders*. Washington, DC: American Psychiatric Press, Inc; 2002:348-361;. Stein MB et al. Pharmacologic treatment of panic disorder. Curr Top Behav Neurosci. 2010;2:469-85.

Therapies With Limited or No Proven Efficacy in PD

PD	GAD	SAD	PTSD
AEDs* ± Bupropion Buspirone (adjunct) Mirtazapine Atypical NLs#	AEDs Atypical NLs Mirtazapine	AEDs Bupropion Atypical NLs	AEDs Atypical NLs Bupropion Buspirone TCAs Trazodone

*AEDs-antiepileptics-gabapentin. topiramate . levetiracetam
NL= neuroleptic

*Atypical NLs Benefits shown in open-label studies with treatment resistant PD. Not first line choice.

Adapted from: Lydiard RB. *Textbook of Anxiety Disorders*. Washington, DC: American Psychiatric Press, Inc; 2002:348-361;. Stein MB et al. Pharmacologic treatment of panic disorder. Curr Top Behav Neurosci. 2010;2:469-85.

Adverse Effects of PD Pharmacotherapy

SSRIs/SNRIs	**Activation , sexual dysfunction, weight gain**
Benzodiazepines	**Not antidepressant , physiologic dependence/ potential withdrawal, initial coordination sedation, fear of addiction**
TCAs	**Limited breadth of efficacy, activation, cardiovascular adverse effects , overdose danger**
MAOIs	**Diet / drug interaction, postural hypotension, insomnia, weight gain, sexual dysfunction, overdose danger**

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Selection Considerations

- Personal Hx efficacy, tolerability
- Safety
- Tolerability
- Half-life
- Drug-drug interactions
- Cost
- Protein binding

*

PD Medications That Don’t Work

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

*

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

*

SSRIs/SNRIs for PD: Advantages

- **Wide safety margin**
- **Relatively low side effect profile**
- **Broad spectrum of mood and anxiety efficacy**
- **No significant cardiovascular effects**
- **No or minimal anti-cholinergic effects**

Stein MB et al Pharmacologic treatment of panic disorder. Curr Top Behav Neurosci. 2010;2:469-85.

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SSRIs/SNRIs For PD: Disadvantages

- May have delayed onset
- Initial activation
- Sexual side effects -25-60%
- Weight gain over 3-12 months in small but clinically significant subgroup

Stein MB et al Pharmacologic treatment of panic disorder. Curr Top Behav Neurosci. 2010;2:469-85.

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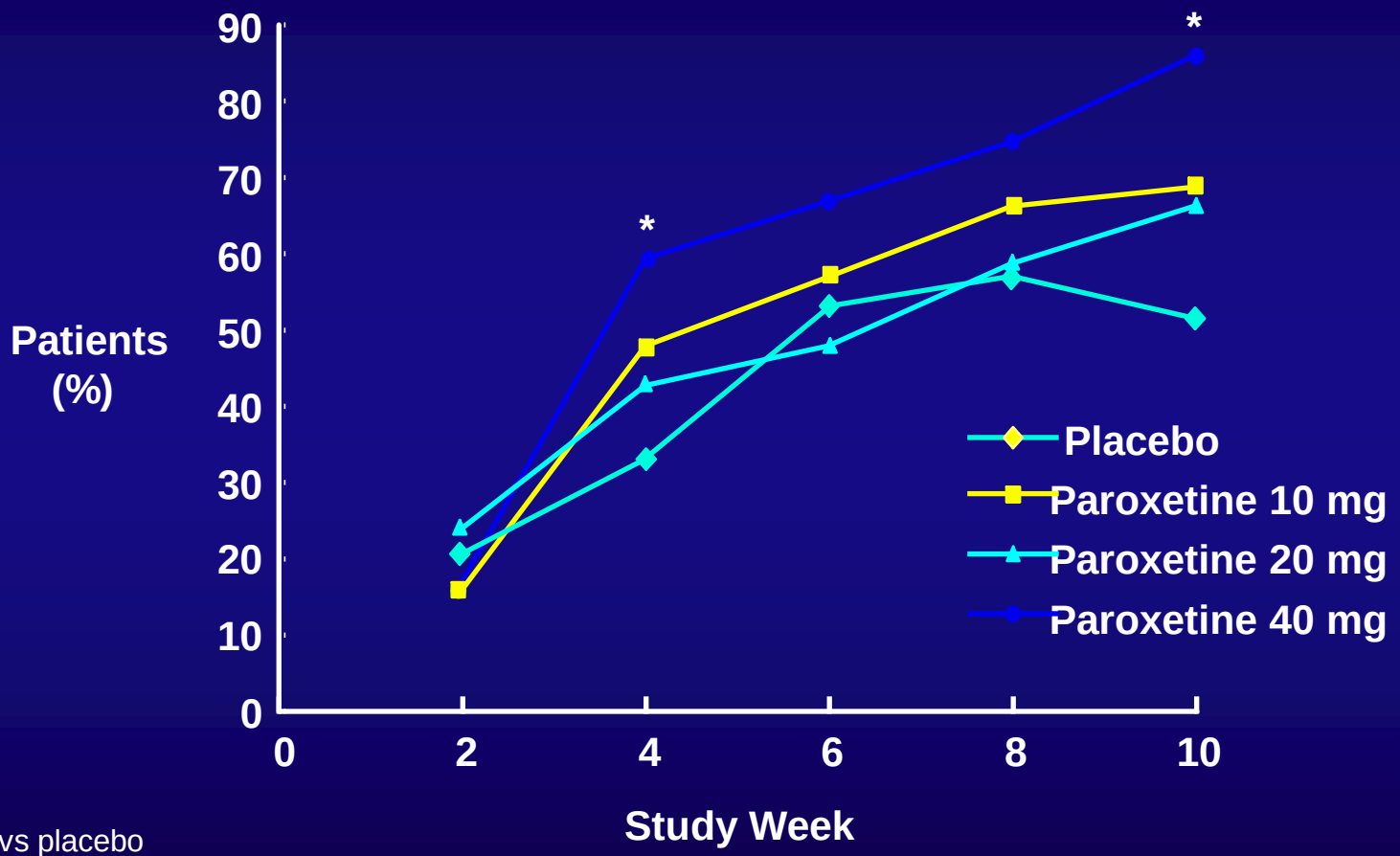
SSRIs/SNRIs

- Initial dose (reduce activation risk)
  - (25–50% antidepressant dose)
    - Sertraline 12.5–25 mg
    - Paroxetine 10–20 mg
    - Fluoxetine 5–10 mg
    - Fluvoxamine 25–50 mg
    - Citalopram 10–20 mg
    - Escitalopram 5-10
    - Venlafaxine 37.5 mg

*

Percent Patients Attaining Panic-Free Status Paroxetine Fixed-Dose Study

The 40 mg dose was statistically better than placebo. 10 and 20 mg were not, but were effective for many--no one dose dose is THE dose for 'all patients

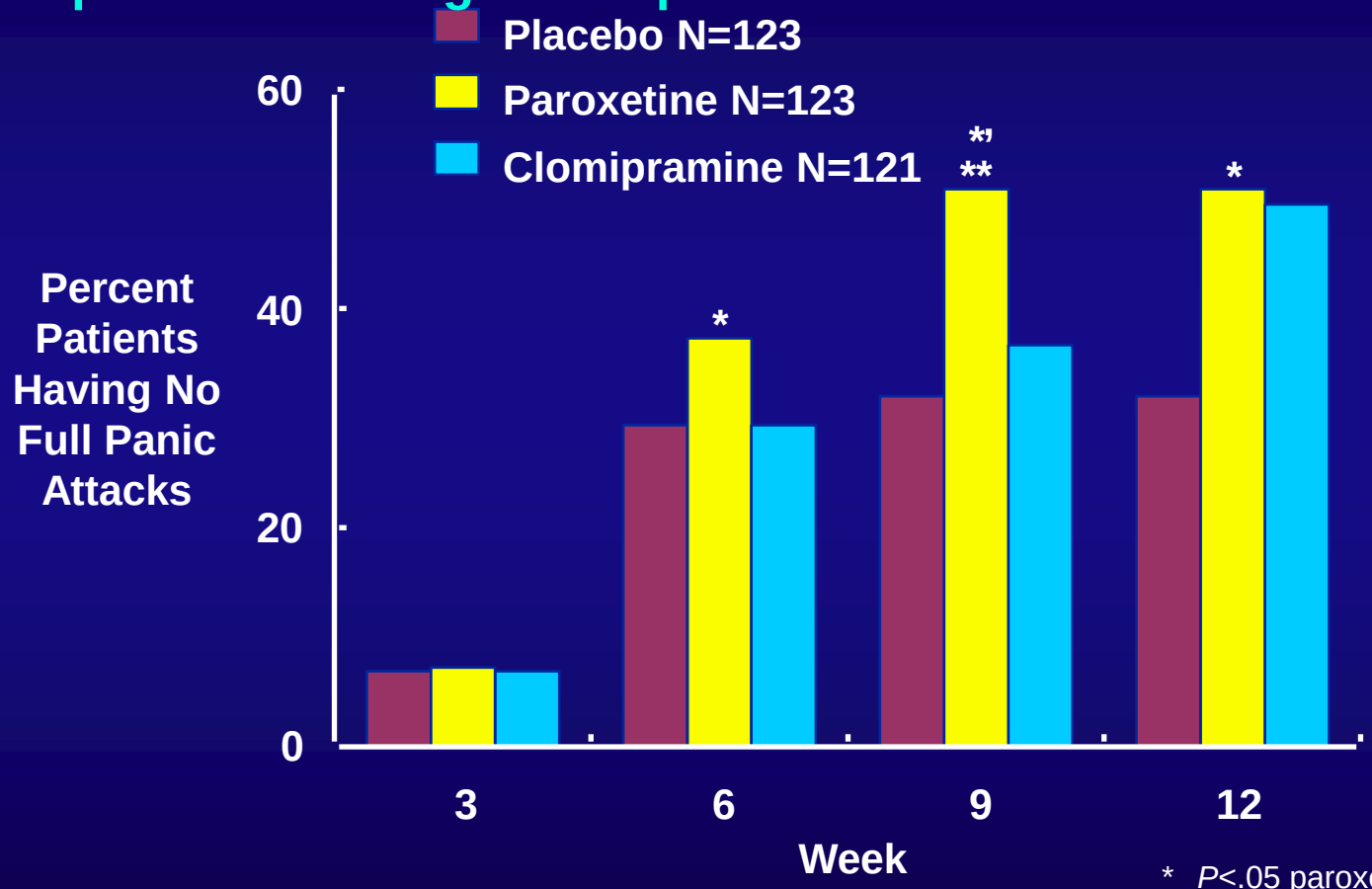


*P<.019 vs placebo

Ballenger et al. *Am J. Psychiatry*1998; 155:36-42

Paroxetine vs Clomipramine† Treatment Of PD

CMI patients had higher dropout rates due to side effects

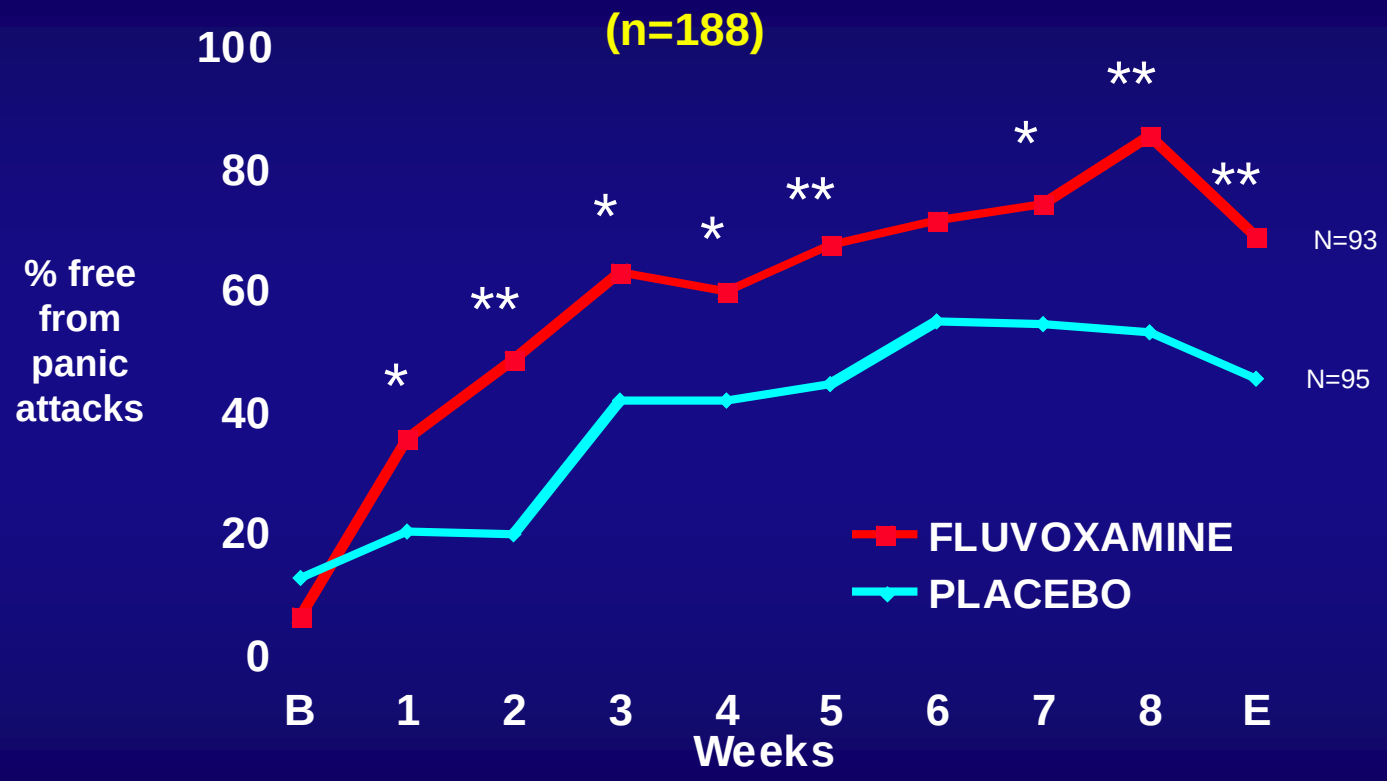


* *P*<.05 paroxetine vs placebo.

** *P*<.05 paroxetine vs clomipramine. Lecrubier et al Acta Psychiatrica Scand 1995; 95:145-152

†Not indicated for treatment of panic disorder in US.

Fluvoxamine vs Placebo
% Free from Panic Attacks

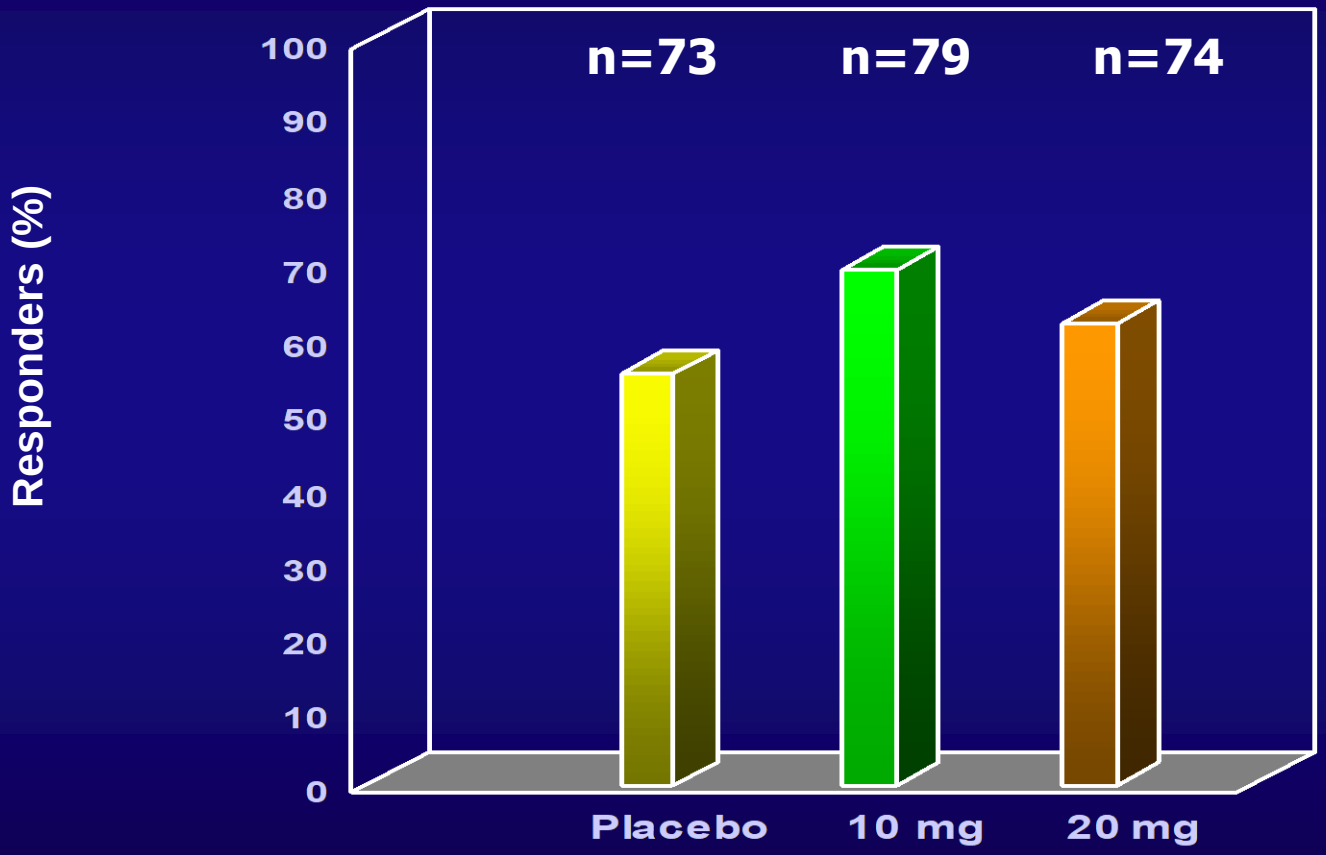


* p < 0.05*; *p < 0.01 vs placebo

Asnis et al, Psychiatry Res. 2001 Aug 5;103(1):1-14..

*

Panic Disorder: 10 Weeks' Treatment
Fluoxetine 10 or 20 mg vs Placebo: CGI Responders

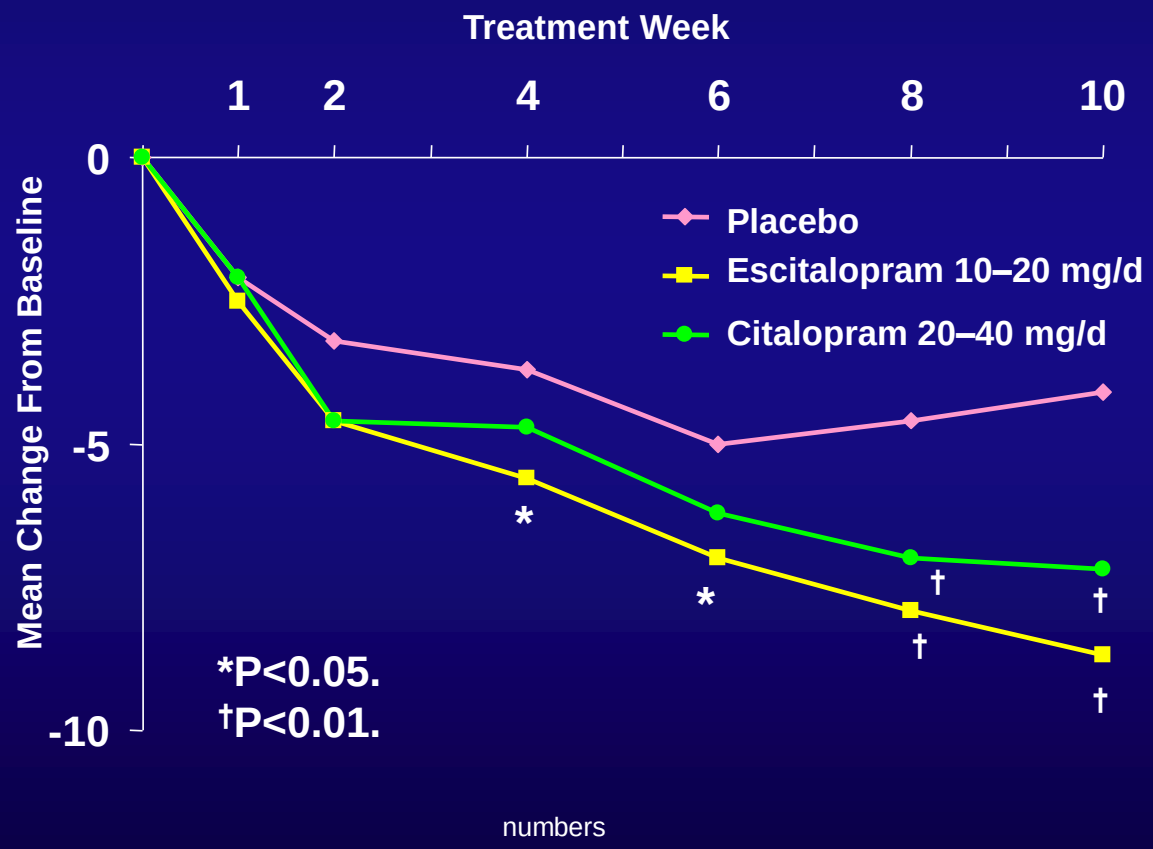


*

Michelson D, Lydiard RB, Pollack MH, Tamura RN, Hoog SL, Tepner R, Demitrack MA, & Tollefson GD. *Am J Psychiatry* 1998; 11: 1570-77.

Escitalopram Treatment of Panic Disorder

Panic and Agoraphobia Scale



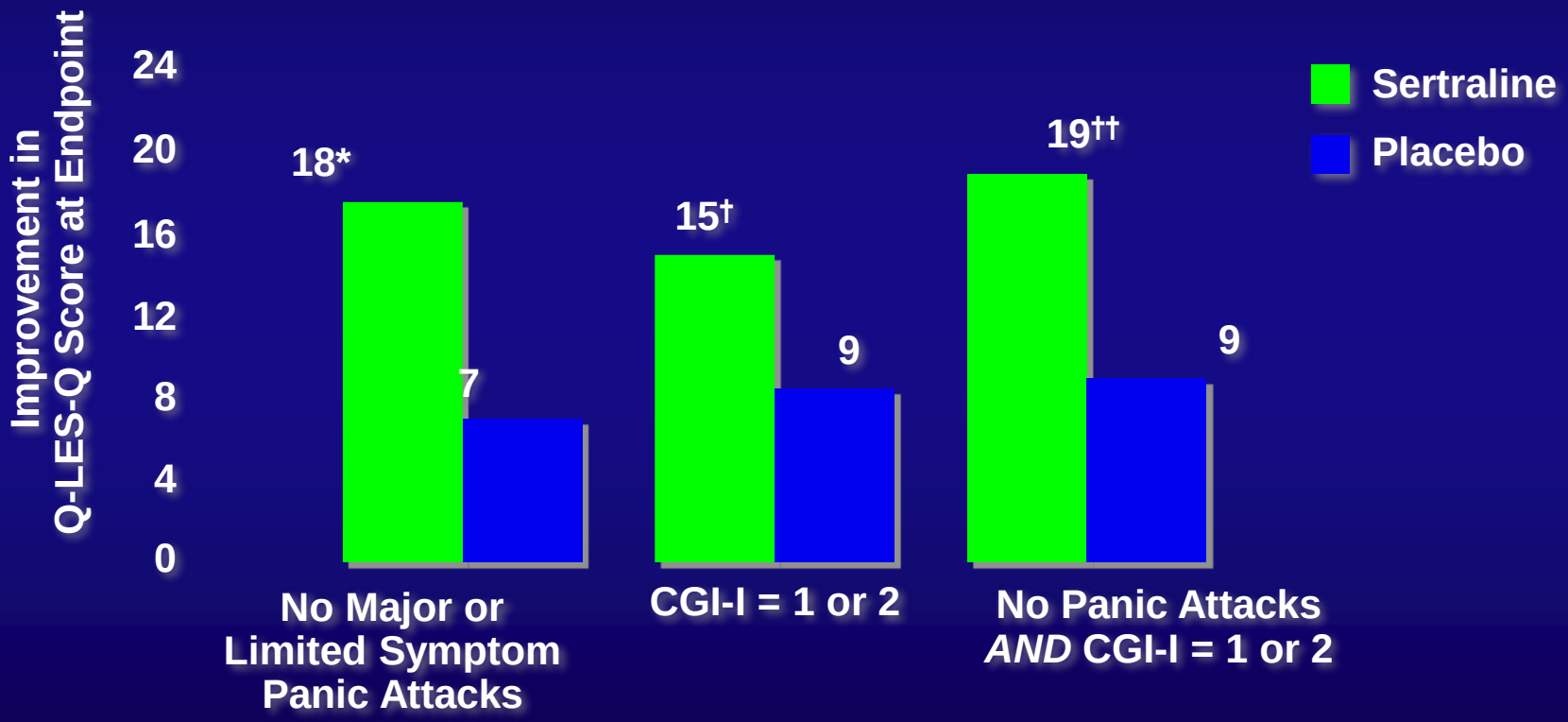
numbers

*

Stahl, SM et al APA, 2002

Quality of Life Measures- A Better Way to Assess Outcome?

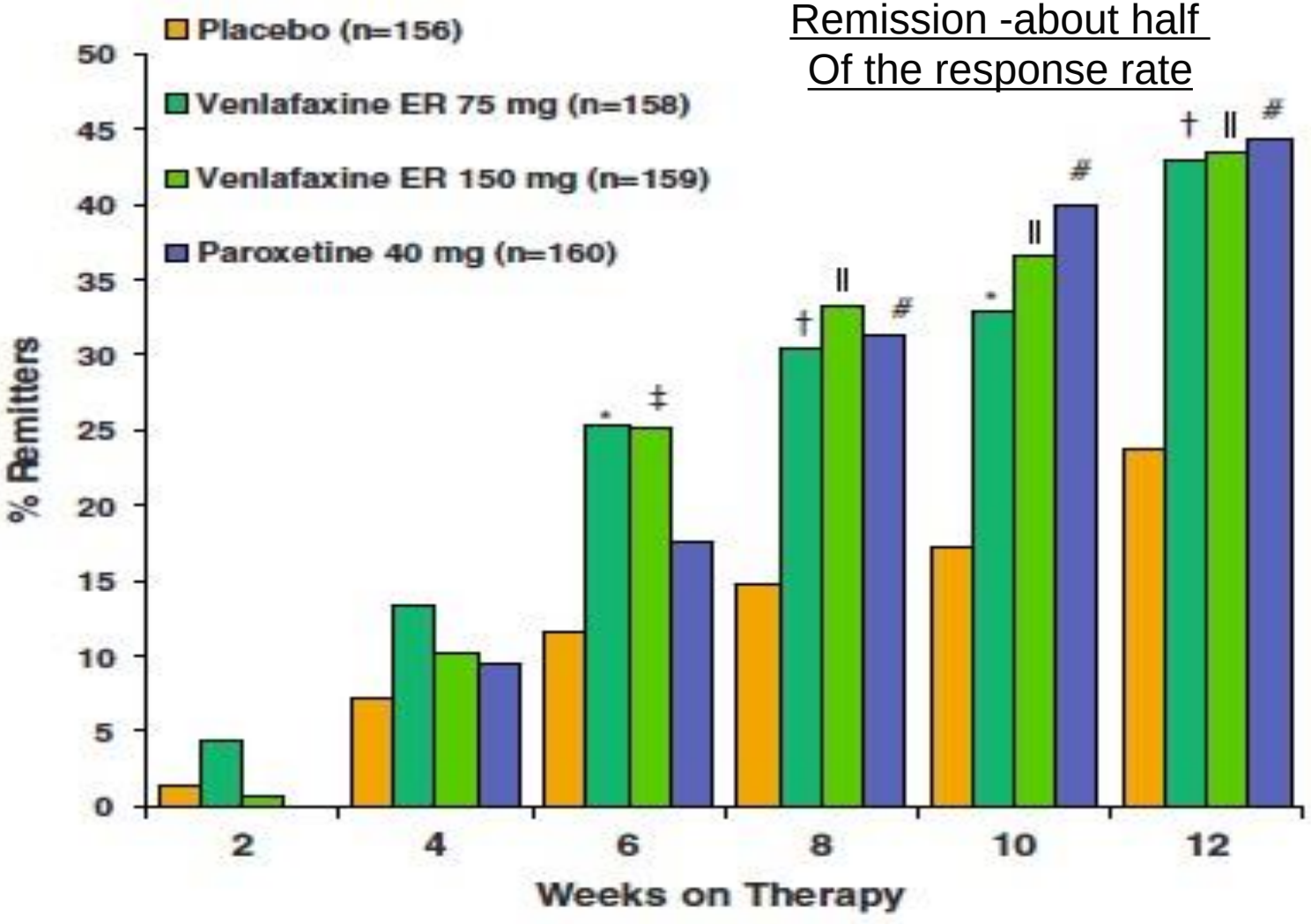
Sertraline Responders Report Significantly More Quality of Life Improvement Than Do Placebo Responders



Pairwise Comparison of Adjusted Mean Change Scores:
* *P*<0.001 † *P*<0.007 †† *P*<0.003
Rapaport et al., 1998

*

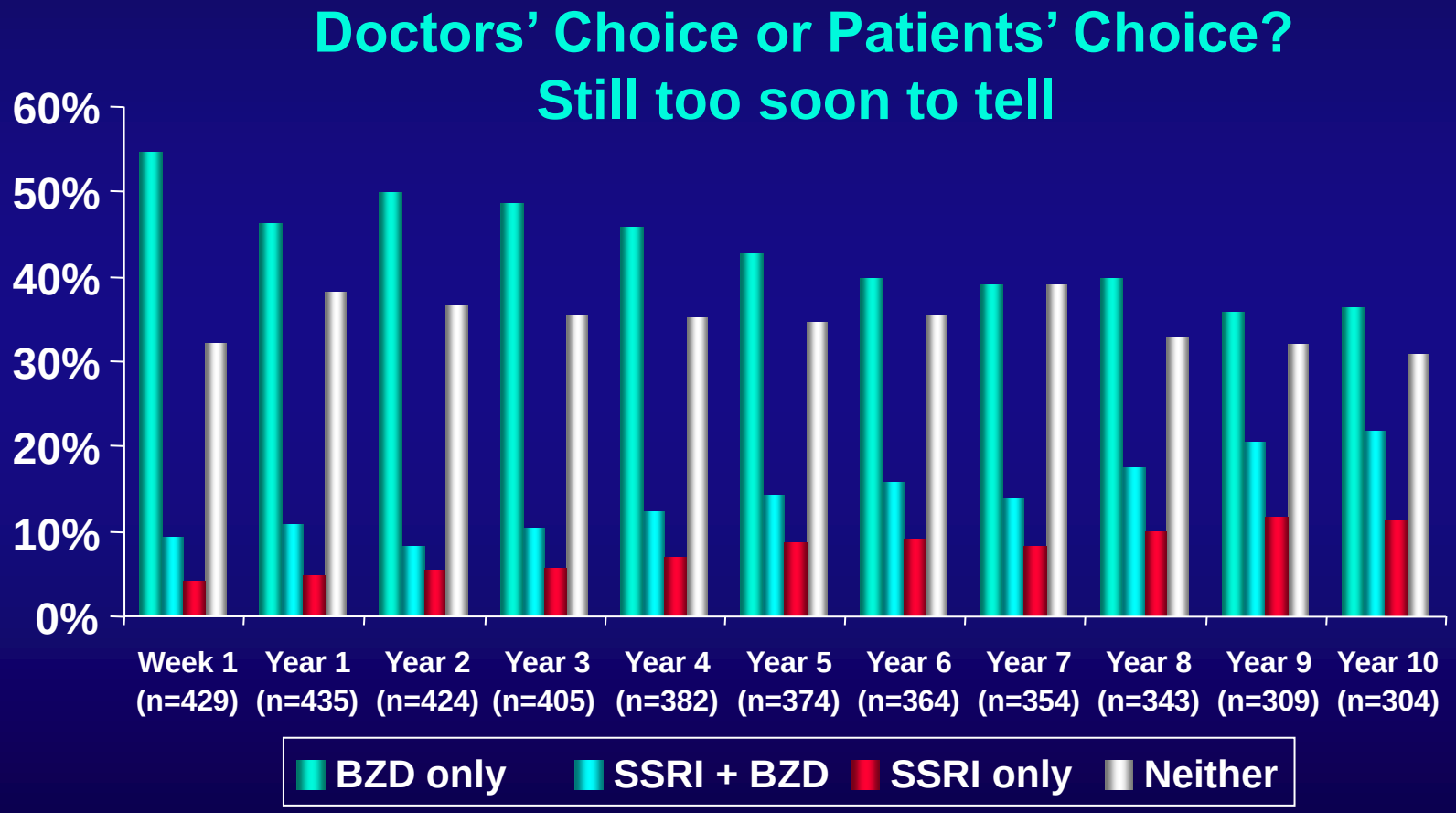
SSRI vs SNRI vs PBO



Remission -about half
Of the response rate

Pollack et al, Depression and Anxiety 2007; 24:1–14

Long-term Pharmacotherapy Received by PD Patients (1989–2001)



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Bruce SE et al. Am J Psych 2003l 160:: 1432-8; BZD= benzodiazepines

TCAs: Advantages

- Antidepressant
- Volume of clinical experience
- Imipramine Rx--[imipramine + desipramine] ≥ 100 ng/ml likely effective for many patients

*

TCAs: Disadvantages

- Delayed onset of action
- Significant side effects burden
  - Jitteriness--start with 10 mg daily
  - Weight gain
  - Sexual dysfunction 25-40%
- Anticholinergic effects
- Cardiotoxicity
- Danger with overdose
- Not useful for social anxiety disorder

*

Antidepressant Discontinuation

- Gradual taper (≥ 2 months)
- Properties of agent affect timing and severity of discontinuation Sx
  - Shorter t 1/2 -earlier
  - No active metabolite-earlier
  - Extended release formulation does not protect

*

Discontinuation/Withdrawal Symptoms Following SSRI Treatment

- Anxiety/agitation
- Light-headedness
- Insomnia
- Fatigue
- Nausea
- Headache
- Sensory disturbance

*

Zajecka et al. J Clin Psychiatry 1997;58:291.

Benzodiazepines: Advantages

- Effective
- Rapid onset
- Tolerability
- Safety

*

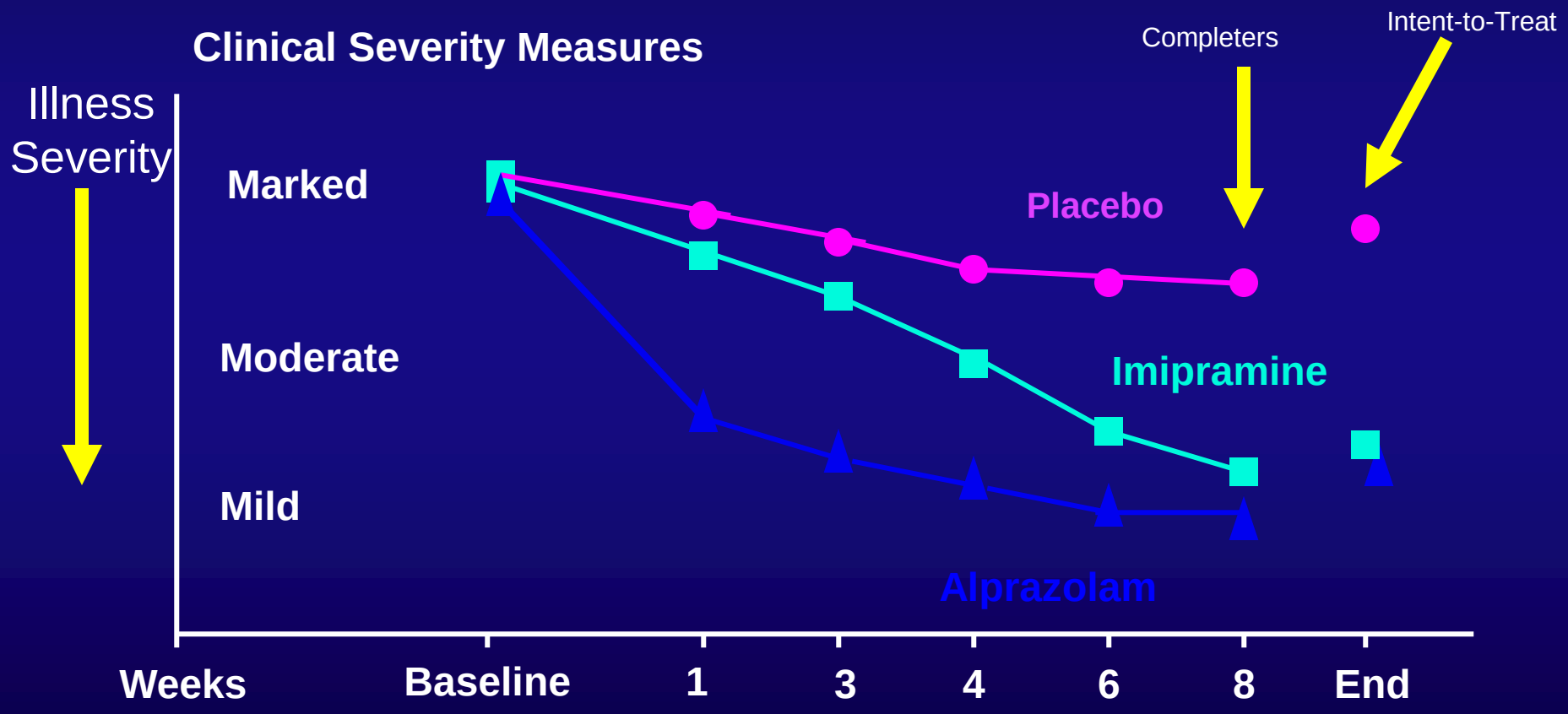
Benzodiazepines: Disadvantages

- Not antidepressant
- Physiologic dependence
- Sedation and coordination problems
  - (2 - 4 weeks)
- Subjective memory loss
  - Inconsistent empirical evidence

*

*Comparative Efficacy of Alprazolam, Imipramine and Placebo in 1080 Panic Disorder Subjects

(Diagram reflects general pattern of improvement in clinical measures over 8 weeks)



Cross-National Collaborative Panic Study Br J Psychiatry 1992 Nov;161:724

Benzodiazepines: Long-Term Follow-up

- 60 PD patients
- 2.5 year average follow up
- Alprazolam Rx + behavioral group
- 18 (30%) discontinued
- 36 (60%) lower dose
- 3 (5%) same dose
- 3 (5%) increased dose

*

Nagy et al, *AGP* 1989;46:993

Polypharmacy-SSRI plus:

- Benzodiazepines
  - Jitteriness, anticipatory anxiety, insomnia
- Beta Blockers
  - Tremor, palpitations, sweating
- Bupropion
  - Sexual side effects

*

Definition of Response

- **Symptoms**
  - **Panic attacks: at least 50% decrease**
  - **Other PD symptoms clearly much or very much improved (anticipatory anxiety, phobic symptoms)**
- **Time frame**
  - **to response: 6-12 weeks**
  - **of response: 4 -8 weeks**

*

Definition Remission

- Full recovery of pre-morbid functioning
- Full relief of symptoms
- No panic attacks (or not more than 1 mild one in a 4-8 week period)
- No clinically significant anxiety
- No clinically significant phobic symptoms
- Lasting remission may be elusive due to undulating course of illness

*

Inadequate or Non-response

- Identify element (s) unimproved
  - Panic attacks, avoidance, anticipatory anxiety, depression
- Medication dose and duration inadequate?
  - No-->Increase?
  - Yes-->Augment?
  - Yes-->Change?
- All adequate?-->Add CBT
- Reconsider diagnosis

*

Resistant Panic Disorder -Approach

PROBLEM REVIEW	DIFFERENTIAL DIAGNOSIS	COMMENT
Persistent panic attacks	• Inadequate treatment • Dose • Duration • Situational attacks • Medical condition • Other psychiatric disorder causing attacks • Medication-related	• Adjust dose (plasma levels may help) • Switch or add agent to existing • At least 8 weeks • CBT/exposure • Address specific conditions (Table 3) • Rule out social phobia, OCD, PTSD
Persistent anticipatory/ generalized anxiety	• Activation • Akathisia • Substance-related • Interdose rebound from short-acting BZ • BZ or alcohol withdrawal • Residual anxiety	• Adjust dose, add BZ or beta blocker • Adjust dose, add beta blocker, BZ • Switch to longer-acting agent • Assess and treat as indicated • Add/increase BZ, add buspirone
Residual phobia	• Other etiology • Residual agoraphobia	• Review for other phobic disorders, depression • CBT/exposure, adjust medication treatment
Other disorders	• Mood disorder • Anxiety disorder • Social phobia • OCD • PTSD • Alcohol use disorder • Personality disorders • Medical disorder	• Antidepressant treatment plus anxiolytic; valproate for bipolar disorder • SSRIs, MAOIs, BZs, CBT • SSRIs, CBT, anxiolytics as indicated • Specific treatment for symptoms present, SSRIs, CBT, others • Psychosocial treatment for alcohol-related behavior • SSRIs, TCA, avoid BZs • Specific psychotherapy • Review and modify treatment as indicated
Environmental event/stressor(s)	• Review work, family events, patient perception of stressor	• Family/spouse interview and education • Environmental hygiene as indicated • Brief adjustment in treatment plan(s) as necessary
Other	• Poor adherence • Sexual side effects • Inadequate understanding of panic disorder/treatment	• Add/switch agents,consider brief drug holiday • Patient/family education • Make resource materials available

Dosing Suggestions for Panic Disorder

CLASS/AGENT	STARTING DOSE (MG/D)	TYPICAL EFFECTIVE DOSE (MG/D)*
SSRIs		
Sertraline	12.2–25	150–300
Escitalopram	5	10–30
Fluoxetine	2–5	40–80
Fluvoxamine	25	150–300
Paroxetine	5–10	40–60
SNRI		
Venlafaxine	18.75–37.5	150–300
Benzodiazepines		
Alprazolam	0.5–1.0	2–10
Clonazepam	0.25–0.5	2–6
Tricyclics		
Clomipramine	10	>200
Desipramine	10	>300
Imipramine	10	>300
MAOIs		
Phenelzine	15	>90
Tranylcypromine	10	>70
Antiepileptics		
Valproate	250–500	1,000–2,000
Gabapentin	100–200	600–3,400
Levitracitam	250–500	1500–3000**
Tiagabine	unknown	unknown
Vigabatrin	unknown	unknown

* 4–6 weeks should be allowed to assess effectiveness
** Information on dosing is anecdotal

Based on literature and experience of the authors;

Holt RL, Lydiard RB. Management of treatment-resistant panic disorder. Psychiatry (Edgmont). 2007 (10):48-59

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

*

Effective Long-term Treatments for Panic

- SSRIs and other antidepressants
  - Preferred for long-term treatment
- Benzodiazepines
  - Monotherapy effective; risk for emergent depression
- Novel agents (anticonvulsants)
- CBT
- Combination

*

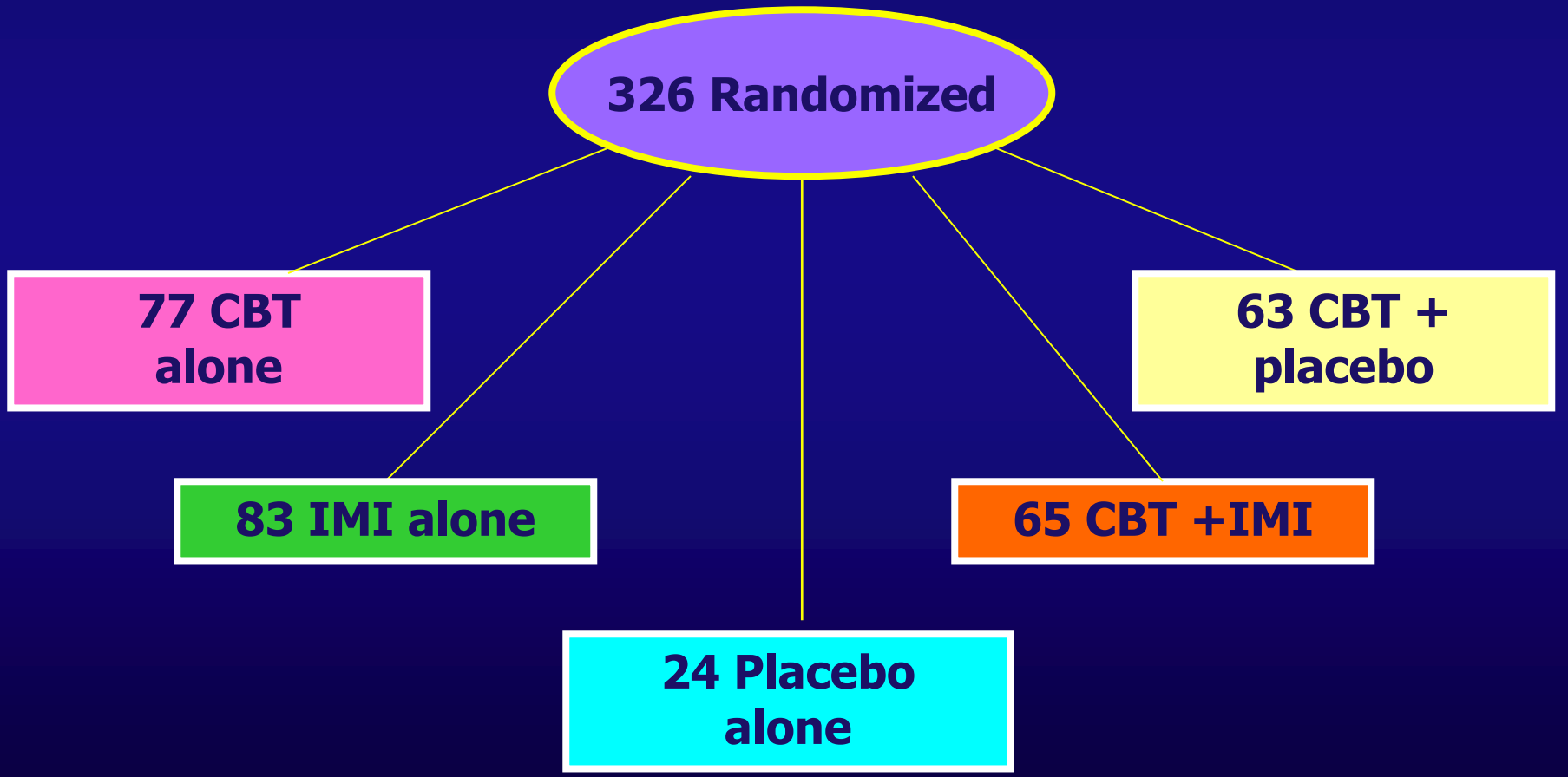
Combination Treatments

Meds + CBT

Meds + Meds

CBT, IMI or CBT +IMI

Treatment for Panic Disorder



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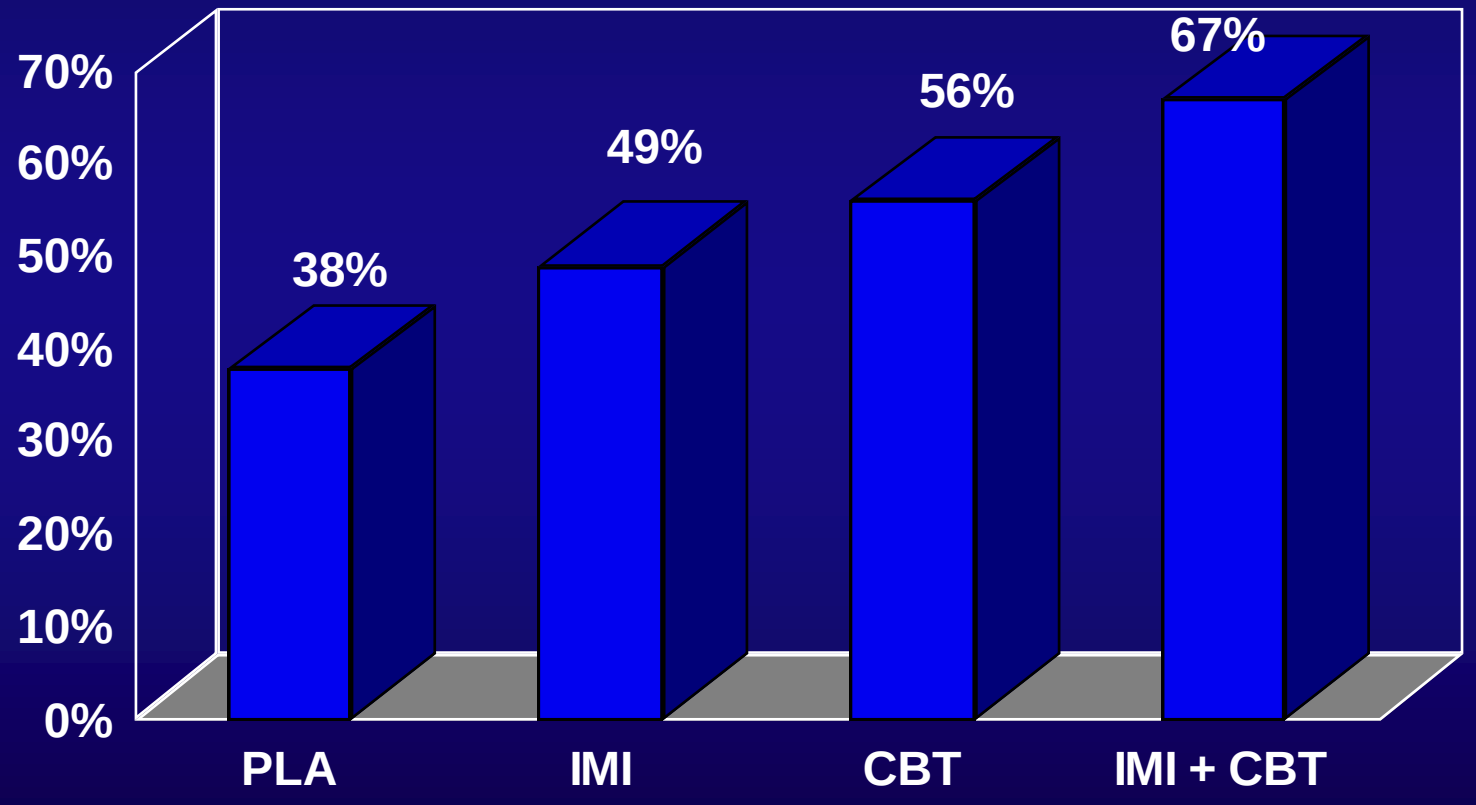
Barlow D. et al., *JAMA* 2000; 283: 2529-36.

3-Month Responders

Multicenter Comparative Treatment Study

(intent-to treat)



X^2 p =0.03; C+I vs I : p = 0.03; C+ I vs P p = 0.02;

*

Barlow D. et al., *JAMA* 2000; 283: 2529-36.

Meta-Analysis of Combined Treatments for PD

- 106 Studies, short-term treatments
- N= 5011 Pre-Rx, 4016 Post-Rx
- 222 Treatment conditions
- Variables were
  - med alone
  - med + exposure in vivo
  - placebo + exposure in vivo
  - exposure in vivo plus psych management

Van Balcom et al JNMD1997 185:510-16

*

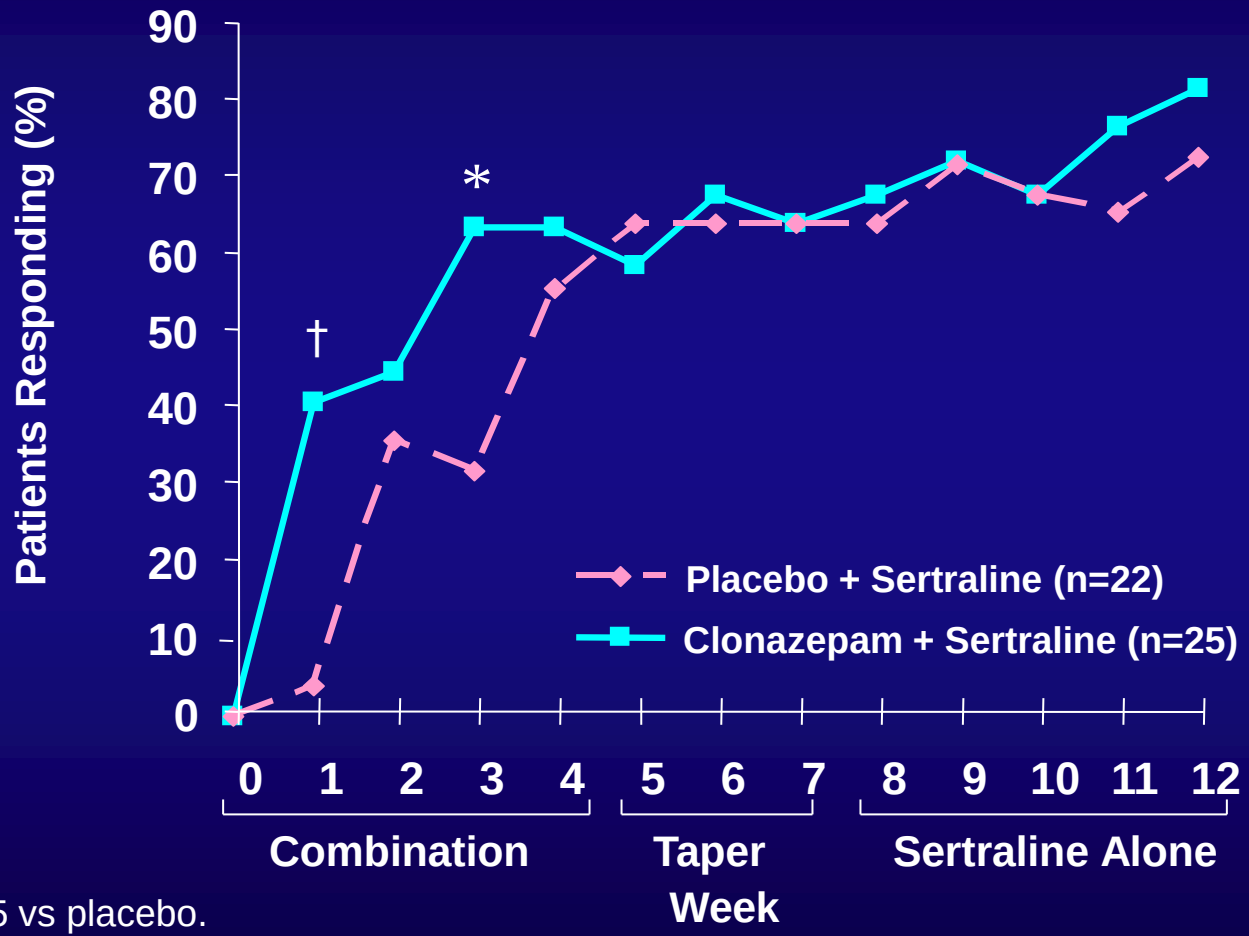
Meta-Analysis of Combined Treatments for PD

- All treatments superior to placebo conditions for agoraphobic avoidance; CBT = other treatments
- Antidepressant superior to PBO for panic attacks
- Exposure not effective against panic attacks but worked for agoraphobia

*

Combining Medications For Panic Disorder

Sertraline + Clonazepam or PbO



* *P*<0.05 vs placebo.
†*P*<0.003 vs placebo.
Goddard et al. *Arch Gen Psychiatry.* 2001;58:681.

Atypical Neuroleptic Monotherapy for Anxiety

- FDA did not approve indication for quetiapine monotherapy for GAD or MDD (April,2009)
  - 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

This section is optional
-prn use

Benzodiazepines-

Lots of heat, little light

Benzodiazepine Pearls

- **Benzodiazepines**
  - **Abuse in anxious patients *very rare***
  - **Tolerance to anxiolytic effects very rare**
  - **Lower maintenance than acute doses often sufficient**
  - ***Altered and lower number of BZ receptors in PD--higher doses may be needed***

*

Patients Can Discontinue BZs if:

- Motivated and well-informed about taper plan
- Clinician concurs
- No stressful events expected
- Very gradual taper is used
- Patient understands that
  - Return of original Sx is **NOT FAILURE**
  - Continued Rx may indicated

*

Discussing Patient Concerns About Dependence

- Patients often express concerns about becoming dependent on medication
- Question: is it worth it to wear eyeglasses?
  - *Should you expect to continue to see properly after 6-12 months?*
  - *If you could not see as well, would you feel as if you were "dependent" on glasses?*
- Use other medical analogies, such as utilizing insulin for diabetes or inhalers for asthma

*

Withdrawal and Dependence

- *Physiologic Dependence*
- **Physiologic adaptation produced by repeated administration of a drug, necessitating continued administration to prevent the appearance of *discontinuation* symptoms.**
- **Can occur with antidepressants, other agents**

*

Addiction and Abuse

Medical vs Non-medical Psychoactive Substance Use

See also notes section on Additional Resources slide

*

Medical vs Nonmedical Use

	Medical Use	Nonmedical Use
Intent	To treat diagnosed illness	To "party" or to "treat" distressing effects of alcohol or other drug abuse
Effect	Makes life of user better	Makes life of user worse
Pattern	Stable, medically sensible	Unstable, usually high dose
Control	Shared honestly with physician	Self-controlled
Legality	Legal	Illegal (except alcohol use by adults)

*

DuPont RL. *Bull Menninger Clin.* 1995;59(suppl A):A53-A72.

Key Features of Addiction

Use eyeglasses and heroin addiction as models to help illustrate to patient what is and is not addiction

*

DuPont RL. *Bull Menninger Clin.* 1998;62:231-242.

Time to Stop?
Using the BZD Checklist

- **Problem being treated**
  - **Does problem justify continued use of BZD?**
  - **Has patient significantly benefited from BZD treatment?**
- **BZD use**
  - **Does patient's use of BZD remain within prescribed limits and duration of treatment?**
  - **Has the patient avoided the use of other prescribed or nonprescribed agents?**

DuPont RL. *Benzodiazepines: The Social Issues – A Guide for the Physician.* Rockville, Md: The Institute for Behavior and Health, Inc.; 1986. (cont)

*

Using the BZD Checklist

- **Toxic behavior**
  - **Has the patient been free of any signs of intoxication or impairment from the use of the BZD medication, either alone or in combination with other agents?**
- **Family monitor**
  - **Does the patient's family monitor confirm that there have been no problems with BZD use and that the patient has benefited from the use of the medication?**

*

DuPont RL. *Benzodiazepines: The Social Issues – A Guide for the Physician.* Rockville, Md: The Institute for Behavior and Health, Inc.; 1986.

How to Discontinue Medication for Panic Disorder

Step 1: Patient and physician alliance

Step 2: Taper → Symptoms appear → Wait 2-3 weeks*

Step 2: Taper → Symptoms persist → May need to continue treatment*

Step 2: Taper → Symptoms disappear → Continue taper

- **Symptoms may be withdrawal or reemergence of panic**

*

BZ Taper Outcome

- **Panic-related symptoms which stably persist reappear during taper**
  - **Clinically informative outcome of taper attempt**
  - **Indicate that continued Rx necessary**
- **Options**
  - **Continue pharmacotherapy**
  - **Add CBT, attempt taper again later**
  - **Combined**

*

BZ Taper Strategy

- ~10% reduction in dose / 2-3 wks
  - No more than 25% per week
- At 50% of initial dose, slow taper
- Short-acting BZ: Maintain multiple daily doses to minimize plasma level fluctuations
- Switch to long-acting agent may be useful but probably not necessary
- CBT may enhance taper success

*

Recurrence of Sx during Taper Suggested Strategy

- Stop taper
  - May increase dose to tolerable discomfort level
- Hold at same dose 2-4 weeks
  - If Sx Persistent =Probably Panic-related
  - If Sx gone= Probably BZ taper -related
- New Sx more likely withdrawal
  - Sensitivity to noise and light
  - Dysesthesia, others

*

Is Long Term BZ for Panic Disorder Acceptable?

- PDR: BZ are ok for 4 months--
  - Then what???
- American Psychiatric Association Formally Supports Use of Long-term BZ As Needed (Salzman)
  - For Panic Disorder, GAD
  - Intolerance to other meds
  - Incomplete response

*

Long Term BZ May Be Justified

- Document rationale for long-term requirement in record
- Significant other(s) can corroborate if:
  - Continued benefit
  - No non-medical BZ use (abuse)
  - No BZ-related toxicity
- Consultation from colleague to document medico-legal and clinical clarity

*

Pearl: If it's Anxiety ,
there is risk for Depression

Pearl: When in Doubt, Treat as if Depression was Imminent

Summary
Treatment Decisions

- Initial pharmacotherapy: SSRIs
- Start with low dose
- Use ≥ 2 different SSRIs before changing classes
- Utilize CBT to reduce attrition, reduce fear of bodily sensations, eliminate phobic avoidance, and facilitate discontinuation of medication

Summary

- "If it quacks like a duck and waddles, it is likely a duck."
- Panic disorder is common and disabling, and is treatable
- Under-recognized and under-treated
- Functional status -NOT panic attack frequency to assess outcome

Additional Resources

- Anxiety Disorders Association of America
  - www.adaa.org
- National Institute for Mental Health: Anxiety Disorders
  - www.nimh.nih.gov/anxiety/anxietymenu.cfm
- See notes section on this slide for review of benzodiazepine use

Acknowledgements

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Harvard Medical School

In memory of

Nicholas Ward, MD

University of Washington, Seattle

Question #1

True or False

Males Have a Higher Lifetime Frequency of Panic Disorder in the U.S. as Compared to Females.

Question #2

True or False

When PD and MDD co-exist, the risk for suicide attempts increased

Question #3

Panic Disorder increases the risk for other psychiatric disorders : GAD, OCD, social anxiety disorder, major depression

Which usually precedes panic disorder?

Question #4

What is the APA recommend as

First Line Pharmacotherapy for Panic Disorder?

Question #5

Which sub-cortical structure is the critical brain nucleus for fear conditioning?

Answer #1

False!

Female – 5% Lifetime Frequency

Male – 2% Lifetime Frequency

Answer #2

True, True, and True!

Answer #3

Social Anxiety often precedes panic disorder

Answer #4

SSRIs

Answer #5

Amygdala