Treatment of Panic Disorder

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Question #1

- Panic disorder is often comorbid with which of the following?

a. Major Depression
b. Substance Abuse
c. Bipolar Disorder
d. Agorophobia
e. All of the above

Question #2

Which statement is *false*?

a. Panic disorder runs in families
b. Female/male ratio of cases is 2/1
c. Prevalence is higher in Latino Americans
d. Age of onset is typically in the 20s

Question #3

First-line treatments for panic disorder include all of the following *except*:

a. Benzodiazepies
b. SSRIs
c. Beta Blockers
d. SNRIs
e. CBT

Question #4

About 2/3rds of patients with panic disorder treated with any first line drug can expect to achieve remission within 12 weeks.

a. True
b. False

Question #5

CBT is somewhat less effective than first-line medications in treating panic disorder.

a. True
b. False

Panic Disorder without Agoraphobia: DSM-5 Diagnostic Criteria

- Recurrent *unexpected* panic attacks
- ≥ 1 month of worry re recurrence, implications, consequences, or
- ≥ 1 month of changed behavior – to avoid attacks; or consulting health care providers
- Not due to substance or medical disorder
- Not better accounted for by other psych dx, e.g., PTSD, OCD, social phobia

DSM-5 Panic Attack Symptoms

≥ 4 Sx, which 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 heat sensations
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

Panic Disorder

Evaluation

Making the Diagnosis

- Assess panic attacks
  - Unexpected and “cued” (stimulus-bound). Note: attacks may awaken the patient from sleep.
  - How frequent and severe are attacks?
- Cognitive distortions?
  - Fear of medical implications or social consequences of panic attacks?
- Avoidance behaviors or use of alcohol/drugs due to fear of having another panic attack?

Thorough Assessment

- Other psychiatric and medical conditions
  - Agoraphobia? Major depression? Substance abuse?
- Past psychiatric history
- General medical history
- Major life events (personal history)
- Social and family history
- Current medications and prior treatments
- Mental status examination
- Physical examination and dx tests

Agoraphobia

- May occur in panic disorder, but is a separate DSM-5 diagnosis, characterized by marked fear of ≥ 2 of:
  - Using public transport
  - Being in open spaces
  - Being in enclosed places
  - Standing in line or being in a crowd
  - Being outside of the home alone

Epidemiology of Panic Disorder (1)

- Prevalence: 2-3%, F/M = 2/1
  - Lower in Latinos, African Americans, Asian Americans compared to non-Latino whites.
- Age at onset typically 20s
- Course is typically chronic, waxing and waning if untreated. May be episodic
- Risk higher in smokers, and adults abused as children
- Runs in families:
  - Risk = 4-7x higher in first degree relatives

Epidemiology of Panic Disorder (2)

Cultural syndromes:

"hit by the wind" – Vietnamese

ataque de nervios – Latin Americans

"soul loss" - Cambodians

Comorbidities:

- Major depression – lifetime 50%-60%
- Alcohol/substance abuse or dependence
- GAD, OCD, PTSD
- Bipolar I and II - 11%-22%

PD: Psychiatric Differential Diagnosis

- PD: fear of *the attacks*
- Panic attacks also occur in:
  - Social Anxiety Disorder – from social cues
  - OCD - a reaction to obsessional cues
  - PTSD – from trauma-related cues
  - Specific phobia – from specific cues (snakes, storms, etc.)
  - Major Depression

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

PD: Medical Differential Dx

- Caffeinism
- Hyperthyroidism
- COPD
- Stimulant abuse
- Cannabis use
- Alcohol withdrawal
- Hypoparathyroidism
- Vestibular problem
- TLE
- Cardiac arrhythmia
- Steroids
- Bronchodilators
- Pheochromocytoma
- Hypoglycemia

Further Medical Evaluation Is Indicated If:

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

PD: Patient Approach

- Name the diagnosis – many patients have been told there is nothing wrong.
- Relieve the patient of self-blame re failure to overcome the symptoms 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."

Hirshfeld DR, et al. Panic disorder and its treatment, 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, as in diabetes or asthma
- Immediately and repeatedly re-frame attacks as “Distressing, but not medically dangerous.”
- Educate significant other or family about PD
- Warn about the need to limit caffeine intake

Patient Education

Useful web sites for patients include:

- Anxiety Disorders Association of America
  - www.adaa.org
- National Institute of Mental Health
  - http://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml
- Association for Behavioral and Cognitive Therapies
  - www.abct.org

PD: Patient Approach *(cont.)*

- Be patient
  - Repeat information as needed
- Be thorough, credible and realistic
  - Outline a plan and the expected pattern of improvement
  - Improvement occurs in same order as symptom onset (first panic attacks, then phobia)
  - Note time frames for getting “better” and for getting “back to normal” are not the same

PD: Patient Approach *(cont.)*

- Address medication treatment duration as soon as the question 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 the eyeglasses?

PD: Patient Approach *(cont.)*

- Collaborative approach lessens perceived threat and perceived lack of control
- Map out “the plan”, document treatment
  - usual dose needed, necessary duration
  - how you will deal with adverse effects
- Give the patient a sense of 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.”

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

PD: Patient Approach *(cont.)*

- Initial Goals are to Reduce and Stop:
  - Unexpected attacks
  - Situation-bound attacks
  - Fearful anticipation
  - Fearful (phobic) avoidance
  - Distorted, catastrophic cognitions
- Treat comorbid conditions

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PD Outcome Assessment

- Functional status is a key issue
- Panic attacks alone – the least useful measure
  - Poor correlation with other domains
- PDSS – gold standard, assesses multiple domains
  - Phobic avoidance
  - Cognitive distortion
  - Depression
  - Somatic symptoms

*

Shear MK, et al. Panic Disorder Severity Scale. Am J Psychiatry 1997; 154:1571-1575. (also measures panic frequency, severity, impairment)

Definition of Response

- Symptoms
  - Panic attacks: ≥ 50% decrease
  - Other PD symptoms much or very much improved (anticipatory anxiety, phobic symptoms)
- Time frame
  - Response to SSRI: 4 - 8 weeks
  - Full response to SSRI: 6 - 12 weeks
  - Improvement in phobic avoidance and work function continues for > 6-12 months
  - Rx of agoraphobia may require CBT

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Definition of Remission

- Full recovery of pre-morbid functioning
- Full relief of symptoms
- No panic attacks (or ≤ 1 mild attack in a 4-8 week period)
- No clinically significant anxiety
- No clinically significant phobic symptoms
- Lasting remission may be elusive due to an undulating course of illness

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First-line Treatments for Panic Disorder

- CBT (~ 65% much, very much improved)
- SSRI (50-65% panic free, vs 40-55% placebo)
  - Sertraline ≥ 100 mg. Paroxetine 40 mg > 20 mg
  - Citalopram 20-30 mg > 40-60 mg (↑drop-outs)
- Benzodiazepine (60-75% panic free)
- Add CBT later to SSRI (starting both together may poorer long-term outcome)
- Patient education

Stein MB, et al. Practice Guideline for the Treatment of Patients with Panic Disorder, 2nd Ed., 2009. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf

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 will or can
    - Cognitively impaired
    - Severe disorders

American Psychiatric Association. *Practice Guideline for the Treatment of Panic Disorder*. 1998; Ballenger JC. Biol Psychiatry 1999;46:1579-94; Fava GA, et al. *Br J Psychiatry* 1995;166:87-92.

CBT for Panic Disorder

- Includes psychoeducation, self-monitoring
- Targets fear of bodily sensations using:
  - Breathing retraining
  - Cognitive restructuring
  - Exposure to physical symptoms
  - Exposure to feared situations
    - ➢Hierarchy: least to most feared, in that order

Panic Disorder Drug Treatment: General Principles

- SSRIs or SNRI are First-line
  - Other antidepressants, e.g., TCAs, work
  - MAOIs (have a high side effect burden)
  - Benzodiazepines
    - Not antidepressant; are a 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.

Drug Selection Considerations

- Comorbid conditions
- Personal Hx of efficacy, tolerability
- Safety
- Tolerability
- Half-life
- Drug-drug interactions
- Degree of protein binding
- Cost

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Panic Disorder: Medications That Don't Work

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

* Prosser JM, et al. BMC Psychiatry 2009; May 26:9:25

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SSRIs/SNRIs for PD: Advantages

- Relatively low side effect profile
- Wide safety margin
- Broad spectrum of efficacy for mood and anxiety disorders
- Few 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 may occur
- Sexual side effects - 25-60%
- Weight gain over 3-12 months in a 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 (start low, to reduce activation risk)
  - (25–50% of the antidepressant dose)
  - Sertraline 12.5–25 mg
  - Paroxetine 10 mg
  - Fluoxetine 5–10 mg
  - Fluvoxamine 25–50 mg
  - Citalopram 10 mg
  - Escitalopram 5-10
  - Venlafaxine 37.5 mg

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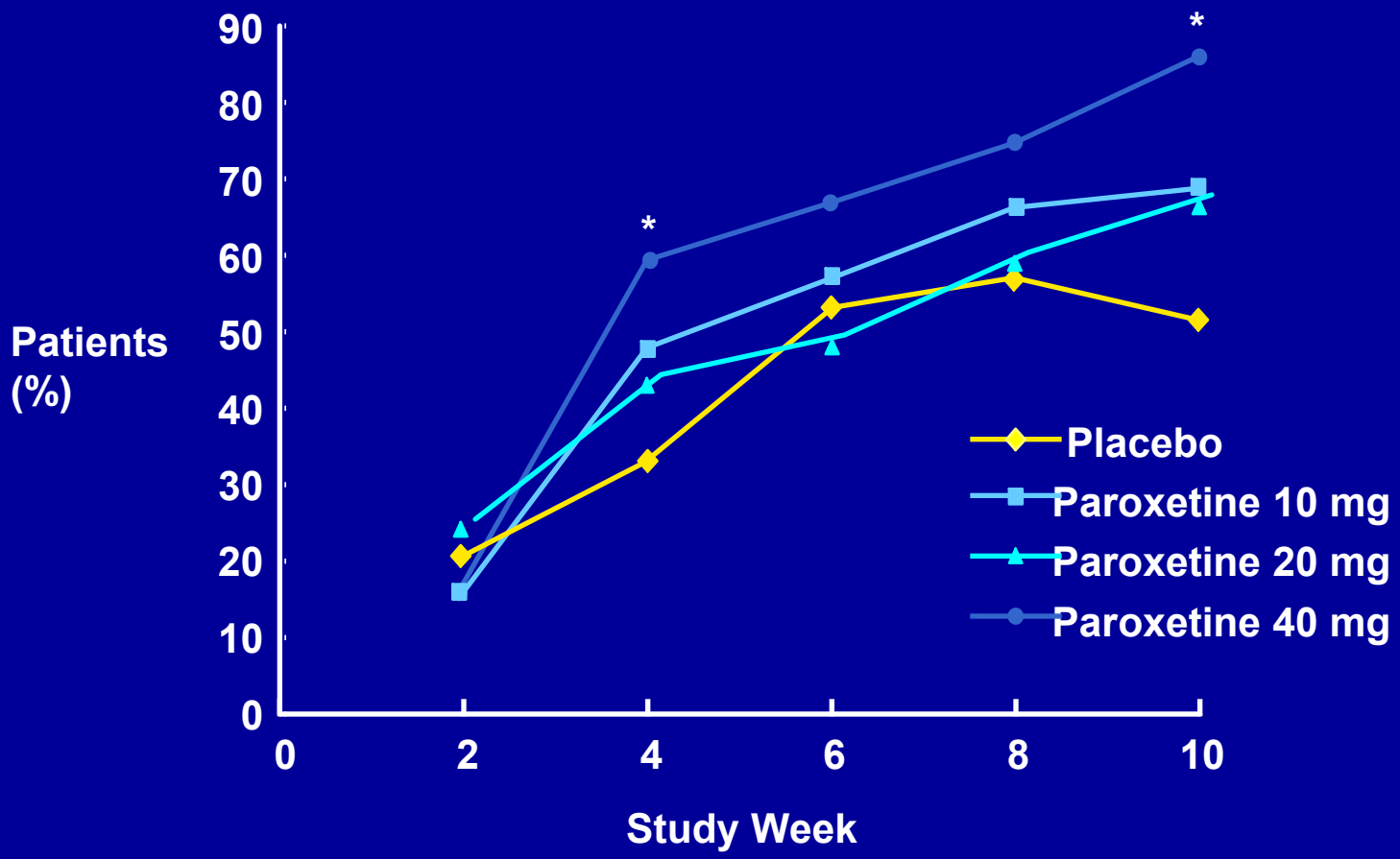
Percent of Patients Attaining Panic-Free Status Paroxetine Fixed-Dose Study

40 mg dose was stat. > placebo. 10 and 20 mg not, but were effective for many. No one dose is THE dose for all patients

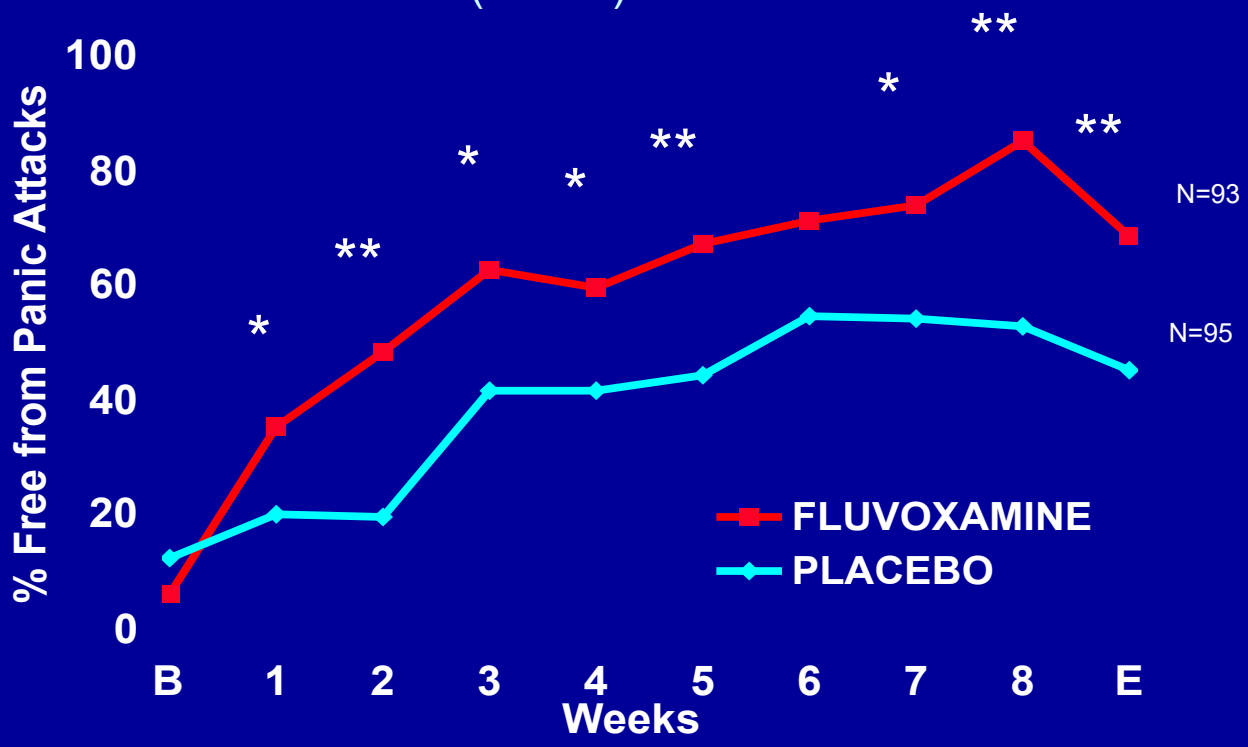


*P < .019 vs placebo

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

Fluvoxamine vs. Placebo
% Free from Panic Attacks

(n=188)

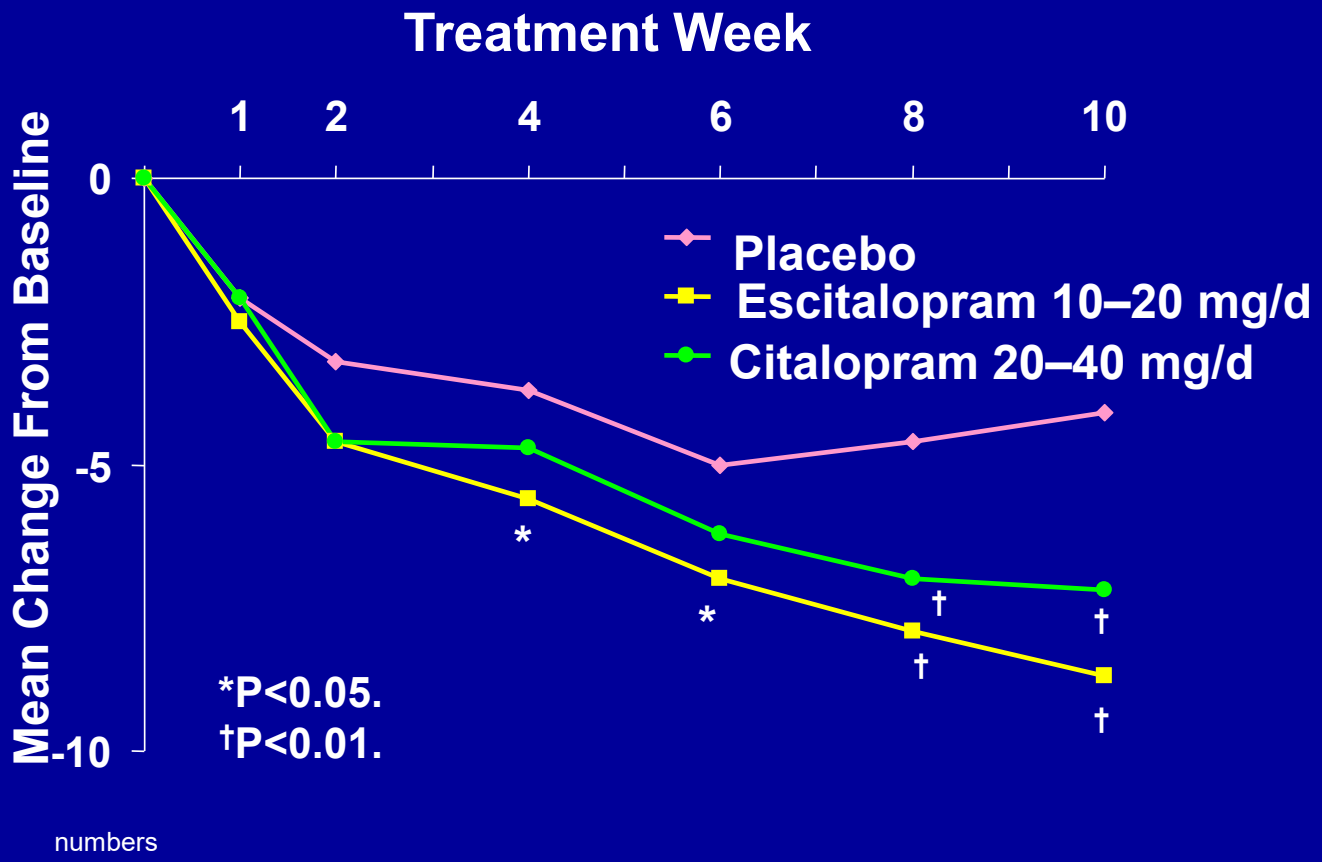


*** p < 0.05*; ** p < 0.01 vs placebo**

* Asnis G, et al. Psychiatry Res 2001 5;103:1-14.

Escitalopram Rx of Panic Disorder

Panic and Agoraphobia Scale



numbers

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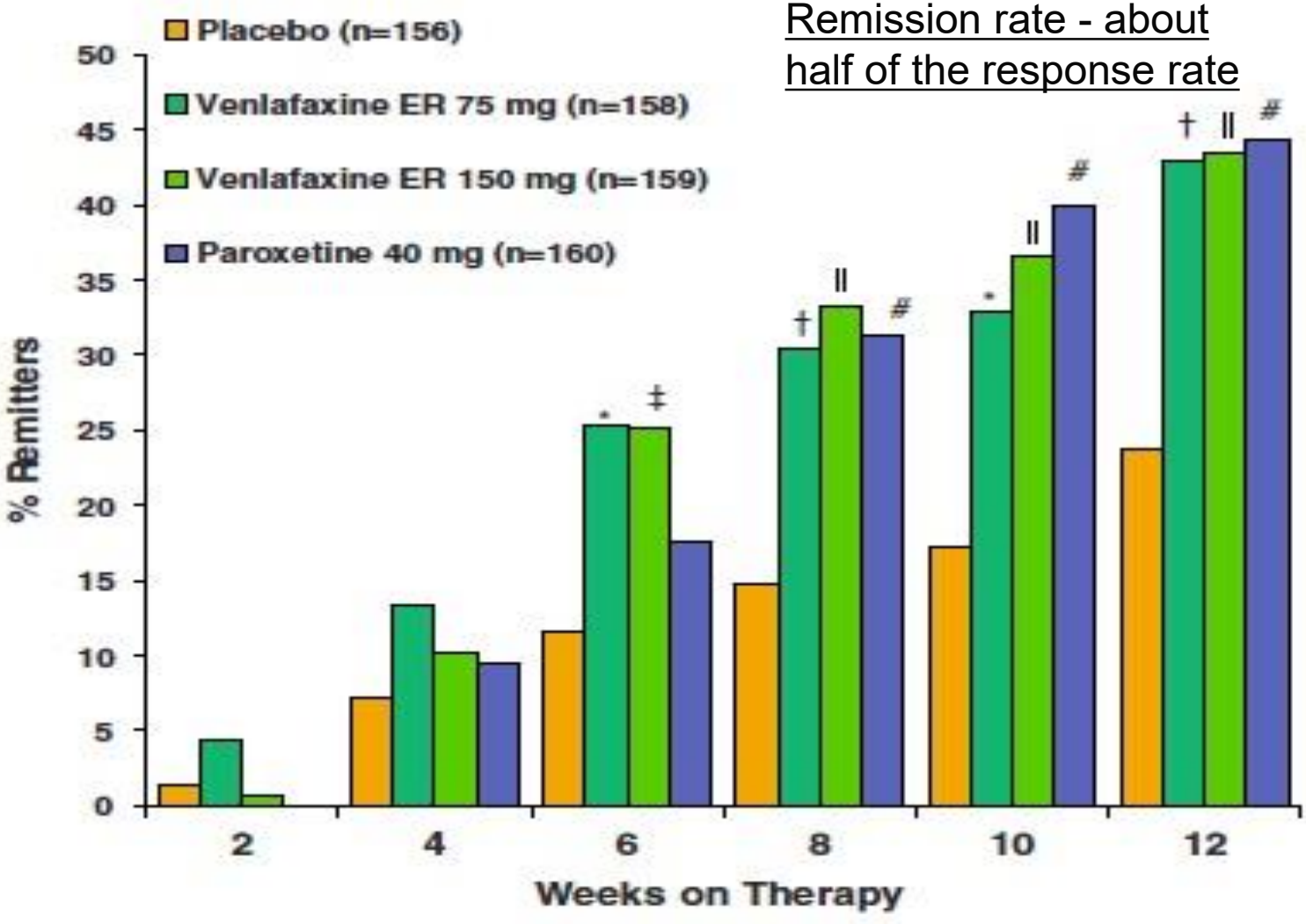
Stahl SM, et al. J Clin Psychiatry 2003; 64:1322-7

SSRI vs SNRI vs PBO



Remission rate - about half of the response rate

Pollack MH, et al. Depress Anxiety 2007; 24:1–14

TCAs: Advantages

- Antidepressant
- Large clinical experience
- Imipramine Rx – [imipramine + desipramine] serum level ≥ 100 ng/ml is likely to be effective for many patients

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TCAs: Disadvantages

- Delayed onset of action
- Significant side effect burden
  - Jitteriness -- start with 10 mg/day
  - Weight gain
  - Sexual dysfunction in 25% - 40%
- Anticholinergic effects
- Cardiovascular side effects and toxicity
- Danger with overdose
- Not useful for Social Anxiety Disorder

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Drug Discontinuation

- Maintain for ≥ 1 year after acute response
- Taper gradually (≥ 2 months)
- Properties of the drug affect timing and severity of discontinuation symptoms
  - Shorter t ½ □ earlier sx onset
  - No active metabolite □ earlier sx onset
  - Extended release formulation does not protect against discontinuation symptoms

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Discontinuation/Withdrawal Symptoms Following SSRI Treatment

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

*

Zajecka J, et al. J Clin Psychiatry 1997; 58:291-7.

Benzodiazepines: Advantages

- Effective
- Rapid onset
- Tolerability
- Safety

*

Benzodiazepines: Disadvantages

- Not antidepressant
- Physiologic dependence
- Sedation and coordination problems
  - Warn re driving and re operating heavy machinery
  - Warn about additive effects with alcohol
- Memory impairment*
- May increase risk of Alzheimer's disease**

* Tannenbaum C, et al. Drugs Aging 2012; 29:639-58

** Billioti de Gage S, et al. BMJ 2014; 349:g5205

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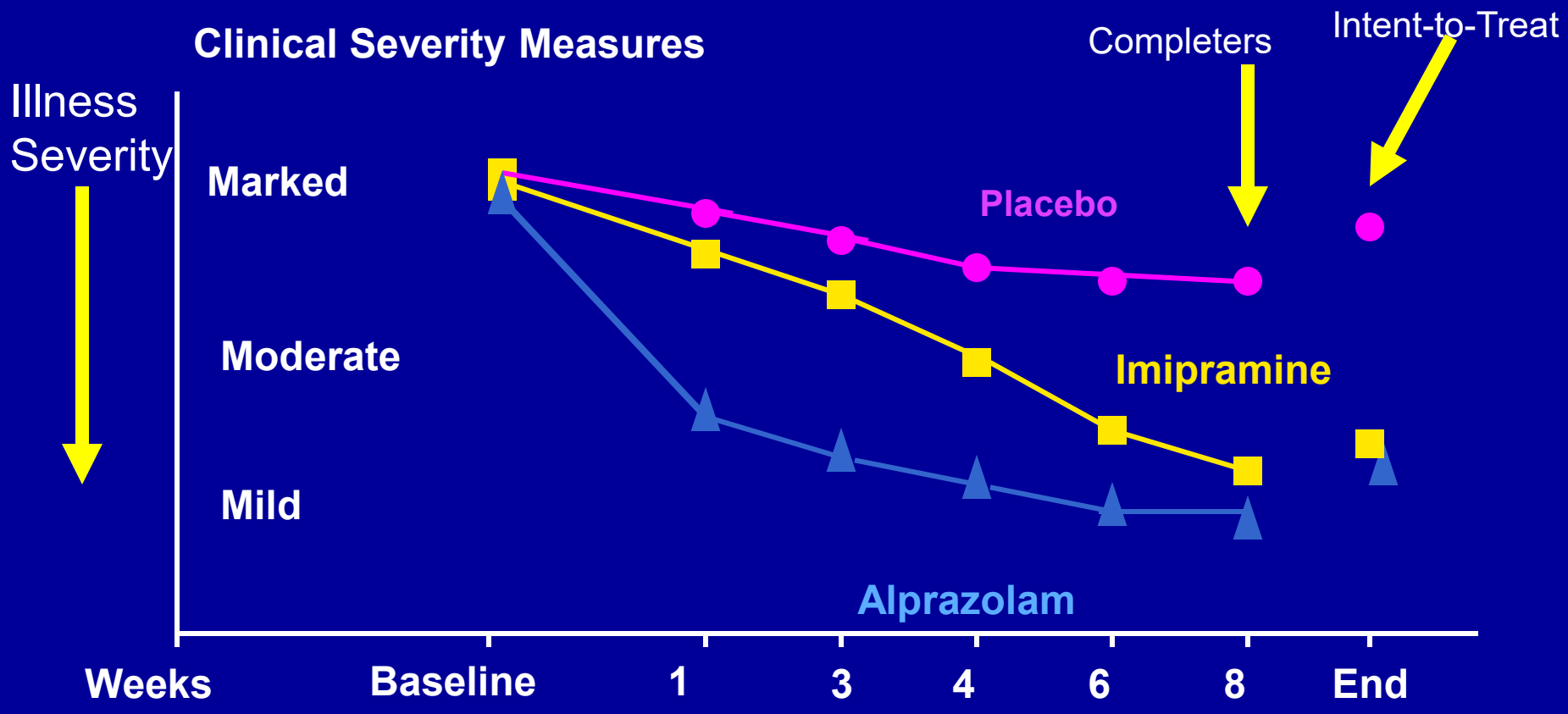
Comparative Efficacy of Alprazolam, Imipramine and Placebo in 1,080 Panic Disorder Subjects

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



Cross-National Collaborative Panic Study, Br J Psychiatry 1992 160:191-205; 161:724 erratum

Benzodiazepines: Long-Term Follow-up

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

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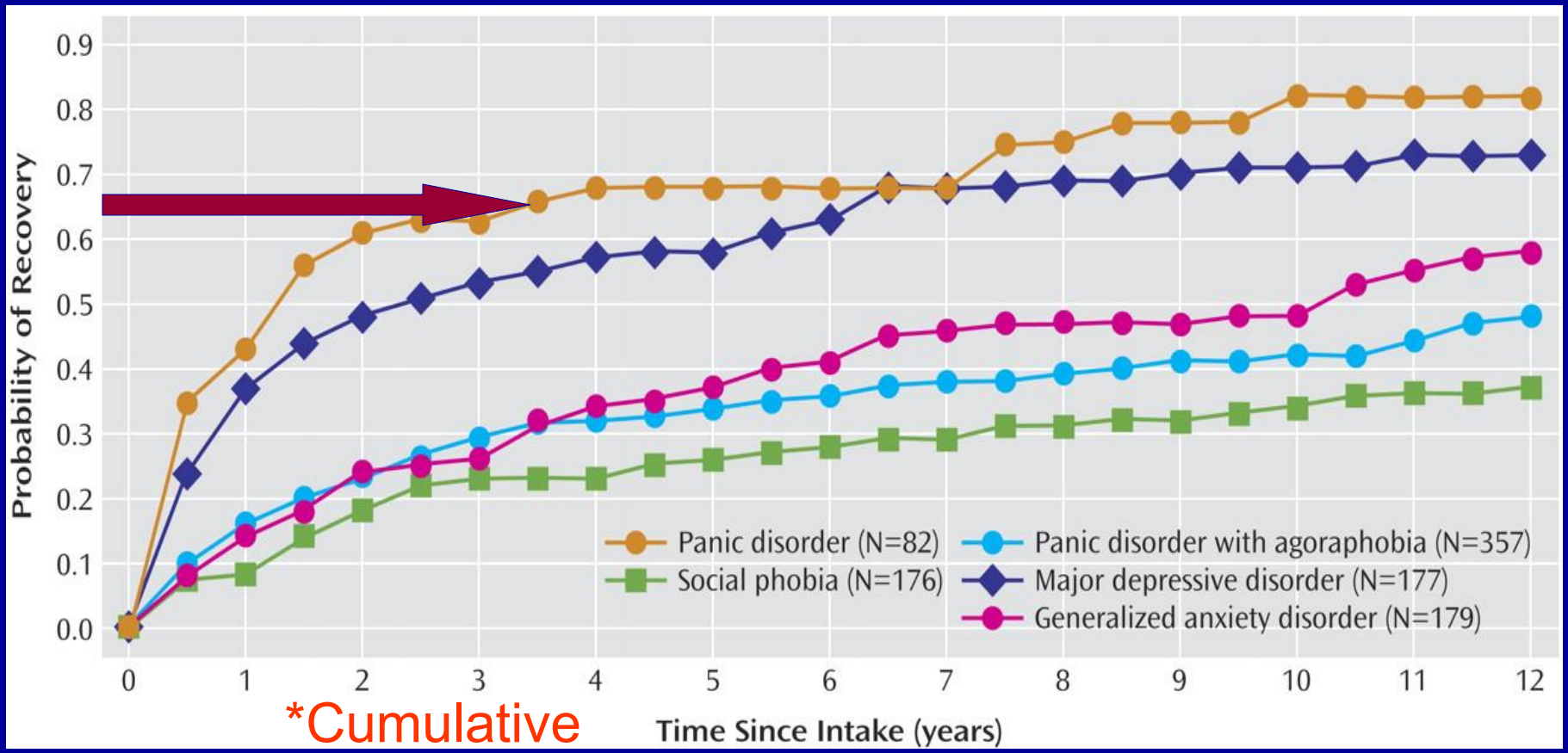
Nagy A. Acta Psychiatr Scand Suppl 1987; 335:47-55

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



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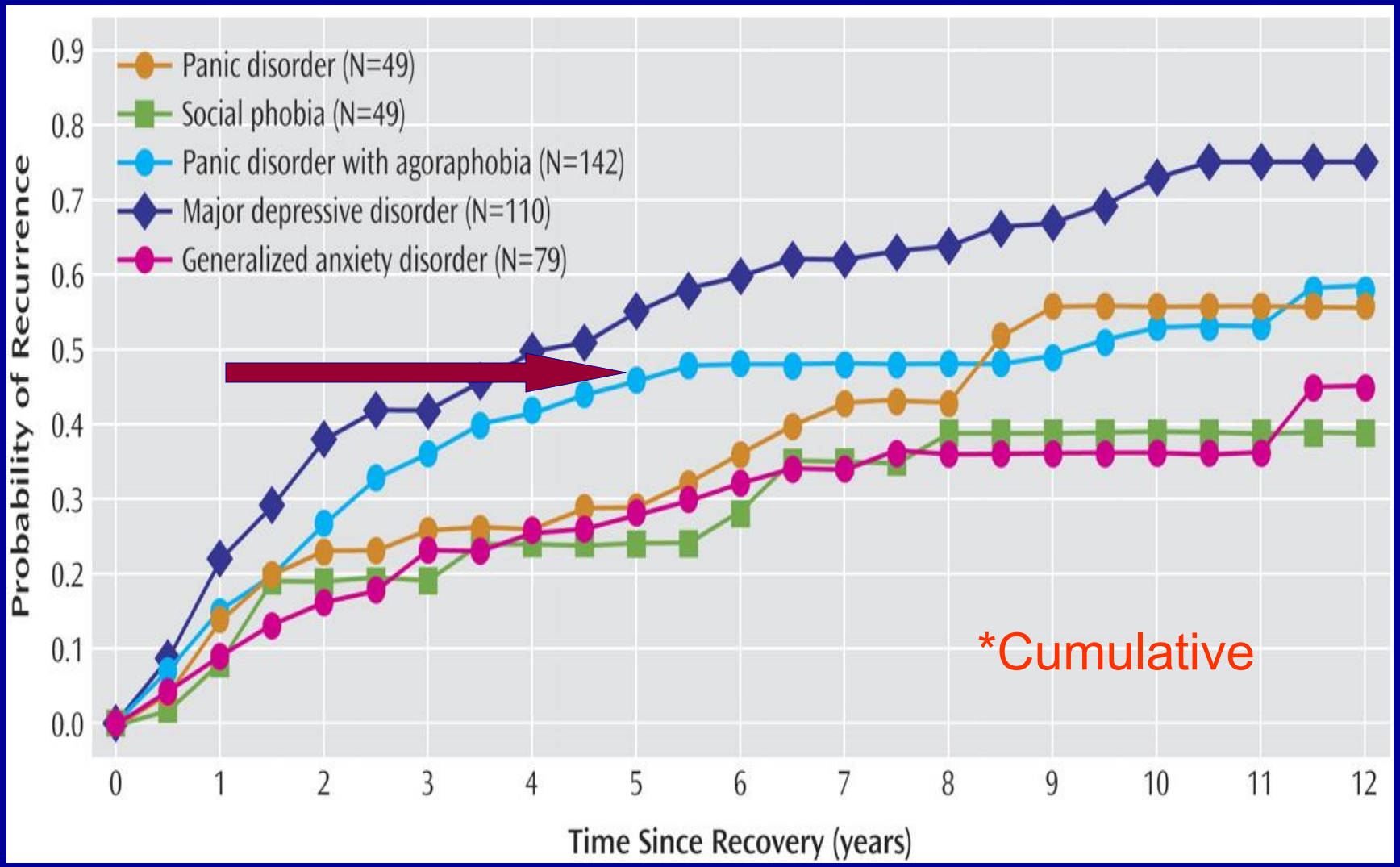
Bruce SE, et al. Am J Psychiatry 2005 162:1179-87

* 12-Year Probability for PD Recurrence: High



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

For Inadequate or Non-response

- Identify element(s) unimproved
  - Panic attacks, avoidance, anticipatory anxiety, depression
- Medication dose and duration adequate?
  - No Increase?
  - Yes Augment with medication or CBT?
  - Yes Change drugs?
- Reconsider diagnosis

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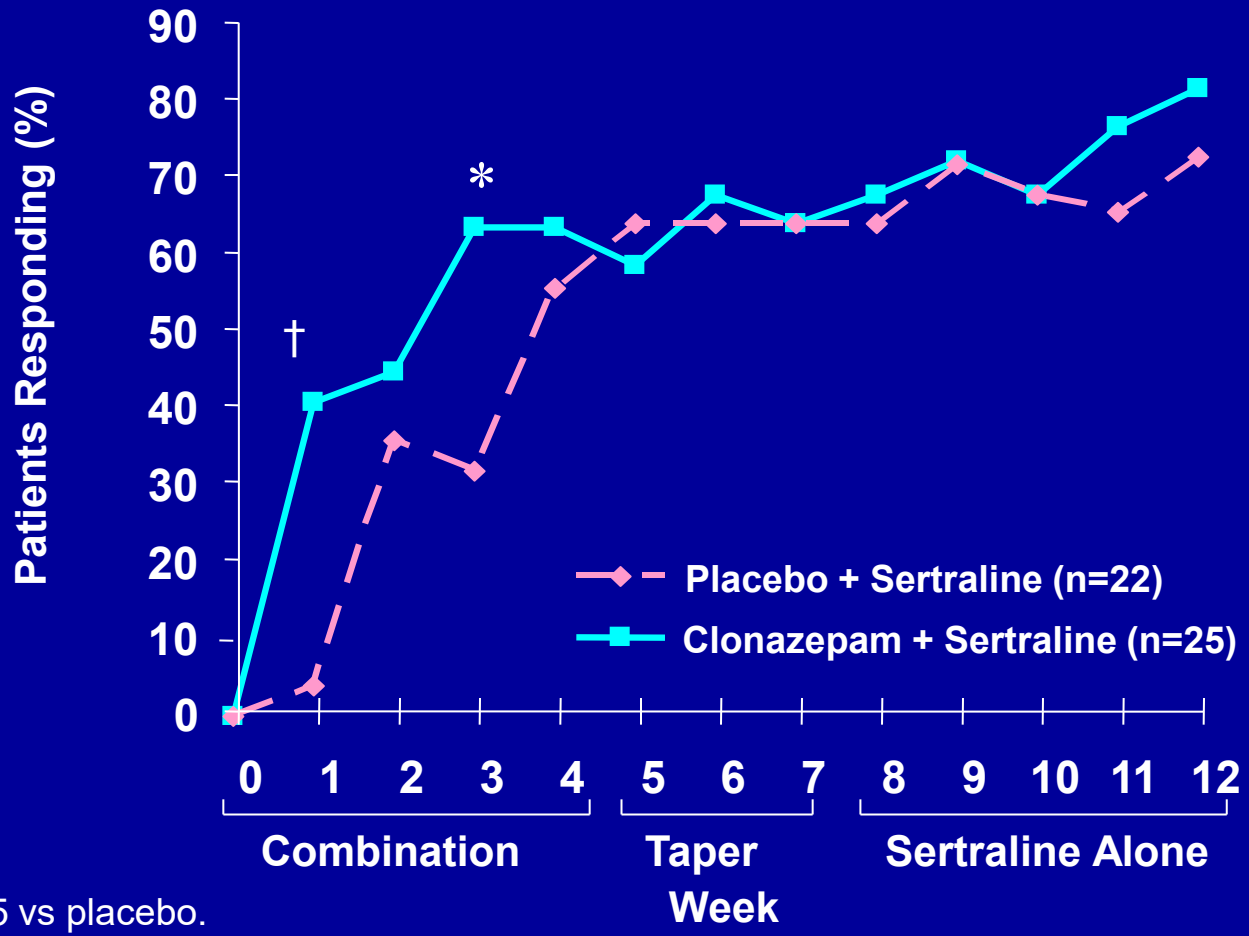
Possible Treatments for Rx-Resistant Panic Disorder

- Add to an SSRI:
  - CBT (controlled trials)
  - high-potency benzodiazepine (double-blind trials)
  - Pindolol (2.5 mg tid) (open trial)
  - Pramipexole (0.25→1.5 mg/d) (cases)
- Switch to a TCA (imipramine 75-150 mg)
- Switch to mirtazapine (1 small trial)
- Add or switch to an atypical antipsychotic

Combining Medications For Panic Disorder

Sertraline + Clonazepam or Placebo



* *P*<0.05 vs placebo.
† *P*<0.003 vs placebo.

Goddard AW, et al. Arch Gen Psychiatry 2001;58:681-6

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Meta-Analysis of Combined Treatments for PD

- 106 Studies, short-term treatments
- N = 5,011 patients Pre-Rx; 4,016 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 AJ, et al. J Nerv Ment Dis 1997; 185:510-16

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Meta-Analysis of Combined Treatments for PD

- All treatments were superior to placebo conditions for agoraphobic avoidance
- CBT efficacy = other treatments
- Antidepressants superior to placebo for panic attacks
- Exposure not effective against panic attacks, but worked for agoraphobia

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Panic Disorder - Neurobiology

- Fear Circuit Dysfunction
- Inherited risk - polymorphism
    - Lower brain serotonin transporter[1]
    - Reduced brain $5HT_{1a}$ receptor binding[2]
    - Non-random patterns of comorbidity
- Challenge studies indicate vulnerability to sx

[1] Meron et al. Psych Res 2004;132:939-45

[2] Nash et al. Br J Psychiatry 2008; 193:229-34

The Fear Circuit Model:
Critical Components Inter-modulate

- Amygdala Central Nucleus: "Alarm button," filters input and has a 'watchdog' function; fear conditioning
- Hippocampus: Stores and retrieves 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.
- Anterior Cingulate Cortex: Monitors likelihood of potential errors

ALL function abnormally in Panic Disorder

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Abnormal GABA and BZ Receptors in PD

Altered Distribution, Sensitivity and GABA concentrations

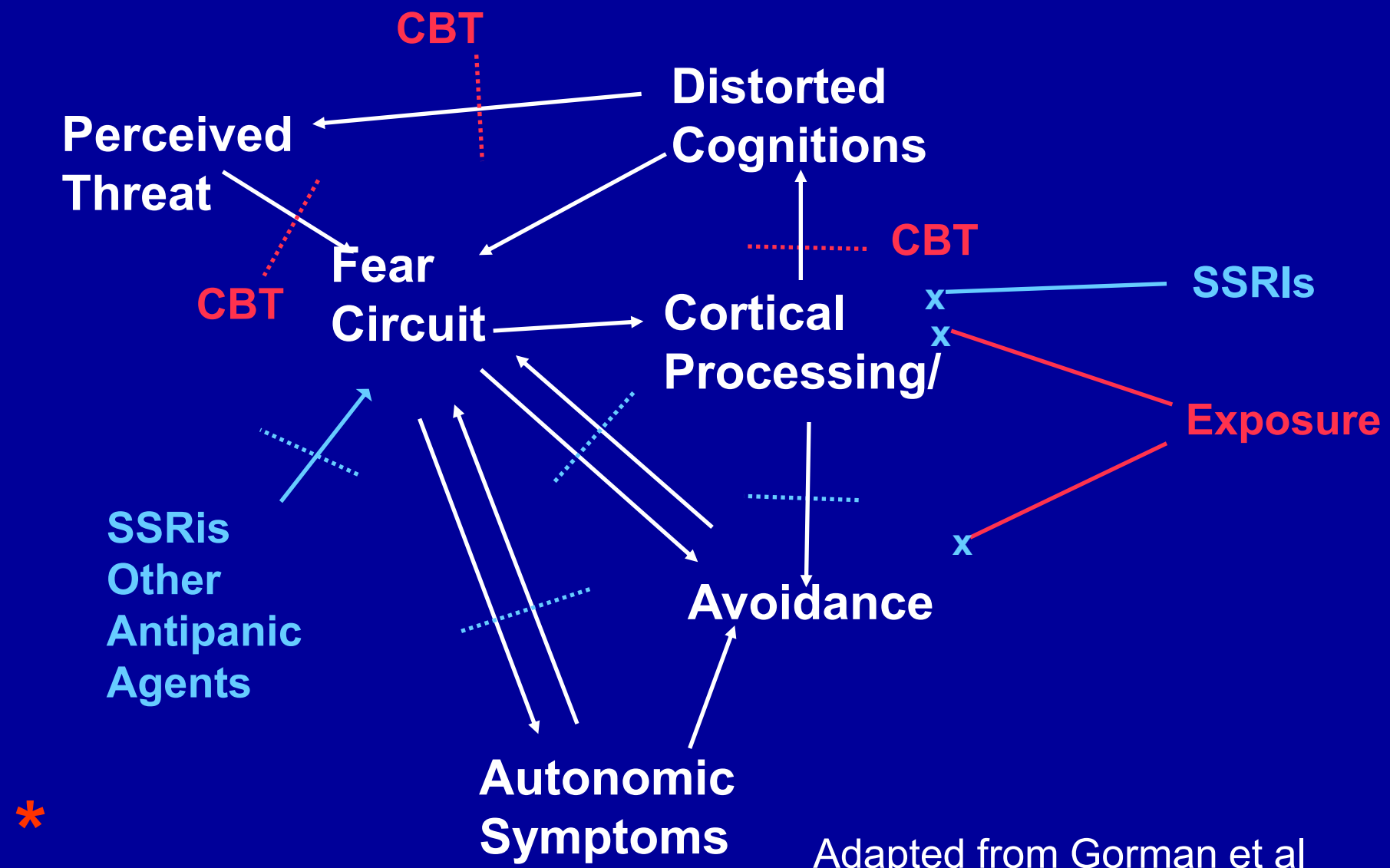
- Reduced sensitivity to i.v. diazepam
  - Roy-Byrne P, et al. Am J Psychiatry 1996;153:1444-1449
- Flumazenil is anxiogenic in PD
  - Woods SW, et al. Psychiatry Res 1991;36:115-127
- Reduced GABA in occiptal cortex; attenuated response to BZs
  - Goddard AW, et al. Arch Gen Psychiatry 2001; 58:556-61;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

Panic Disorder: Imaging Studies

- Reduced post-synaptic 5HT receptors in untreated Panic Disorder
- Reduced volume and function in mPFC and Anterior Cingulate Cortex
- 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

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



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Adapted from Gorman et al

Answers to Questions

- Q1. e (all of the above)
- Q2. c. (prevalence is *lower* in Latino Americans [DSM-5])
- Q3. c. Beta Blockers are not effective in panic disorder.
- Q4. False. Only about half of patients achieve remission within 12 weeks.
- Q5. False. CBT is as effective as first-line drugs in treating panic disorder.