

# Treatment of Panic Disorder

R. Bruce Lydiard, MD, PhD  
Director

Southeast Health Consultants, LLC  
Charleston, SC

<[www.mindyourhealth.net](http://www.mindyourhealth.net)>

# **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 Attack Symptoms

≥ 4, 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 (unreality) or  
depersonalization (detached)
12. Fear of losing control or going crazy
13. Fear of dying

# DSM-IV Panic Disorder

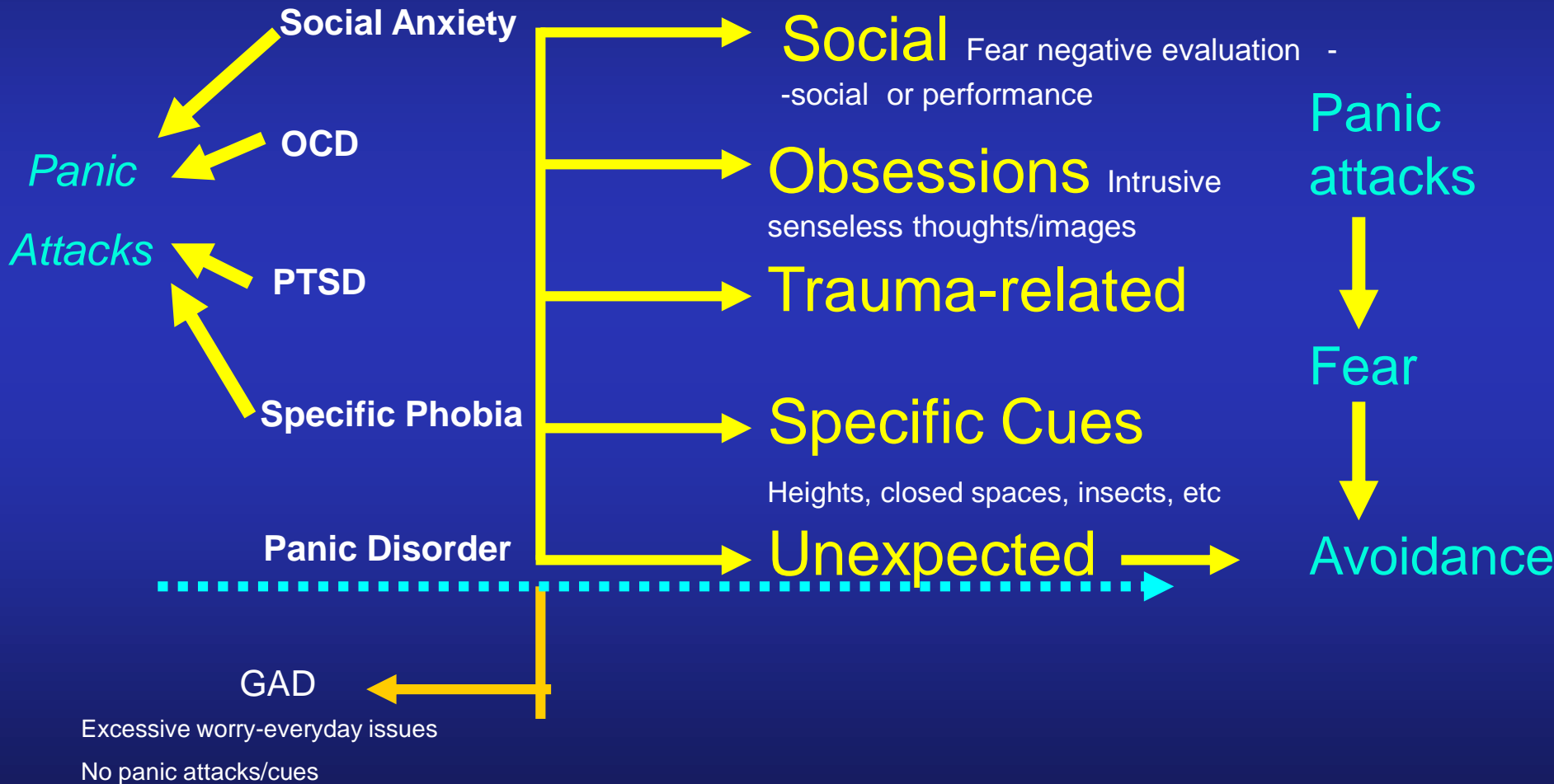
- One or more unexpected panic attacks
- Followed by  $\geq$  1 month of worry or concern over the implications of the attacks
- Changes in
  - Cognition- Distorted: Catastrophic pr potentially serious medical illness
  - Behavior --Avoidance. Health care consultations

# Agoraphobia

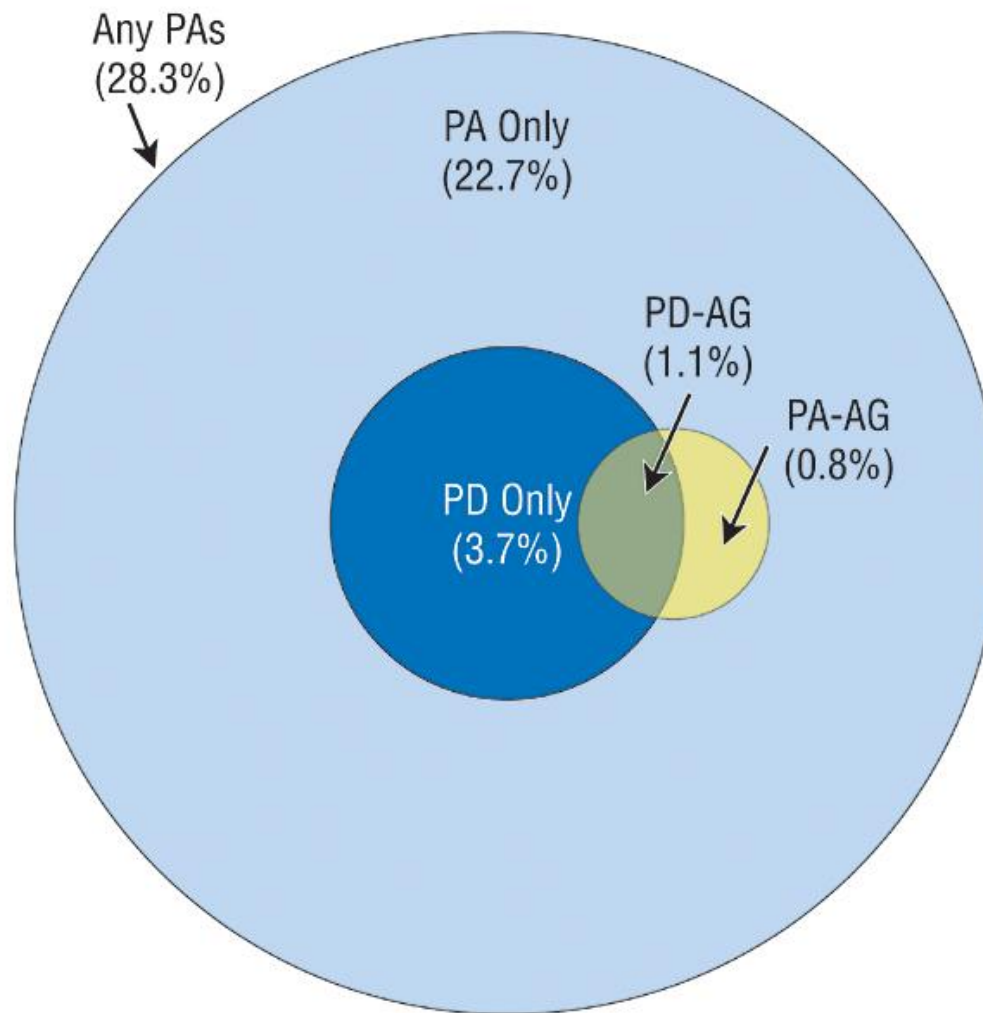
- Order of onset of PA and agoraphobia debated
- Avoiding or enduring with dread
  - Situations in which another PA may occur
  - Dignified and ready exit or help may not be available including crowds, bridges, etc.

# Panic Attacks Differential Diagnosis

## PA Triggers



## Lifetime Prevalence of DSM-IV PAs and PD with and without Agoraphobia



# Prevalence Panic Attacks-Panic Disorder-Agora

## NCS Replication (n=9282)

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



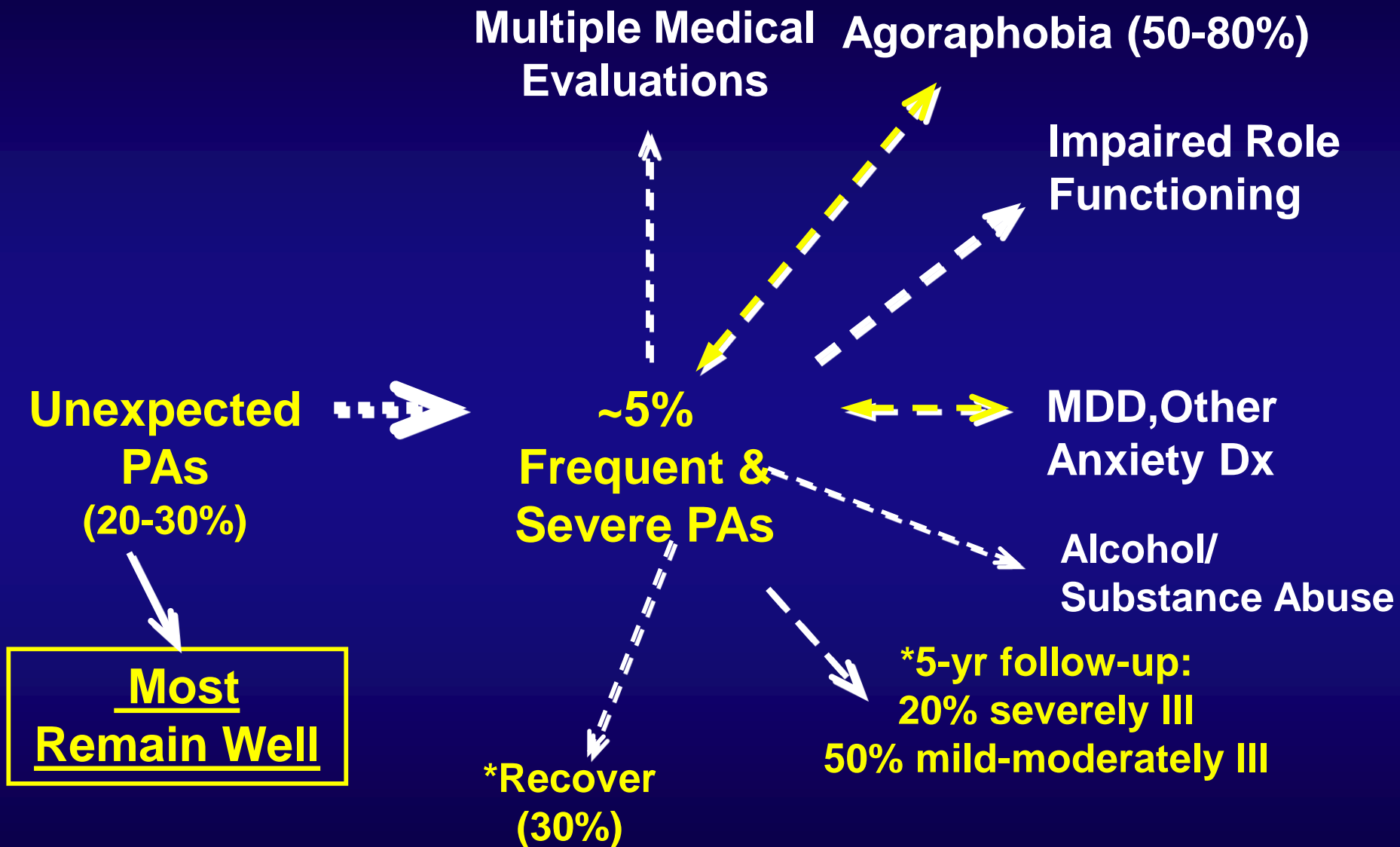
# Theoretical Pattern of Onset and Treatment Response in PD

- **Onset:** Unexpected Panic -anticipatory anxiety>-- cognitive -->agoraphobia
  - Reverse of order of onset
- **Treatment:** Time Frame-Varies Significantly
  - 2-6 weeks-unexpected PA improve
  - 8-12 weeks-Cued PA, anticipatory anxiety
  - 8-? Weeks-Agoraphobic avoidance



Controversy exists re: order of appearance of agoraphobia and PA

# Course, Persistence and Complications

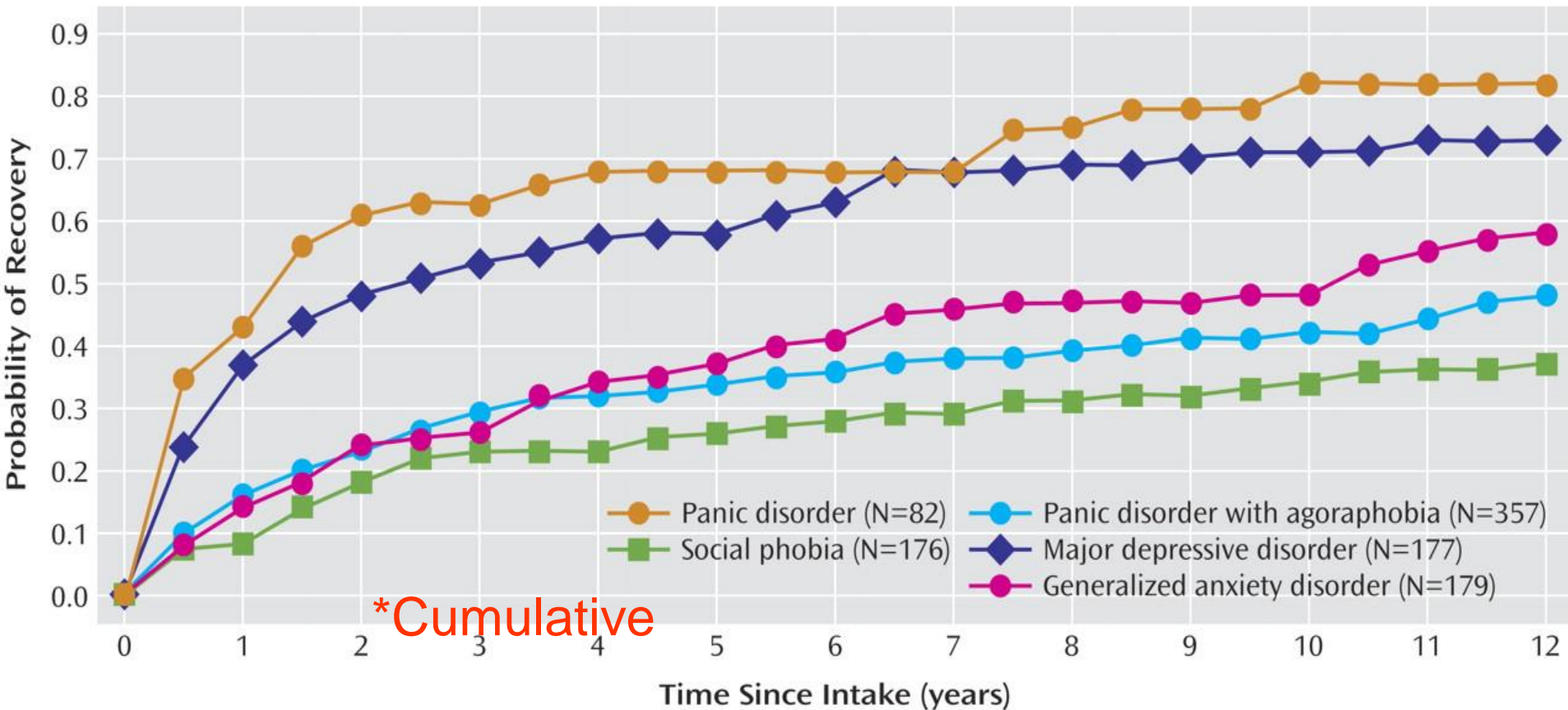


\*423 PD patients treated ; 323 re-interviewed; Katschnig, H. et al Long-term follow-up after a drug trial for panic disorder. Br Psychiatry 1995;167:487-94

\*

# \* 12-Yr Probability of Remission

Panic Disorder - high rate of recovery and recurrence



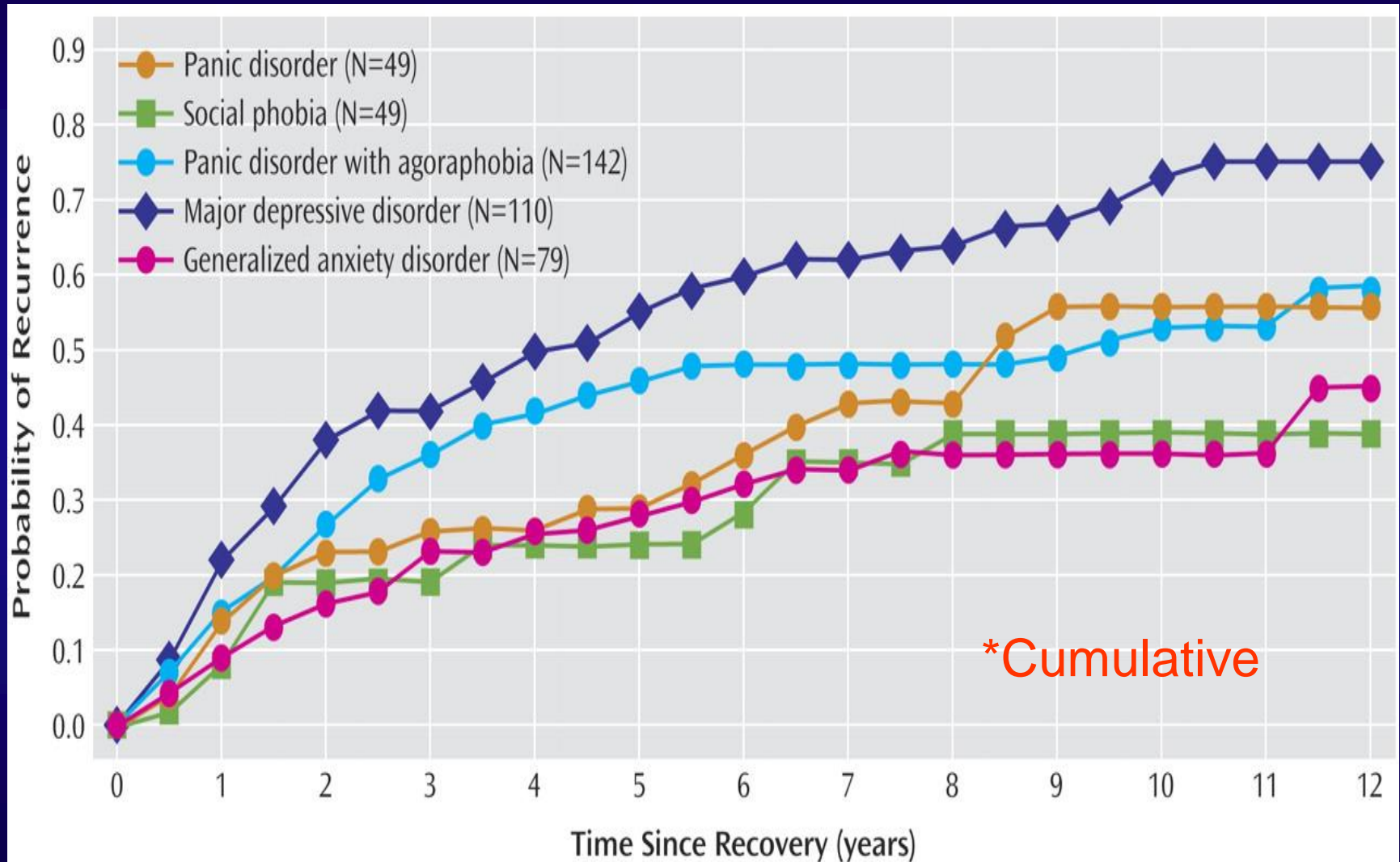
\*Cumulative

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

\*

# 12-Yr Probability for Recurrence

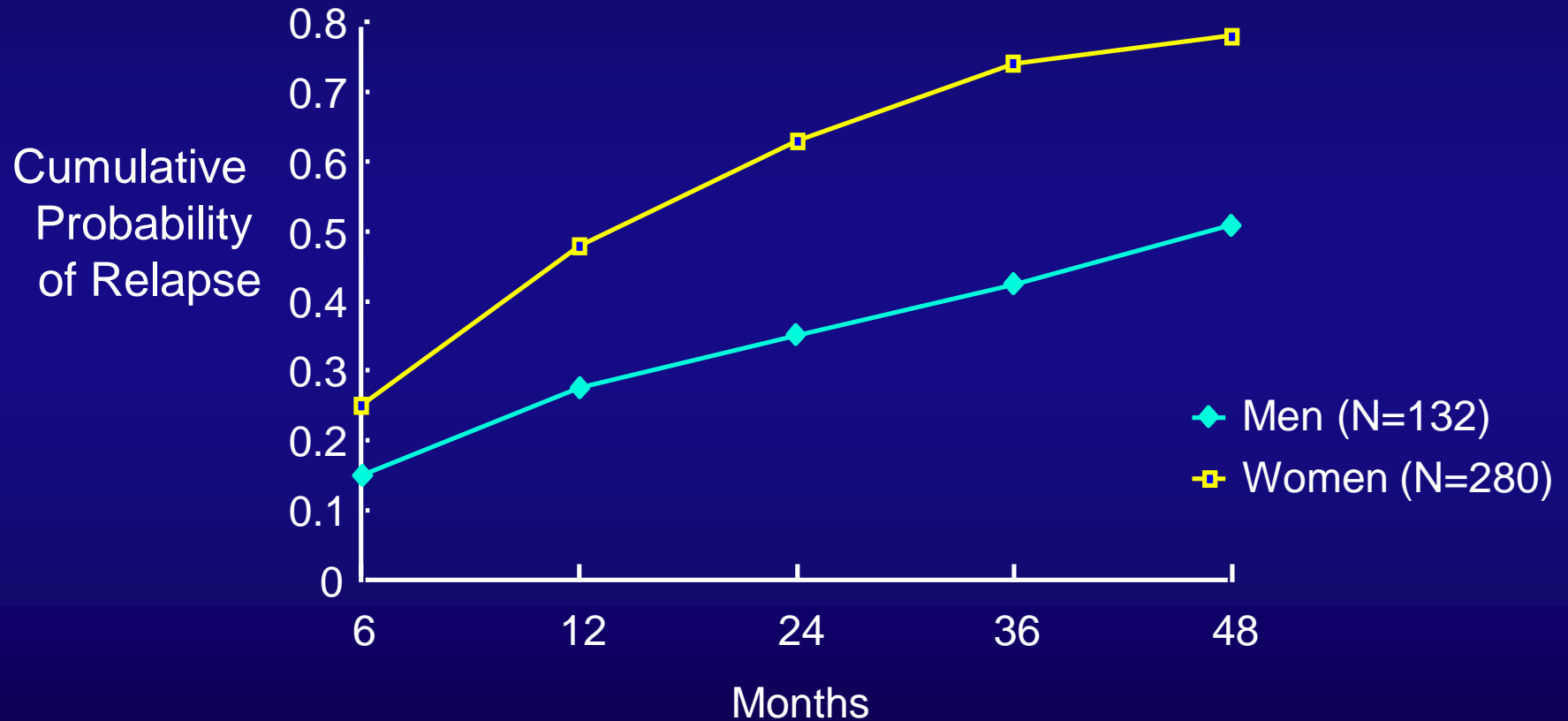
Panic Disorder high rate of recurrence



\*Cumulative

# Relapse after Remission

## Women > Men



# Panic Disorder Neurobiology

- **Women:men= 2:1**
- **Familial**
- **Fear Circuit Model**
- **Comorbidity - Non-random**
- **Challenge studies**
- **Brain Imaging**
  - ◆ **-altered 5-HT<sub>2</sub>, GABA, BZ receptor, NE others**

# The Fear Circuit Model

- Explanation for both CBT and Pharmacotherapy



# Brain Circuits in Anxiety Disorders

- Neurocircuits:
  - Interconnected brain regions that interact
- 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.





# The Fear Circuit Model:

## Critical Components Inter-modulate

### ● Amygdala CeN (central nucleus) = “alarm button”

- Interacts with other brain structures
- Processes information --'watchdog' function
- Encodes conditioned fear

### ● Hippocampus

- Storage and retrieval of contextual and declarative memory

### ● Prefrontal Cortex--Executive Function

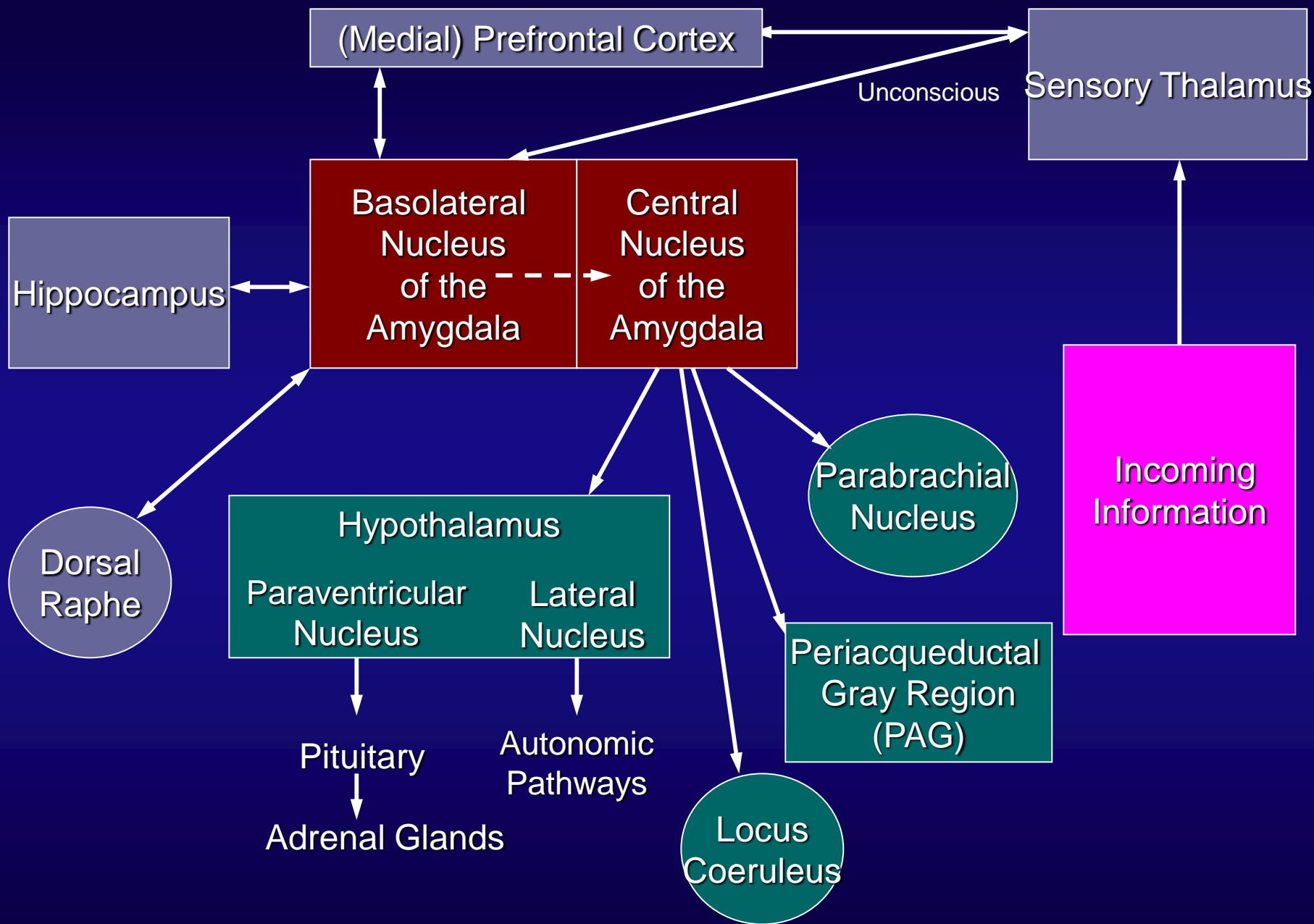
- Coping and problem solving, probability estimation
- Fear conditioning ( phobic avoidance)

### ● Lateral Nucleus of Hypothalamus- Brainstem

- Sympathetic activation
- Locus ceruleus, nucleus solitarius, PAG, parabrachial nucleus, etc.



Conscious processing

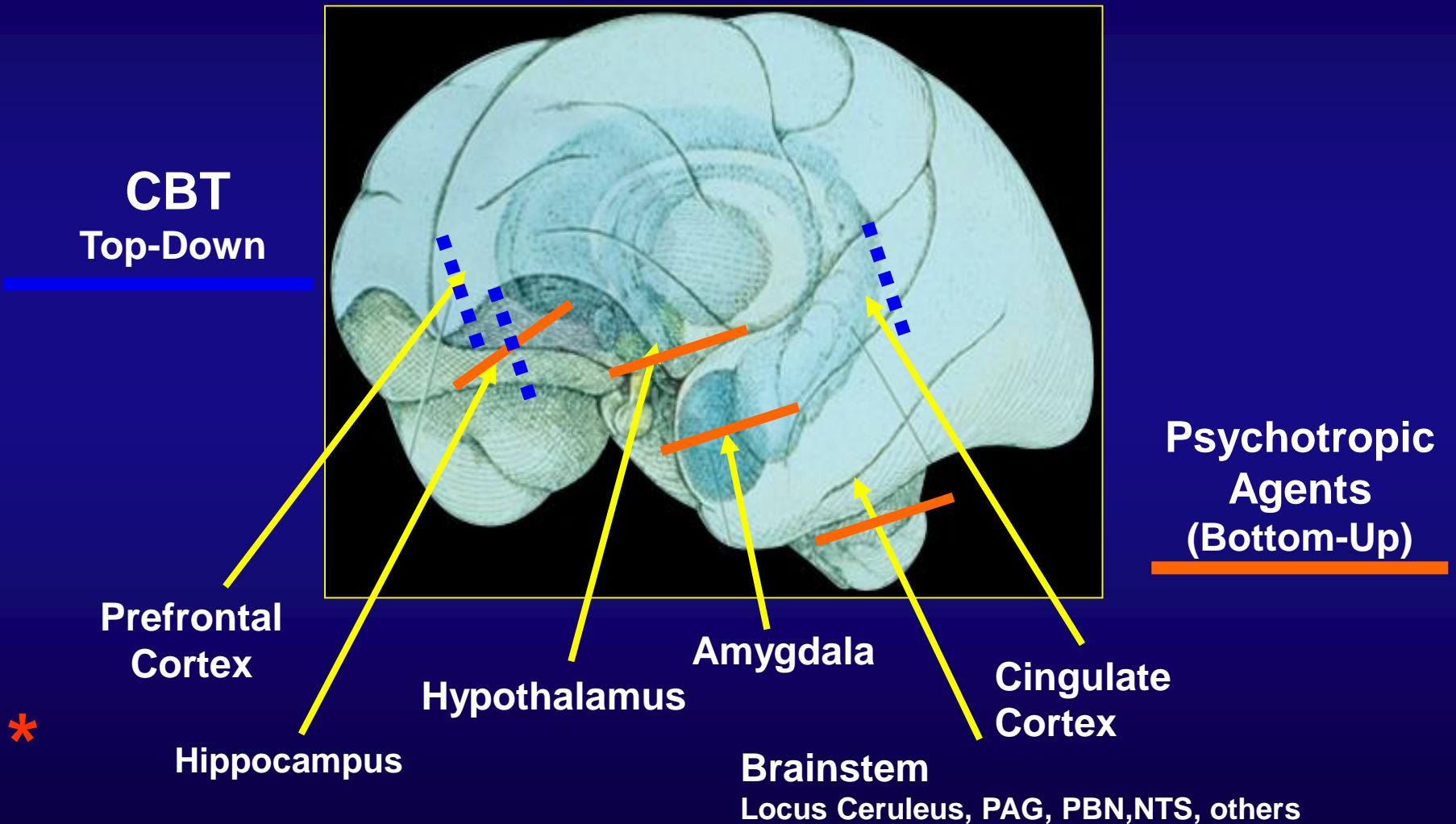


# PD: CBT vs Drug Rx

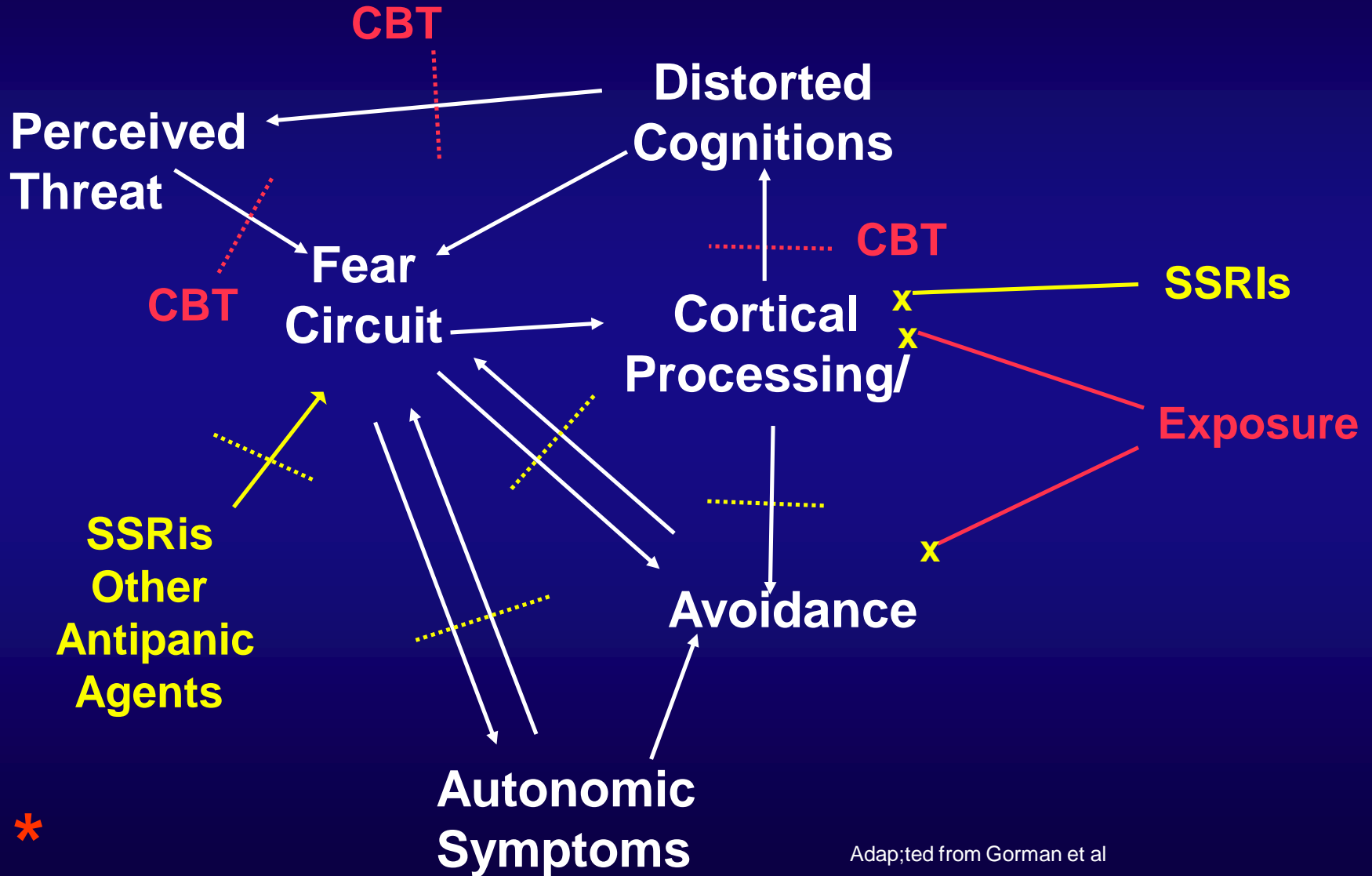
QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

# Model for Actions of Psychotropics and CBT

Fear Circuit Model explains both CBT and Drug Rx  
Enhance inhibition “CeN” Alarm



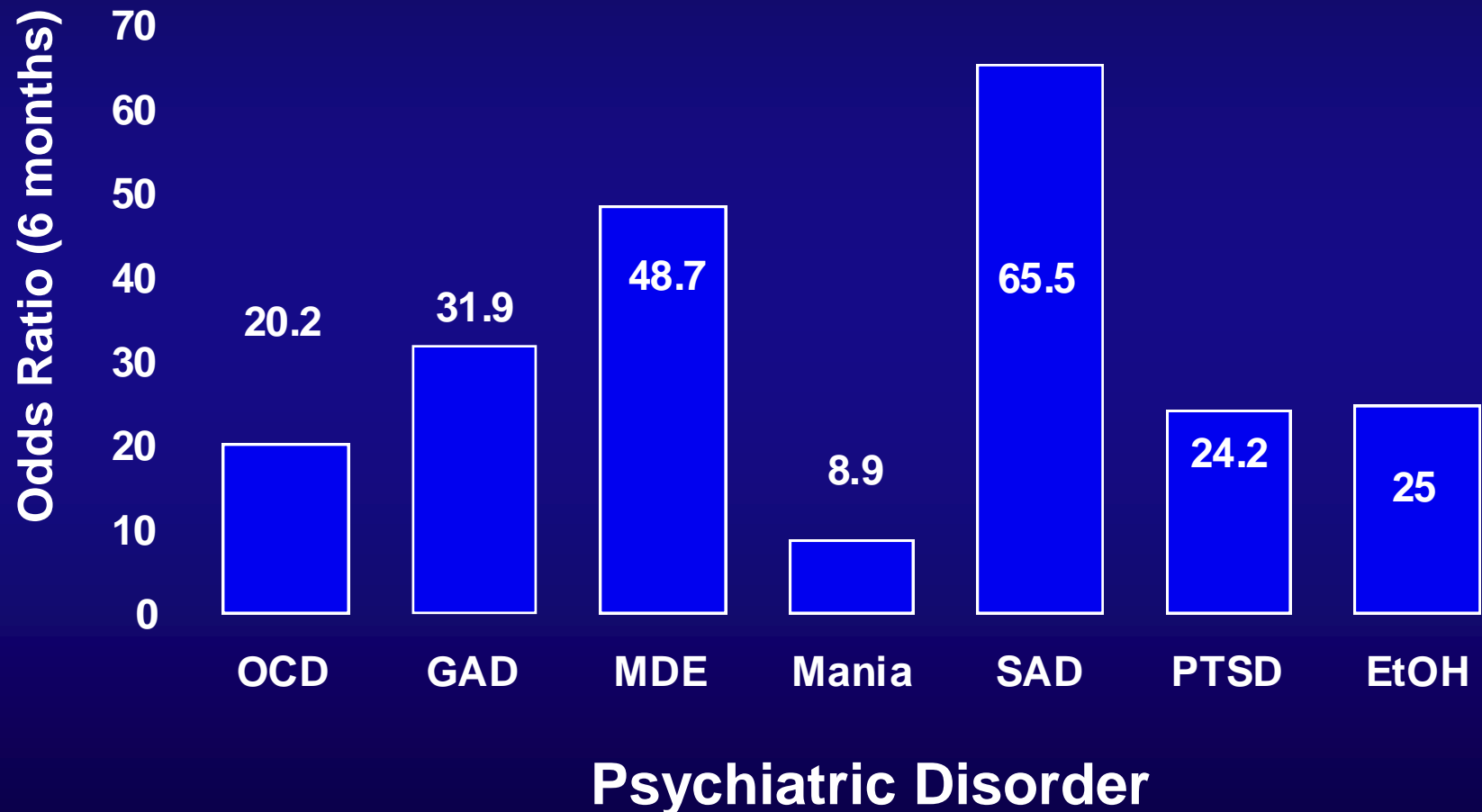
# Theoretical Sites of Action of Antipanic-Antiphobic Treatment(s)



# Challenge Studies in PD

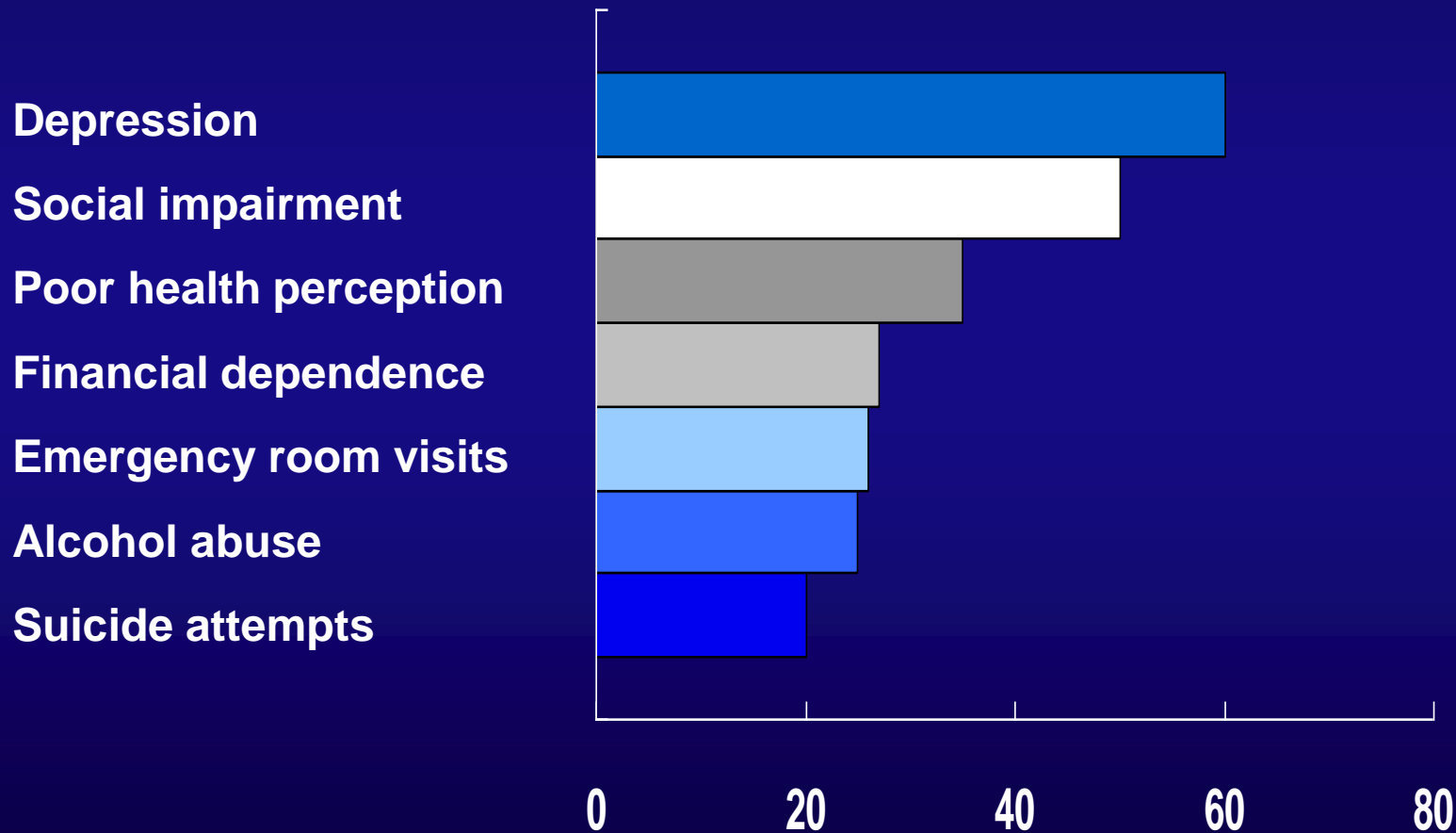
- PD sufferers susceptible to challenge with
  - Lactate infusion
  - CO2 inhalation
  - Yohimbine
  - Cholecystokinin
  - Other

# Panic Disorder with Agoraphobia Risk for Additional Psychiatric Disorders(%)



# Morbidity of PD:

## Epidemiological Catchment Area (ECA) Survey





# Increased Medical Utilization in PD Top 10% of Users

Odds ratio of  $\geq 5$  MD visits

	<u>Males</u>	<u>Female</u>
● MDE	1.5	3.4
● Panic disorder	8.2	5.2
● Phobic disorder	2.7	1.6

Simon and Von Korff, 1991

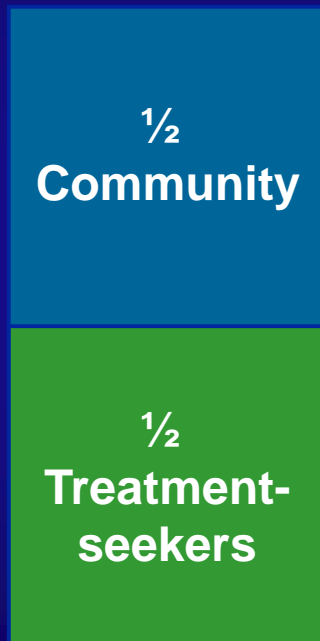
# **Panic Disorder : Increases Stress Vulnerability *and acts as a Stressor***

- **Panic disorder resembles unpredictable stress**
- **\*Criteria for stressor:**
  - Perceived threat or challenge
  - Perceived inability to control it

## WORRIED SICK?

# Health Outcomes with Anxiety Resemble Those Associated with Stress

≈300 Individuals With PD or GAD



1/2 Anxiety first

1/2 Medical first

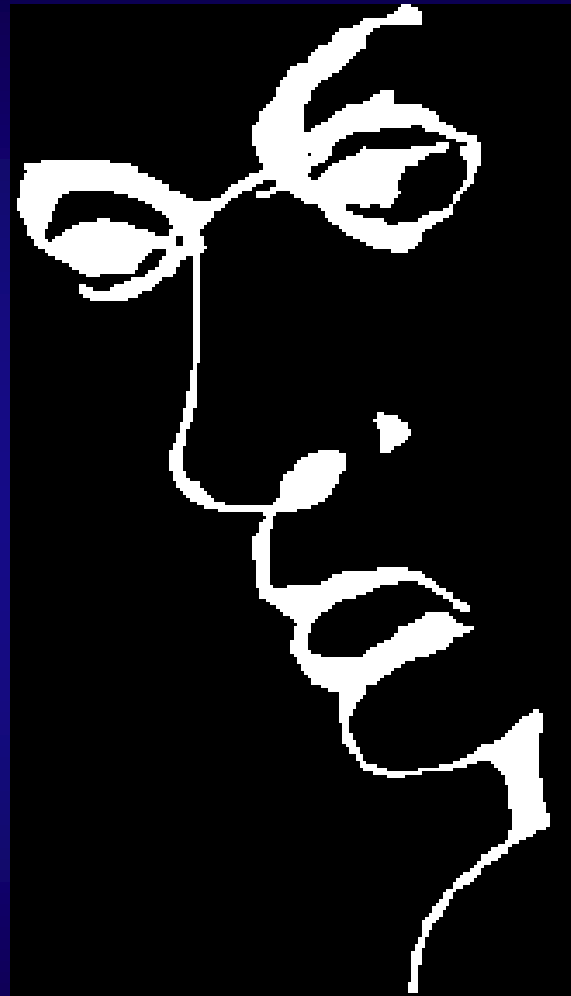
2 to 6 times as many  
medical disorders vs. non-  
anxious\*

- 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: What do you see?



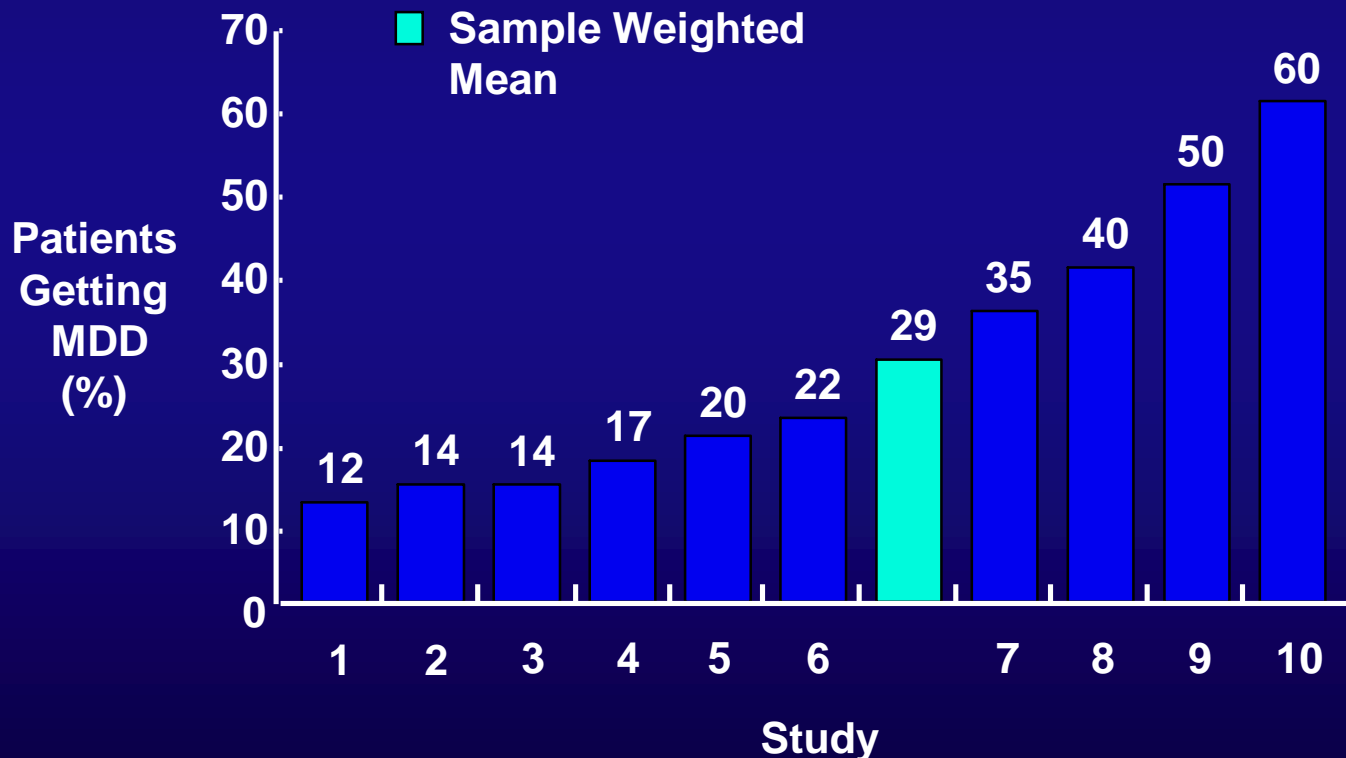
A face... Or the word **Liar**?

# Comorbidity

Comorbid Conditions  
Provide Important  
Clues

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

# Development Of Major Depression In Panic Disorder (10 Studies, 2 Year Median Follow-Up)

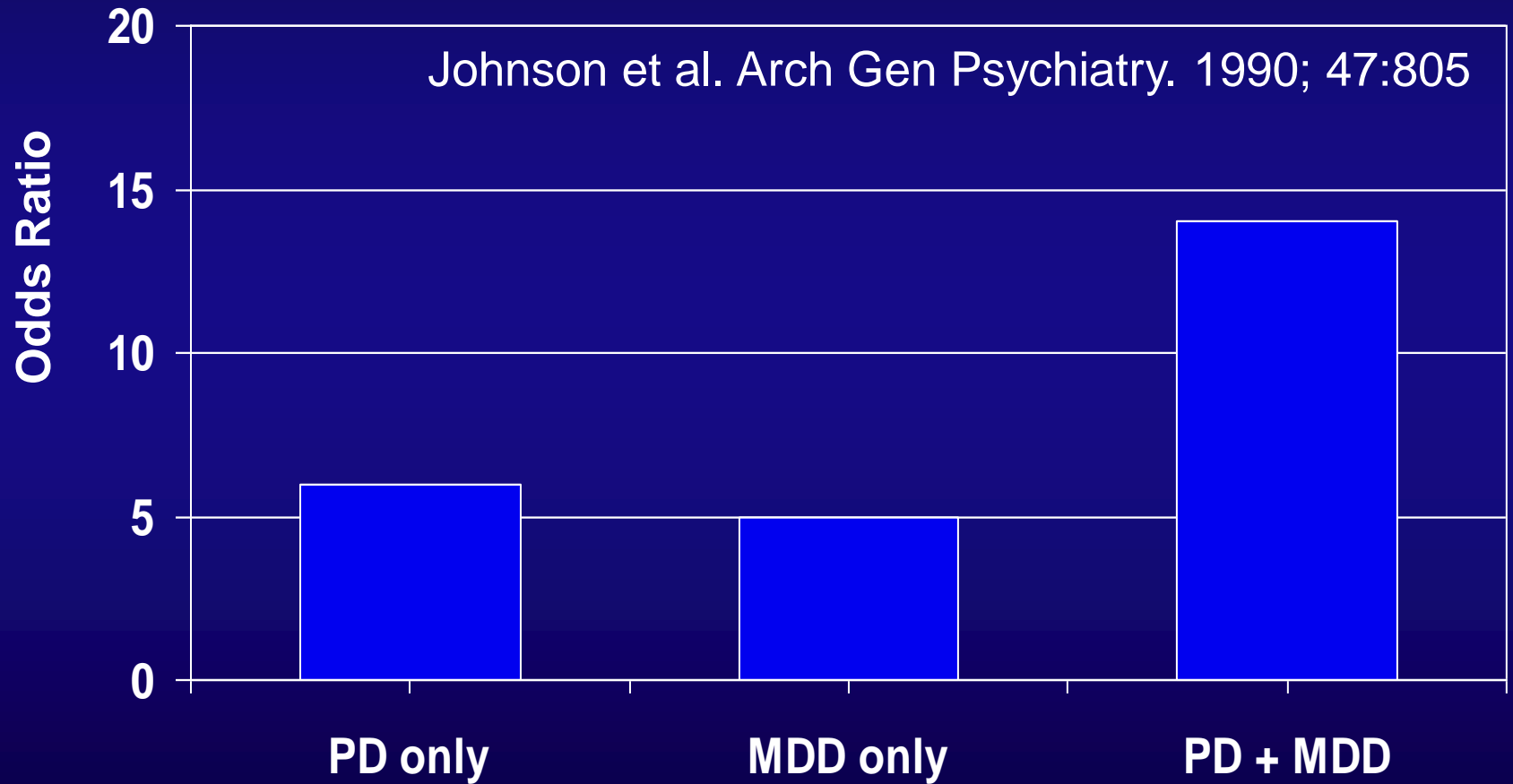


# PD and Major Depression

## Clinical Characteristics

- Over 50% have Melancholia
- More Anxiety
- More Depression
- More Phobia
- Longer Course of Illness

# Suicide Attempts



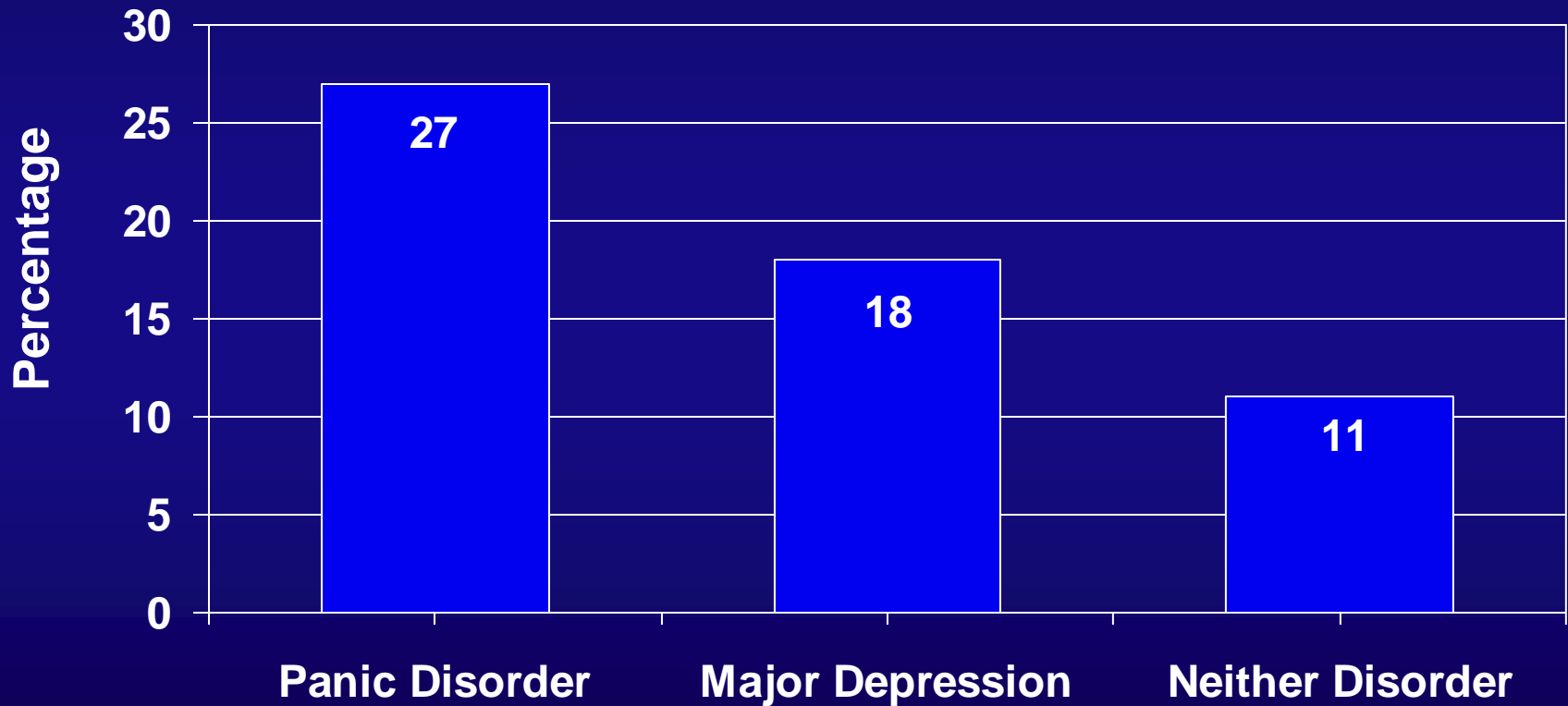


# PD and Major Depression Long-Term Follow-Up

- More Psychosocial Impairment
  - Financial Assistance
  - Disability
- More Hospitalizations
- Poorer Overall Outcome

Von Valkenberg et al. J Affect Disord 1984; 6:627

# Frequency of Alcohol Abuse by Diagnosis



Weissman, 1991, ECA data

# Family History

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

# **Panic Disorder**

## **Evaluation**

# The Diagnosis?

- **Assess panic attacks**
  - What are Sx?
  - Unexpected vs. “cued” / stimulus-bound
  - How frequent and severe ?
- **Cognitive distortion fo change ?**
  - Fear of consequences or implications of PAs?
  - Are there lifestyle / behavioral changes?
- **Avoidance due to fear of panic attacks?**

# Panic Disorder Differential Diagnosis

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

# Other Relevant History

- **Reproductive status/sexual functioning**
  - pregnancy
  - planned pregnancy
- **Changes in Important Relationships**
  - Can enhance compliance with treatment
  - “Safe person”
- **Assess for Occupational, Social, Family Role Impairment**

# Medical Conditions

(Conditions with significant PD overlap)

- Chronic Pain Syndromes
- Mitral valve prolapse
- Migraine
- Chronic Fatigue
- Irritable bowel syndrome
- Chronic fatigue syndrome
- Dizziness
- Hyperventilation syndrome
- Premenstrual syndrome



# Medical Evaluation of PD

## History

- Complete description of physical symptoms
- Medical history
- Family history
- Drug and medication history

# Medical Evaluation of PD

- **Physical Examination**
- **EKG**
- **Laboratory**
  - **CBC**
  - **Electrolytes, BUN, Creatinine, Glucose**
  - **Urinalysis**
  - **T<sub>4</sub> and TSH**

# Indicators for Further Medical Evaluation

- **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**
- **Real vertigo**

# PD: Patient Approach

Don't panic, doctor--this only *feels* like an emergency

- Positive diagnosis is critical; they were told there was 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.”

<sup>1</sup>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.)*

- 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 enhance legitimacy of PD

# 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

# 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.”



# 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**

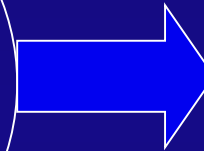
**SSRIs-First Line**



**Panic Disorder  
Treatment  
Options**

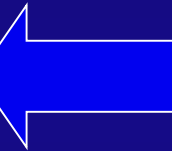
**CBT Alone**

**CBT +Meds**



**Other**

**Antidepressants**



**Benzodiazepines**

**Novel Agents**



# Outcome Assessment

- *Functional status is key issue !!*
- Panic attacks least useful measure
  - They don't correlate with other domains
- Symptoms to target and follow
  - Phobic avoidance
  - Cognitive distortion
  - Depression
  - Somatic symptoms



# CBT: Pros and Cons

## ● Advantages

- It works (70%–85% efficacy)
- It 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

# CBT for PD

- **Based upon empirical evidence for fear of bodily sensations in panic disorder**
- **Target 1: Decrease physical sensations**
  - **Technique: Breathing retraining**
- **Target 2: Interrupt catastrophic misinterpretation of bodily sensations**
  - **Technique: Cognitive restructuring**
- **Target 3 Decrease conditioned fear of bodily sensations**
  - **Technique Interoceptive exposure**
- **Target 4: Exposure to feared situations**
  - **Technique-Hierarchy least to most feared, in that order**

# Treatment: General Principles

- **SSRIs or \*SNRI First Line**
  - Other ADs work
  - MAOIs
  - Benzodiazepines
    - ◆ Not reliably antidepressant
  - Beta-blockers useful adjunctive Rx
    - ◆ Not adequate as monotherapy

\* SNRIs more expensive, less-well studied in PD



# **Panic Disorder: *Who Needs Long-Term Treatment?***

- **The majority of panic disorder patients need long-term treatment**
- **Relapse rates after discontinuation of medication significant**
  - **60% within 3-4 months after stopping medication**
  - **CBT may assist in successful discontinuation**
- **Tapering should be very gradual (3-6 months) with slowest part of tapering at 50% of original dose**

**Ballenger JC. *Biol Psychiatry*. 1999;46:1579-1594. Ballenger JC et al. *J Clin Psychiatry*. 1998;59(suppl 8):47-54.**

# Efficacy of PD Pharmacotherapy

## Agents/ Classes with Proven Efficacy\*

PD	GAD	SAD	PTSD
SSRIs	SSRIs	SSRIs/SNRIs	SSRIs
BZD	BZD	BZD*	MAOIs
TCA	TCA	MAOI	TCA
MAOI	Buspirone	Clomipramine	
Venlafaxine	Trazodone	Gabapentin*	
	Venlafaxine		

\*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;



Adapted from: Lydiard RB. *Textbook of Anxiety Disorders*. Washington, DC: American Psychiatric Press, Inc; 2002:348-361.



# Therapies With Limited or No Proven Efficacy in PD

PD	GAD	SAD	PTSD
<b>AEDs*</b> <b>± Bupropion</b> <b>Buspirone</b> <b>(adjunct)</b> <b>Mirtazapine</b>	<b>AEDs</b> <b>Atypical NLs</b> <b>Mirtazapine</b>	<b>AEDs</b> <b>Bupropion</b> <i>CMI- but not other TCAs</i>	<b>AEDs</b> <b>Atypical NLs</b> <b>Bupropion</b> <b>Buspirone</b> <b>Mirtazapine</b> <b>TCAs</b> <b>Trazodone</b> <b>Venlafaxine</b>

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



Adapted from: Lydiard RB. In: *Textbook of Anxiety Disorders*. Washington, DC: American Psychiatric Press, Inc; 2002:348-3613.

# Adverse Effects of PD Pharmacotherapy

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



# Selection Considerations

- Evidence for efficacy
  - Historical success in that pt
- Safety
- Tolerability
- Half-life
- Drug-drug interactions
- Protein binding



# PD

## Medications That Don't Work

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



# PD: SSRIs -First Line” \*

- Efficacy ~ 50-70% for each SSRI
- Different patients may respond to different SSRIs
  - Try  $\geq$  two SSRIs before switching class
- Initial dose = 1/4 to 1/2 initial antidepressant dose- (or less!)
  - Fruit Juice (“Cran-zac”, “Applezac”), water, applesauce to allow small initial dose
- Final dose may be more than 2x antidepressant dose



# SSRIs 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



# SSRIs 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**



# SSRIs

- Initial dose

  - ◆ (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

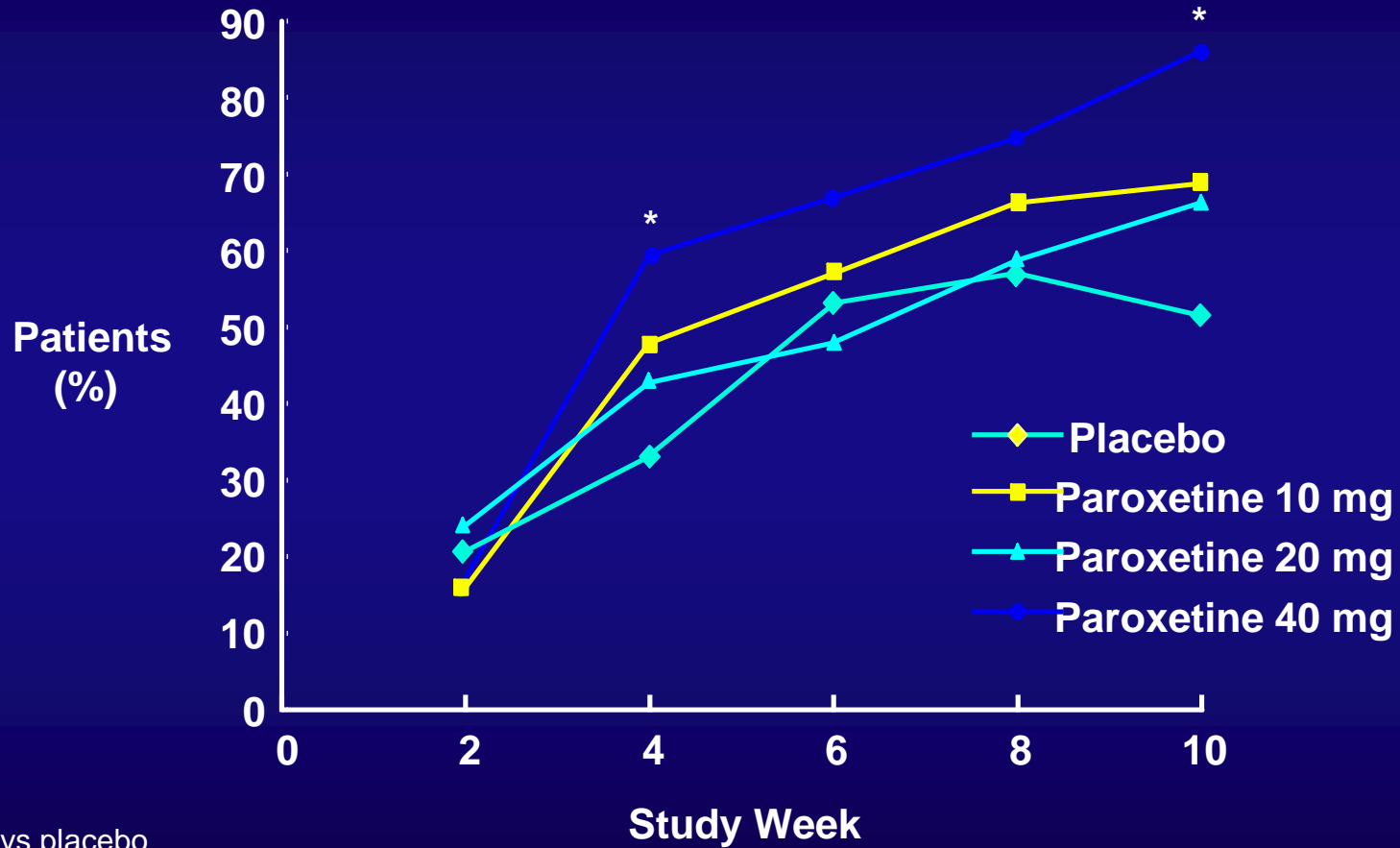
- Effective antidepressant dosage level may be higher





# 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 is THE dose for 'all patients

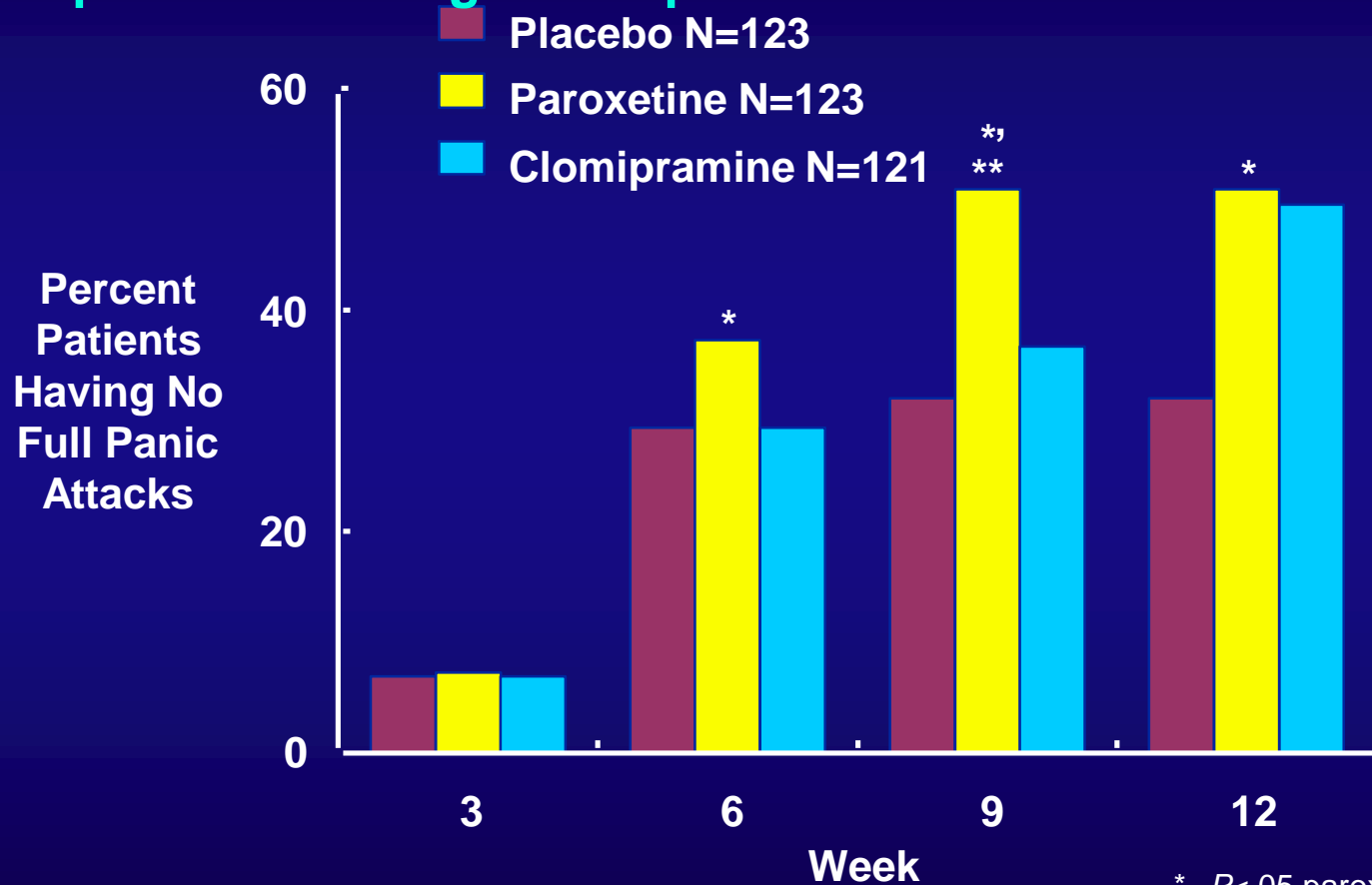


\* $P < .019$  vs placebo

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



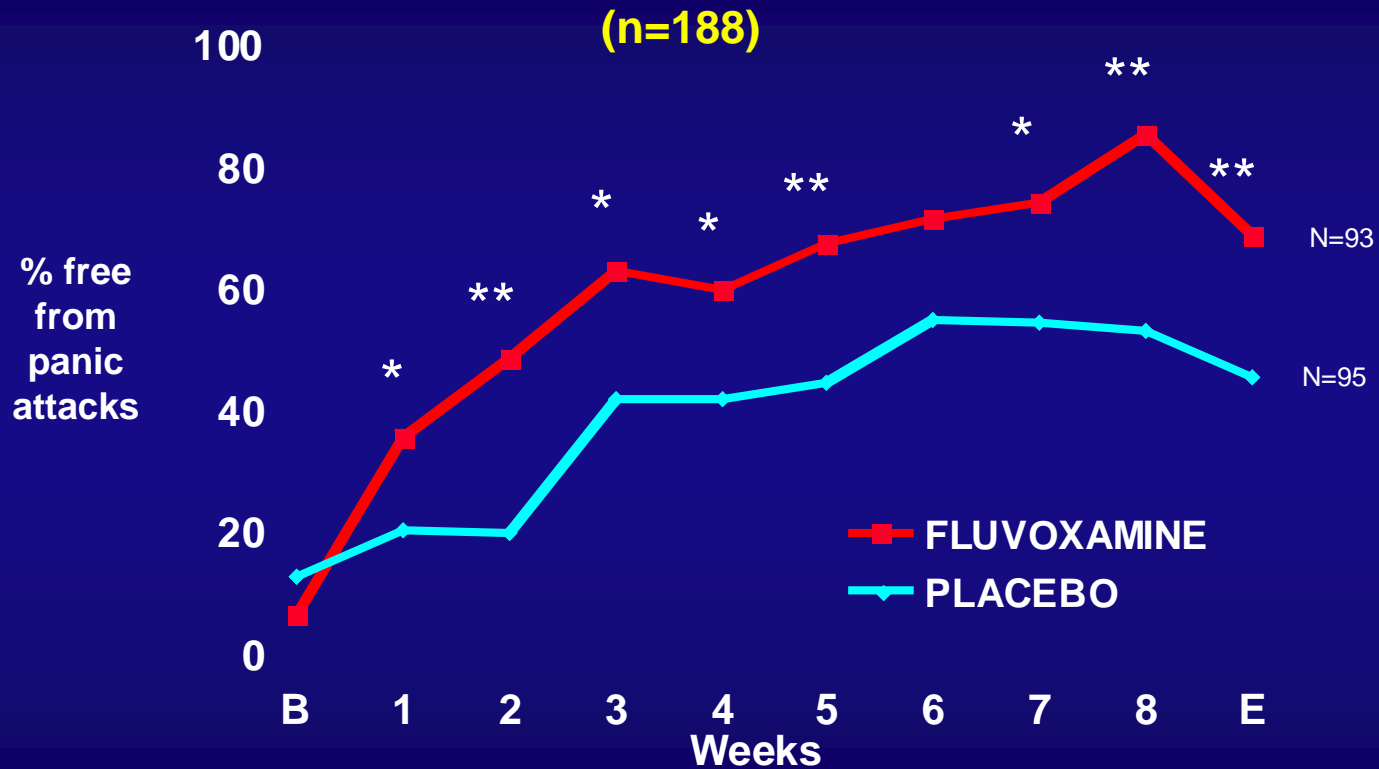
\*\*  $P < .05$  paroxetine vs clomipramine. Lecrubier et al Acta Psychiatrica Scand 1995; 95:145-152

\*  $P < .05$  paroxetine vs placebo.



†Not indicated for treatment of panic disorder in US.

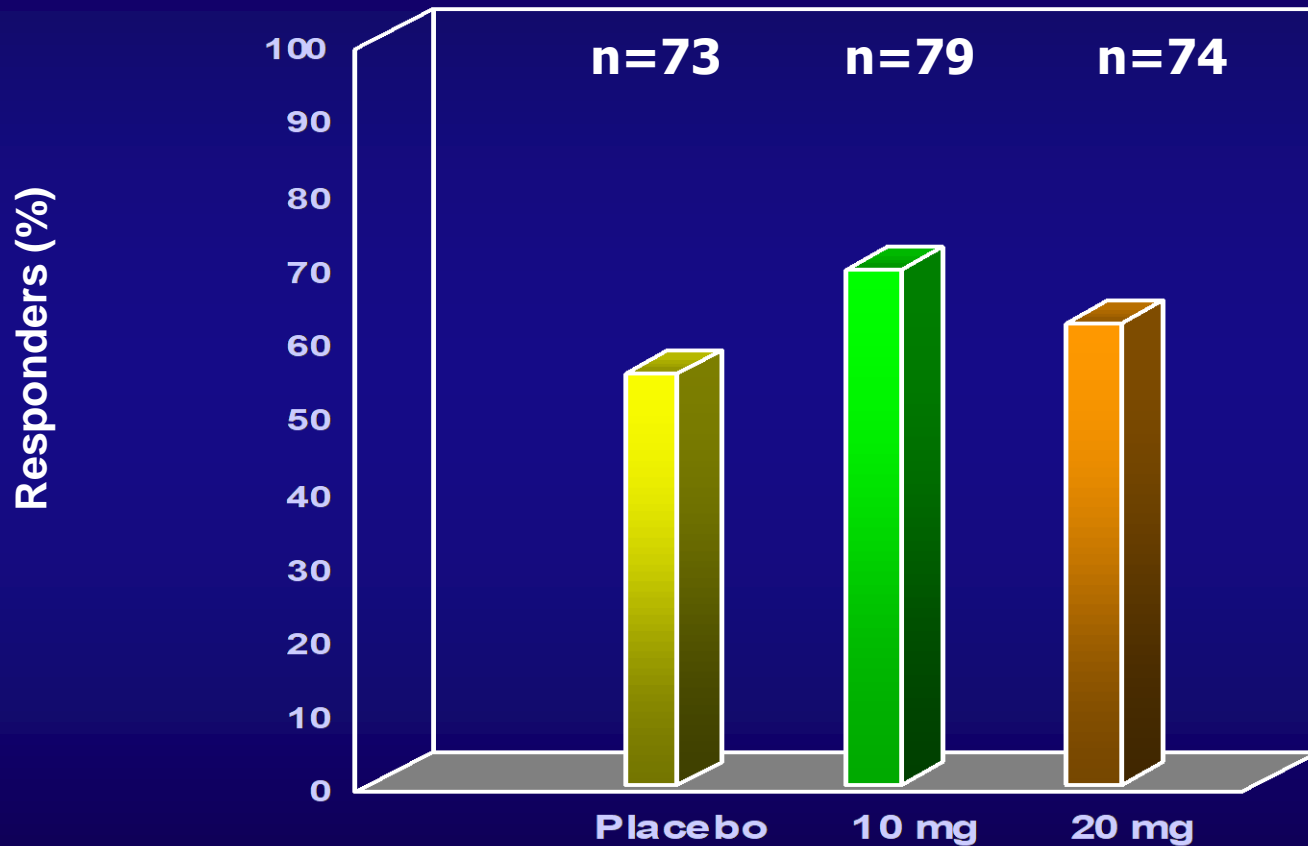
# Fluvoxamine vs Placebo % Free from Panic Attacks



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

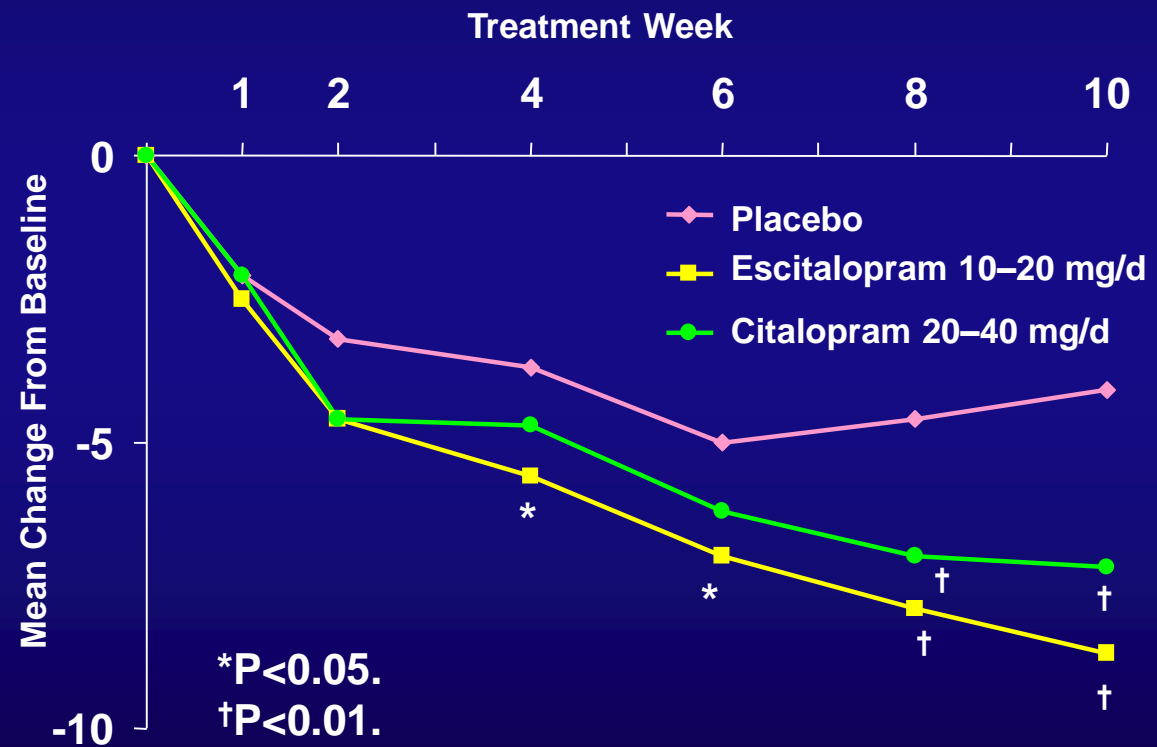


# Panic Disorder: 10 Weeks' Treatment Fluoxetine 10 or 20 mg vs Placebo: CGI Responders



# Escitalopram Treatment of Panic Disorder

## Panic and Agoraphobia Scale

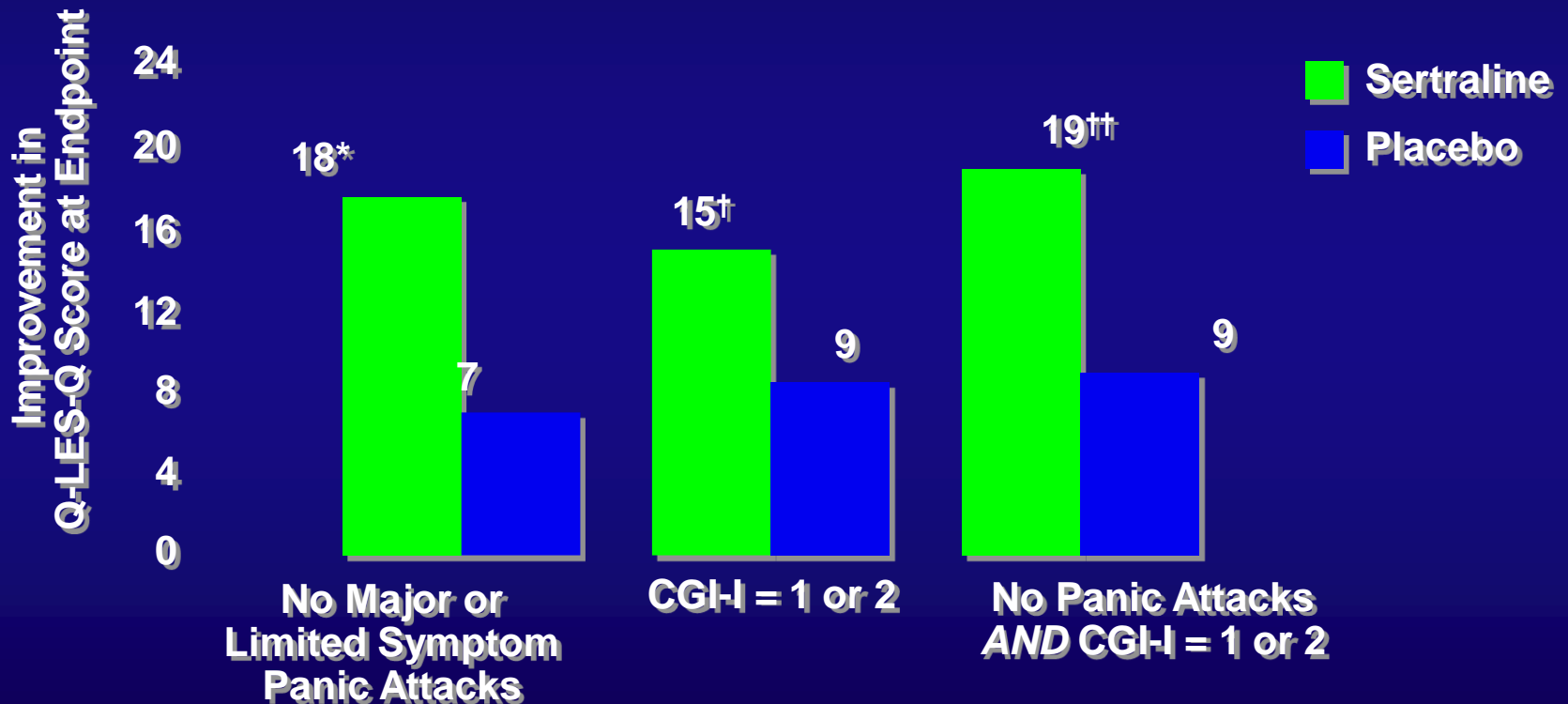


numbers



# 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



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

Doctors' Choice or Patients' Choice?  
Still too soon to tell



# TCAs: Advantages

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





# TCAs: Disadvantages

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



# Antidepressant Discontinuation

- Gradual taper ( $\geq 2$  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



# Benzodiazepines: Advantages

- **Effective**
- **Rapid onset**
- **Tolerability**
- **Safety**



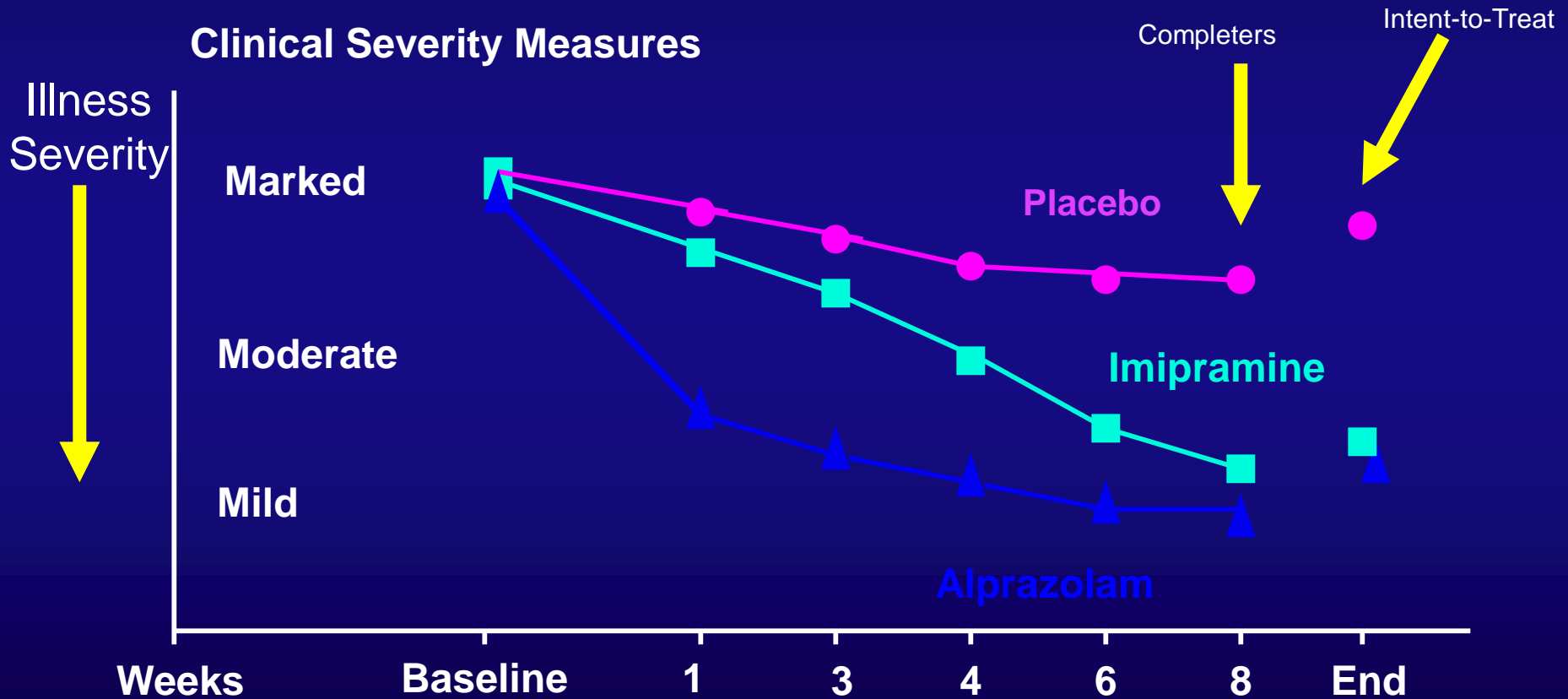
# Benzodiazepines: Disadvantages

- **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)



# 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



# Polypharmacy-SSRI +:

- **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

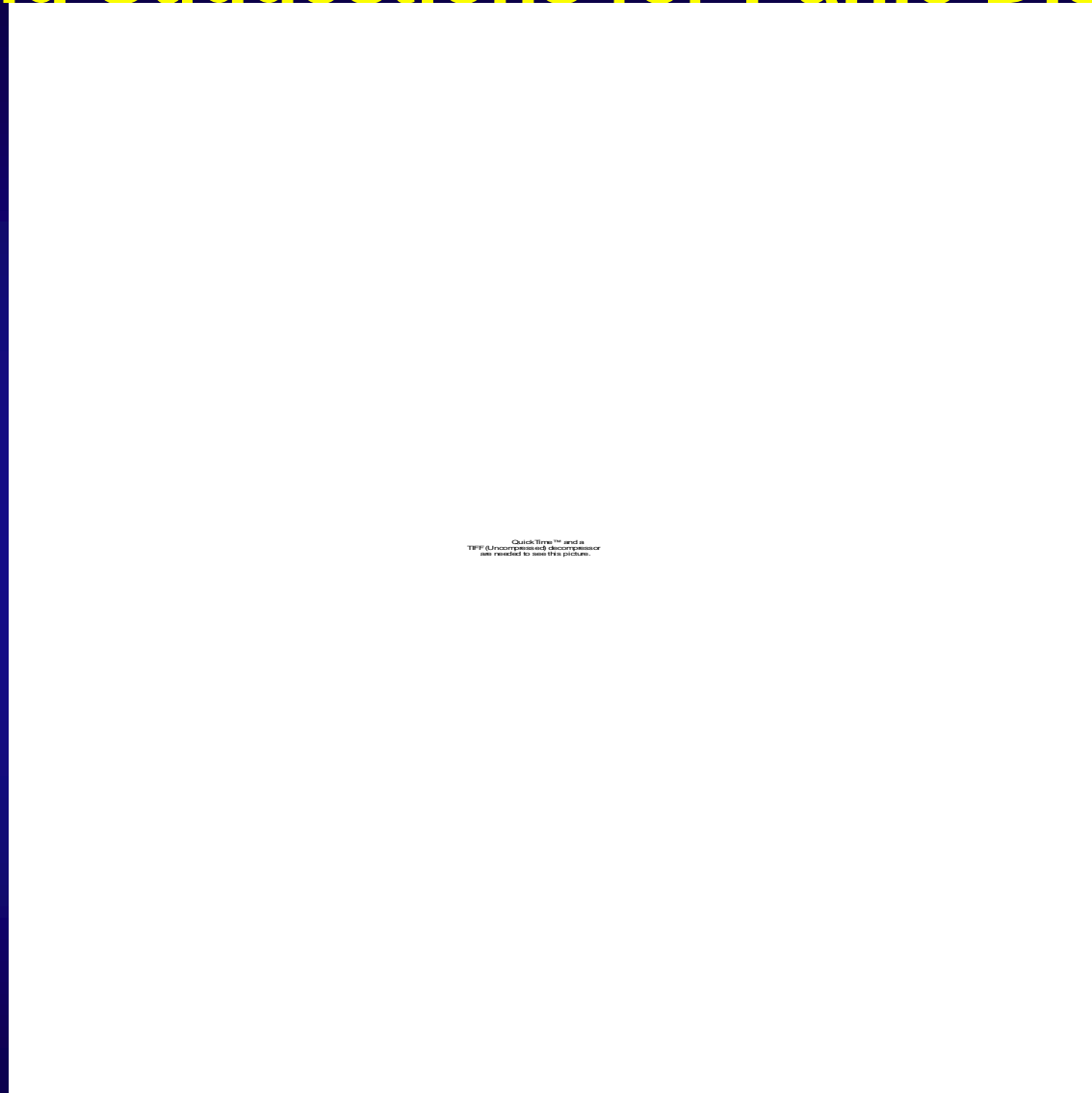
\*

- Reconsider diagnosis

# Resistant Panic Disorder -Approach

QuickTime™ and a  
TIFF (Uncompressed) decompressor  
are needed to see this picture.

# Dosing Suggestions for Panic Disorder



# 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**

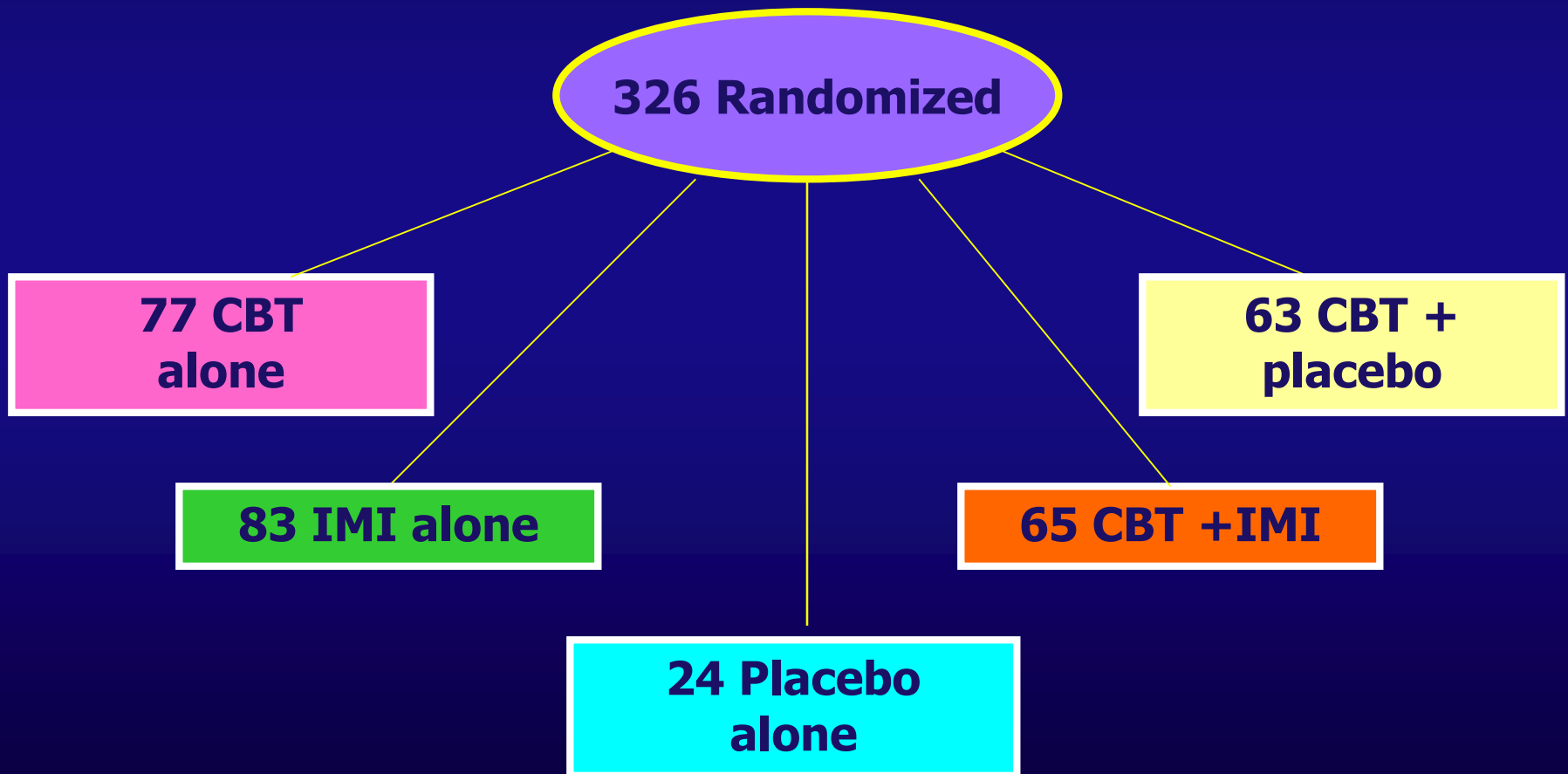
**Meds + Meds**





# CBT, IMI or CBT +IMI

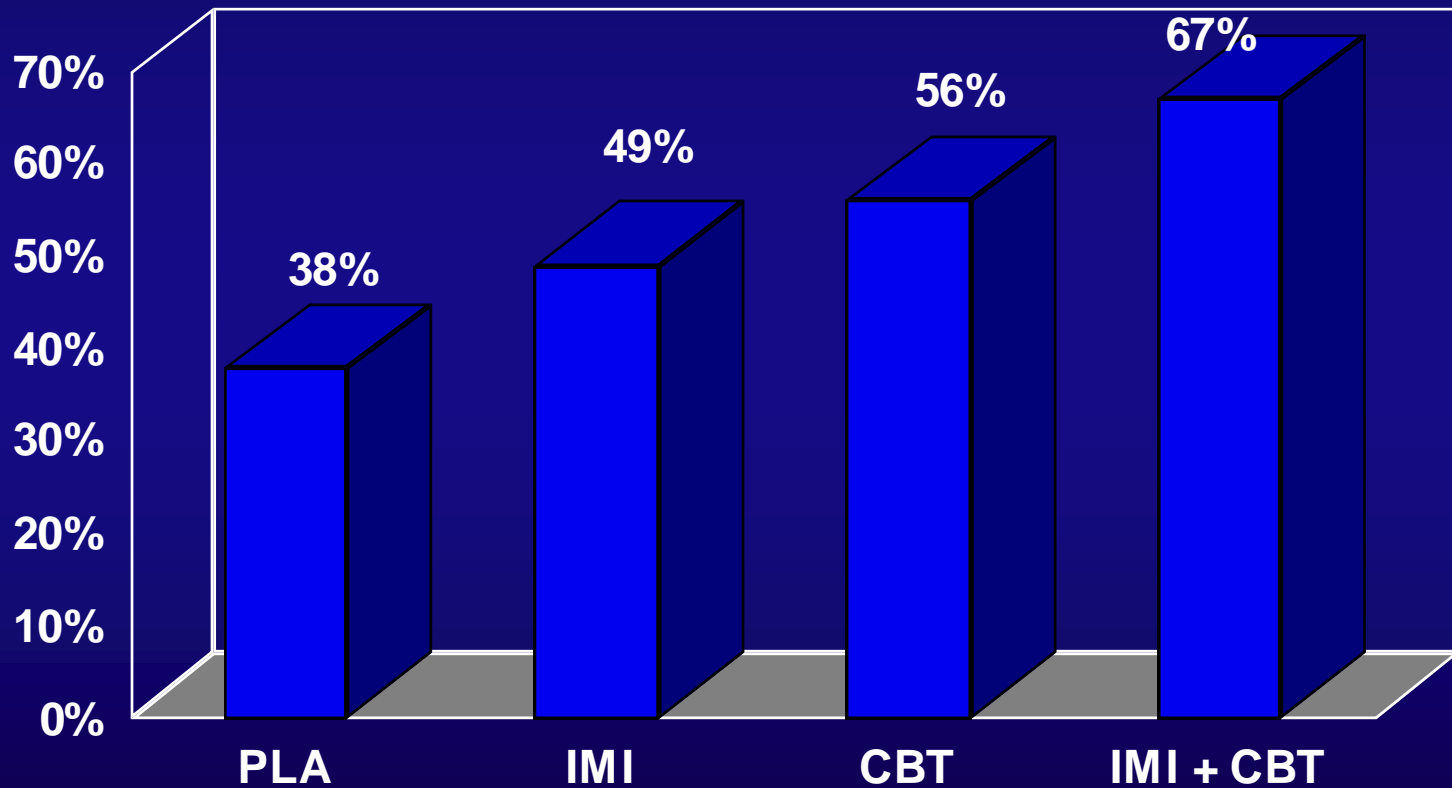
## Treatment for Panic Disorder



# 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  $p = 0.02$ ;



# 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



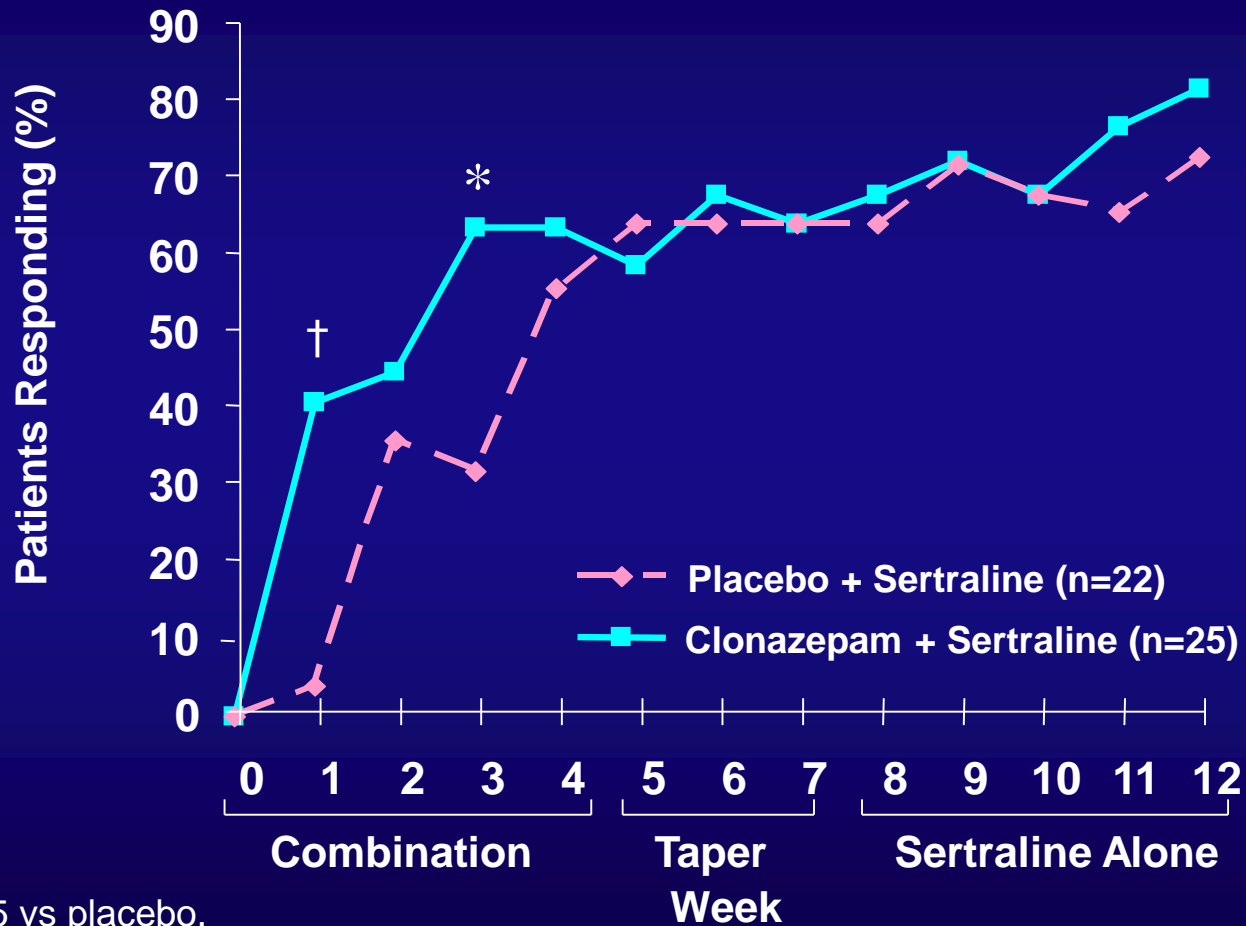
# Meta-Analysis of Combined Treatments for PD

- 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.



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



# Key Features of Addiction



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



# 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?



# 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\*

↓  
Symptoms persist

↘  
Symptoms disappear

→ Continue taper

↓  
May need to continue treatment\*

- 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  $\geq 2$  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<sup>[L]</sup><sub>[SEP]</sub>
  - [www.adaa.org](http://www.adaa.org)
- National Institute for Mental Health: Anxiety Disorders
  - [www.nimh.nih.gov/anxiety/anxietymenu.cfm](http://www.nimh.nih.gov/anxiety/anxietymenu.cfm)<sup>[L]</sup><sub>[SEP]</sub>
- See notes section on this slide for review of benzodiazepine use

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# 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