

Psychopharmacology for Anxiety Disorders

Jerrold F. Rosenbaum, MD

Psychiatrist-in-Chief Emeritus MGH

Director, Center for Neuroscience of Psychedelics

Stanley Cobb Professor of Psychiatry, HMS

Disclosure Regarding Financial Interests and Affiliations

Psy Therapeutics, Inc. (co-founder, BOD, equity)

Sensorium Therapeutics, Inc. (co-founder, BOD, equity)

Entheos Labs Inc (co-founder, BOD, equity)

Reunion Neuroscience (SAB)

Terran Neuroscience (SAB)

Vistagen (SAB)

Cerebral Inc (BOD)

Atai/Beckley (SAB)

Anxiety

- **Symptom**
 - Acute
 - Transient
 - Recurrent
 - Chronic
- **Disorder (Syndrome)**
 - e.g., DSM 5
- **Comorbidity**
 - Psychiatric
 - Medical
 - Iatrogenic

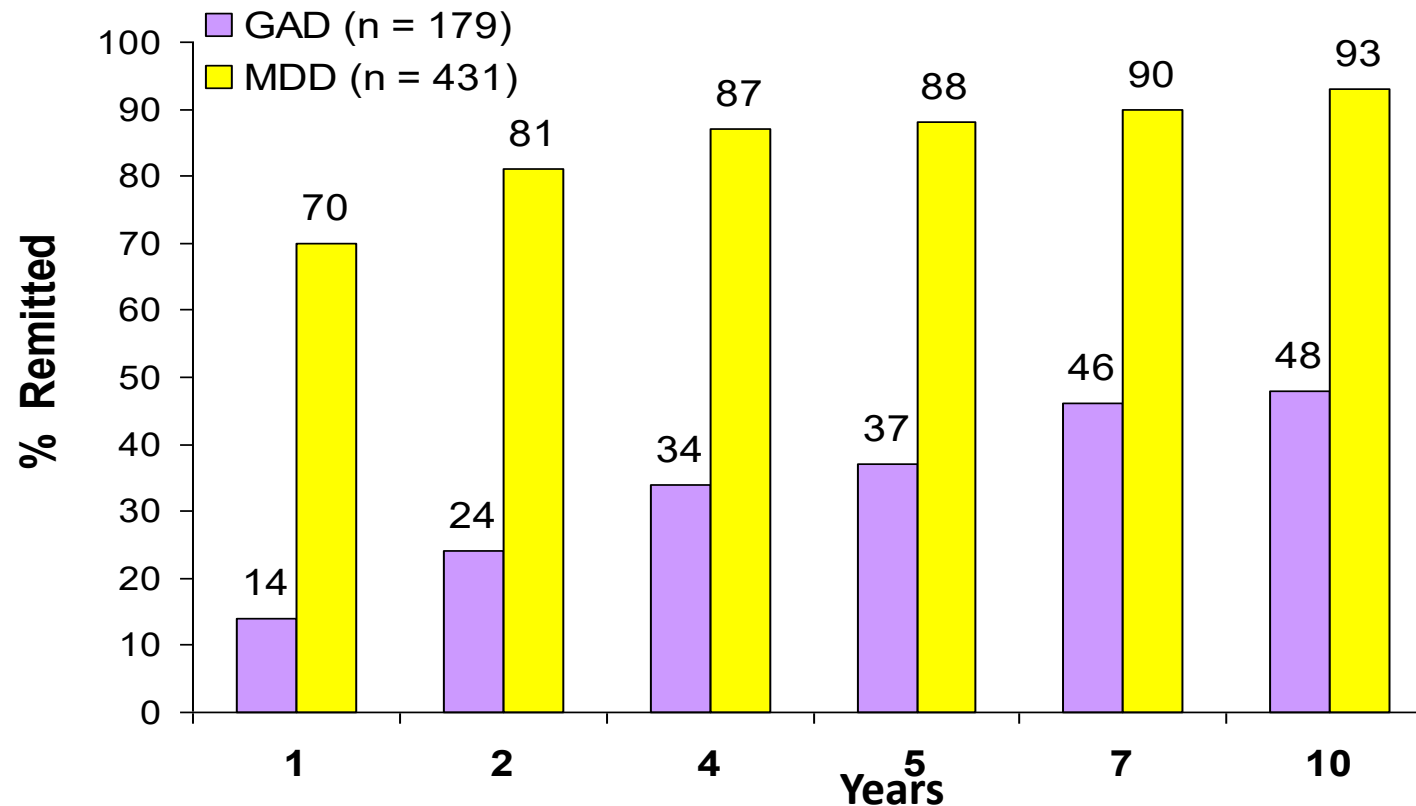
The Nature of Anxiety

- Anxiety disorders symptoms are heterogeneous and include cognitive, physiological, behavioral and emotional components (e.g. worry, social fears, physiological arousal, panic attacks, and avoidance behaviors)
- ~15% born with temperament predisposition to anxiety (behavioral inhibition) which predisposes to social anxiety in adolescence and continuing anxiety in adulthood
- Anxiety and depression are separated by convention but 90% of MDD patients suffer anxiety and as many as 50% could meet criteria for an anxiety disorder
- Anxiety is a risk factor for suicide in depression
- Anxiety disorders are associated with high rates of depression.
 - 20% to 70% in social anxiety disorder
 - 50% in panic disorder
 - 43% in patients with generalized anxiety disorder

Prevalence

- Anxiety disorders have high lifetime prevalence up to 34%
- Generalized anxiety disorder (5-7 % lifetime prevalence),
- Social anxiety disorder (10-13% lifetime prevalence)
- Panic disorder with or without agoraphobia (4-5% lifetime prevalence)
- All psychiatric patients experience anxiety symptoms or comorbid disorders.

Anxiety Disorders tend to be Chronic: GAD and MDD in Two 10-Year Studies



MDD = major depressive disorder. GAD=Generalized Anxiety Disorder.

MDD: Keller MB, et al. *Arch Gen Psychiatry*. 1992;49:809-816.

GAD: Bruce SE, et al. *Am J Psychiatry*. 2005;162:1179-1187.

What Are We Trying to Accomplish?

TREATMENT GOALS

Relieve suffering

reduce acute distress and fear

Restore function

work, school, relationships, health

Facilitate exposure

reduce avoidance and promote mastery

Prevent relapse

long-term planning for chronic illness

Build resilience

restore adaptive emotional learning

Clinical Perspective: Medication can reduce symptoms; recovery often requires behavior change and relearning safety.

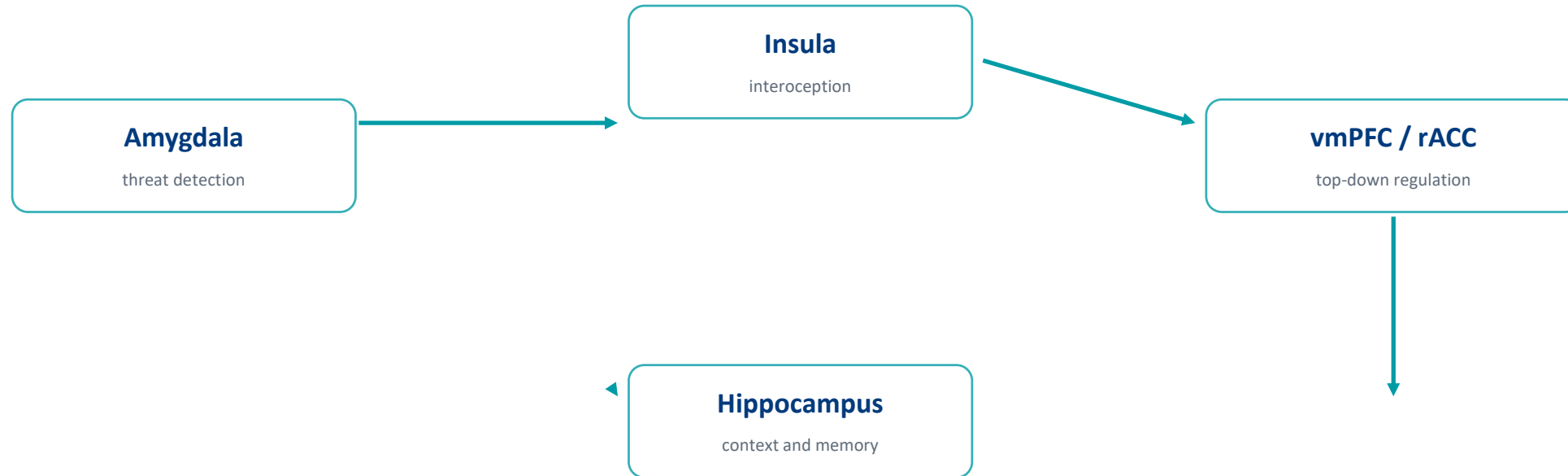
Anxiety as Dysregulated Threat Processing



Massachusetts General Hospital
Founding Member, Mass General Brigham

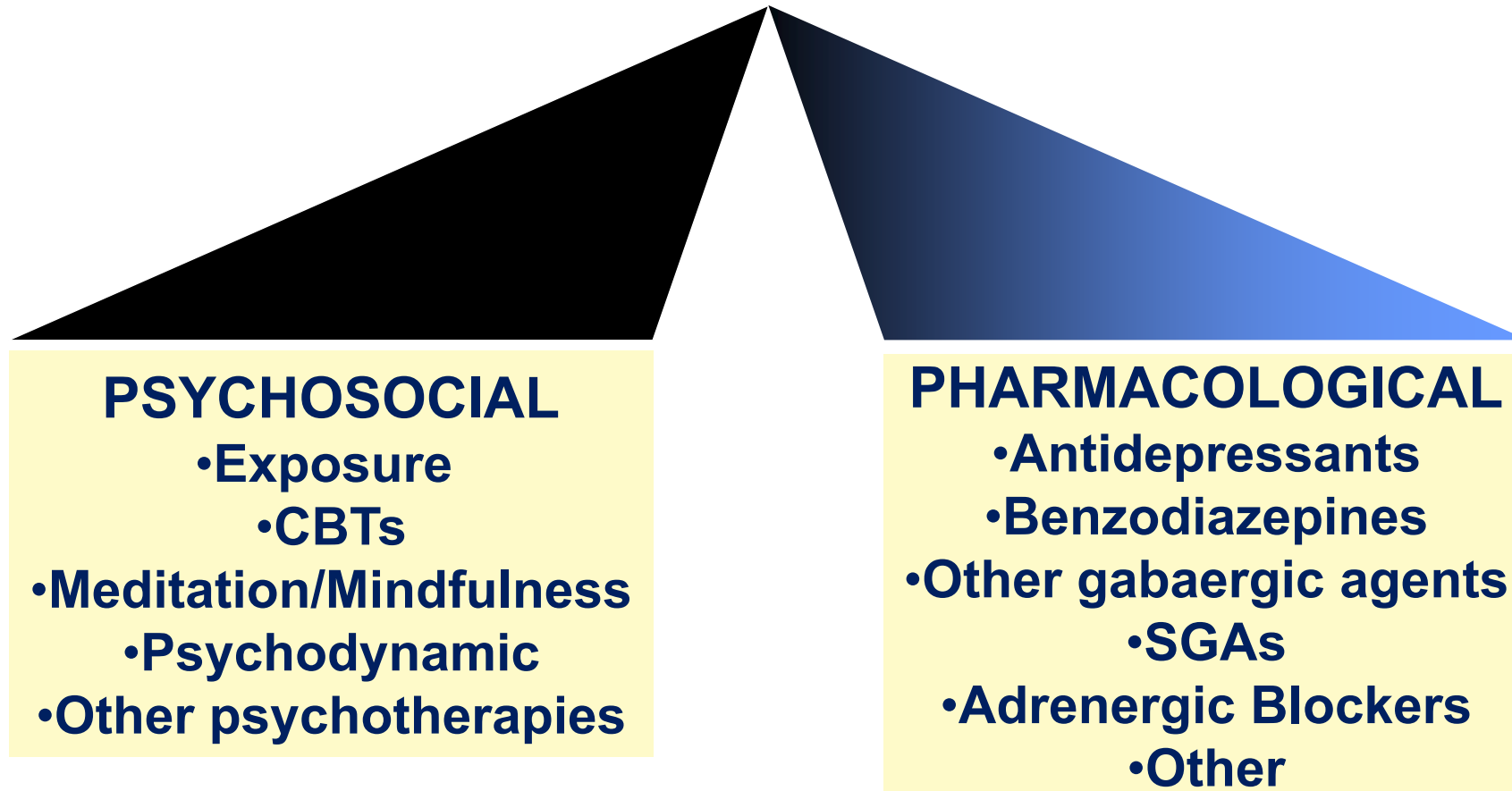
Psychiatry Academy

NEUROBIOLOGY



Clinical Perspective: Treatments differ in how they influence threat detection, physiologic arousal, avoidance, and extinction learning.

Anxiety Disorder Treatment Options



Psychopharmacology of Anxiety

- The need remains for a rapid acting, safe, non-sedating, non-addictive agent without tachyphylaxis or rebound/withdrawal and suitable for as needed or sustained use
- Over 30 million in USA receive over 90 million Rx's for BZDs annually
- Studies of large prescription databases reveal GAD treatment to be a very unsatisfied category with frequent changes, discontinuations, restarts, and combinations (Definium Therapeutics)

Why This Matters

BURDEN

34%

lifetime prevalence
of anxiety disorders

#1

among the most common
psychiatric illnesses

Early

onset often begins
in youth

Chronic

course is often
recurrent or persistent

Treatable

but often
incompletely controlled

Anxiety disorders are not trivial: they are common, disabling, chronic, and clinically consequential.

Anxiety Disorders Are More Common Than We Often Appreciate

EPIDEMIOLOGY



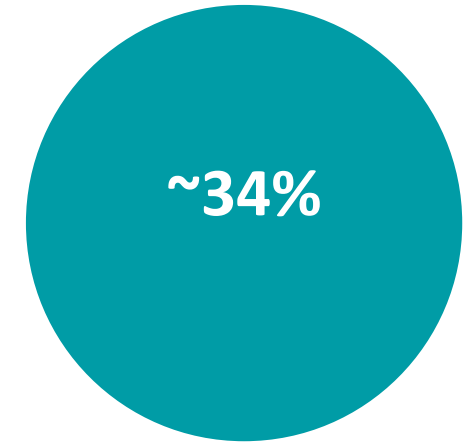
Social anxiety disorder



Generalized anxiety disorder



Panic disorder ± agoraphobia



Any anxiety disorder

All psychiatric patients experience anxiety symptoms or comorbid anxiety disorders.

Anxiety Is Universal. Anxiety Disorders Are Not.

DEFINITION

Adaptive anxiety

Protective
Proportionate
Context-dependent
Transient
Facilitates preparation



Anxiety disorder

Persistent
Excessive
Impairing
Avoidance-reinforcing
Disrupts life and development

Clinical Perspective: The goal is not to eliminate anxiety. It is to restore adaptive functioning.

If You Remember Only Five Things...

TAKE-HOME MESSAGES

- 1 Anxiety and anxiety disorders are not trivial.
- 2 Available treatments help many patients, but all have limitations.
- 3 Treatment selection is a clinical deployment problem: what, for whom, when, and how long?
- 4 Innovative treatments in development are promising and may reshape the field.
- 5 Care should be comprehensive—taking advantage of psychological and biological tools.

Medications for Anxiety Disorders

Antidepressants

Serotonin Selective Reuptake Inhibitors (SSRIs)

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Other Antidepressants

Tricyclic Antidepressants (TCAs)

Monoamine Oxidase Inhibitors (MAOIs)

Benzodiazepines

Other Agents

Azapirones

Beta blockers

Other gabaergic medications

SGAs

Novel Targets and MOAs in development

SSRI and SNRI Antidepressants: First Line for Chronic Anxiety Disorders

- Lack acute efficacy (may worsen anxiety acutely)
- Fewer safety and misuse concerns than BZDs
- Efficacy for comorbid depression
- General efficacy across anxiety states
- Initiate with low doses to minimize early exacerbation of anxiety and other side effects
 - E.g. citalopram 10 mg, sertraline 25 mg, venlafaxine 37.5 mg
 - May co-administer with BZD for initiation
 - Titrate to efficacious dose as tolerated
- Challenges:, initial unpleasant activation/jitteriness, insomnia, sexual dysfxn, GI effects, weight gain, discontinuation symptoms

16. Practical SSRI Prescribing

Clinical pearls

- Start low, titrate thoughtfully
- Prepare patients for delayed benefit
- Continue after remission to reduce relapse
- Encourage exposure throughout treatment

Clinical Perspective

Treat anxiety disorders as chronic illnesses. Success is measured by restored functioning, not symptom scores alone.

Social Anxiety Disorder

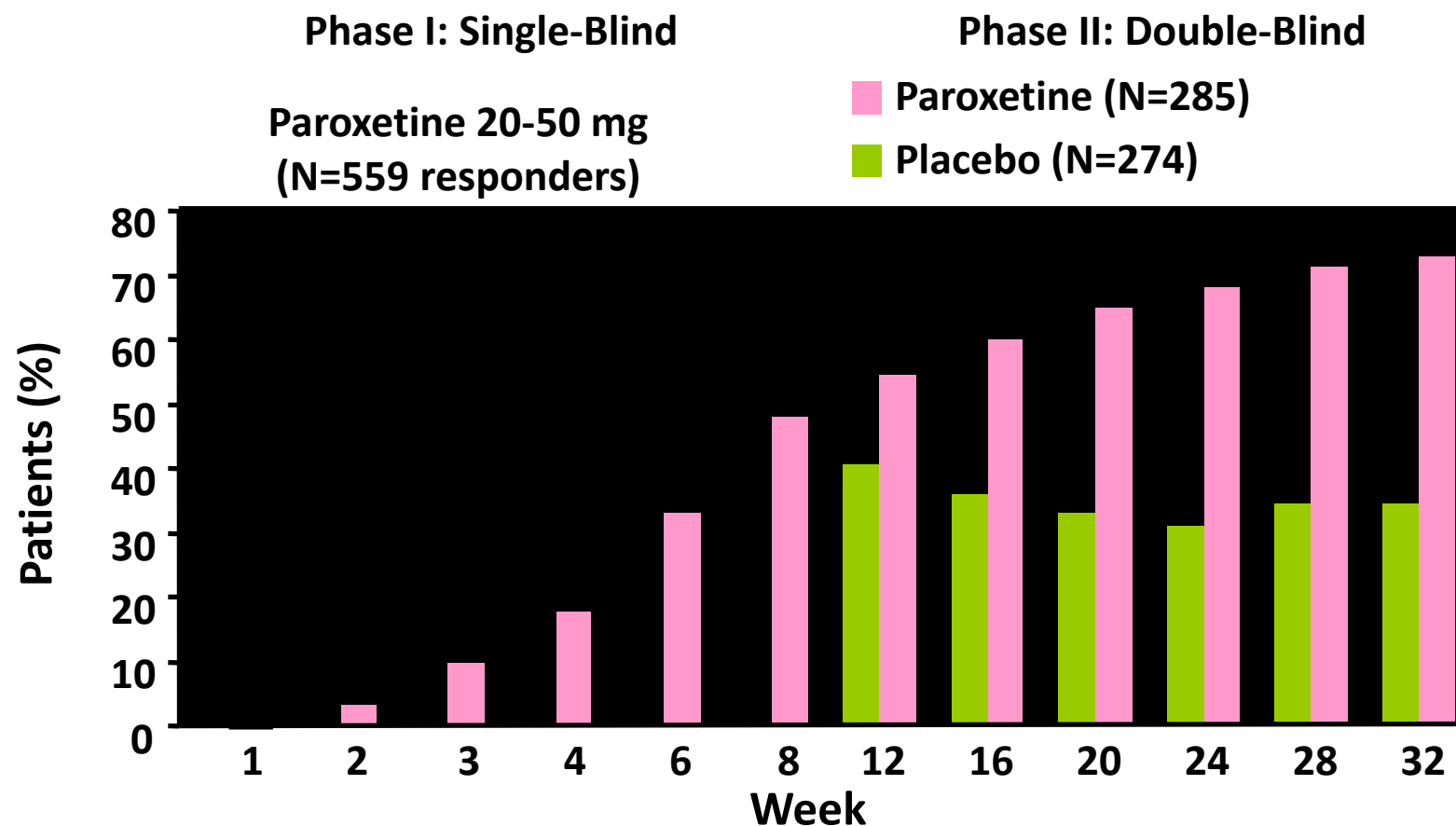
- Multiple RCTs support safety and efficacy of SSRIs (e.g., sertraline, paroxetine, escitalopram) and SNRIs (venlafaxine XR)
- Considered first-line pharmacotherapy (although typically smaller effect size than BZDs)
- Continuing improvement with longer treatment
 - Always encourage “exposure”: Graduated return to avoided situations

Generalized Anxiety Disorder (GAD)

- **Daily Worry and Nervousness $\geq$ 6 months**
- **Not due to acute stressor**
- **Common Symptoms:**
 - **Restlessness or on edge**
 - **Fatigue**
 - **Difficulty concentrating**
 - **Irritability**
 - **Muscle tension**
 - **Sleep disturbance (difficulty falling asleep, staying asleep, or restless unsatisfying sleep)**



GAD: Remission Rates with Long-Term Treatment



* $p < 0.01$ vs. placebo; LOCF dataset; Remission defined as HAM-A ≤ 7

Stocchi F, et al. *J Clin Psychiatry*. 2003;64:250-258.

Tricyclic Antidepressants

- Efficacious but now rarely used due to side effect profile (e.g., cardiovascular, anticholinergic) and lethality in overdose
- Imipramine: most RCT data in panic; clomipramine
- No evidence of lesser efficacy compared to SSRIs/SNRIs for panic but lacks efficacy data for Social Anxiety Disorder
- Also can see initial anxiety worsening (initiate with “test” dose—e.g., 10 mg/d imipramine)

Benefits of Benzodiazepines

- Efficacy
- Rapid onset of therapeutic effect
- Well-tolerated
- Rapid dose adjustment feasible
- Can be used “PRN” for situational anxiety or rescue
- No early antidepressant-induced unpleasant activation
- Meta-analyses (e.g., GAD*) suggest:
 - greater effect size than serotonergic antidepressants
 - greater effect size with higher HAMA baseline scores

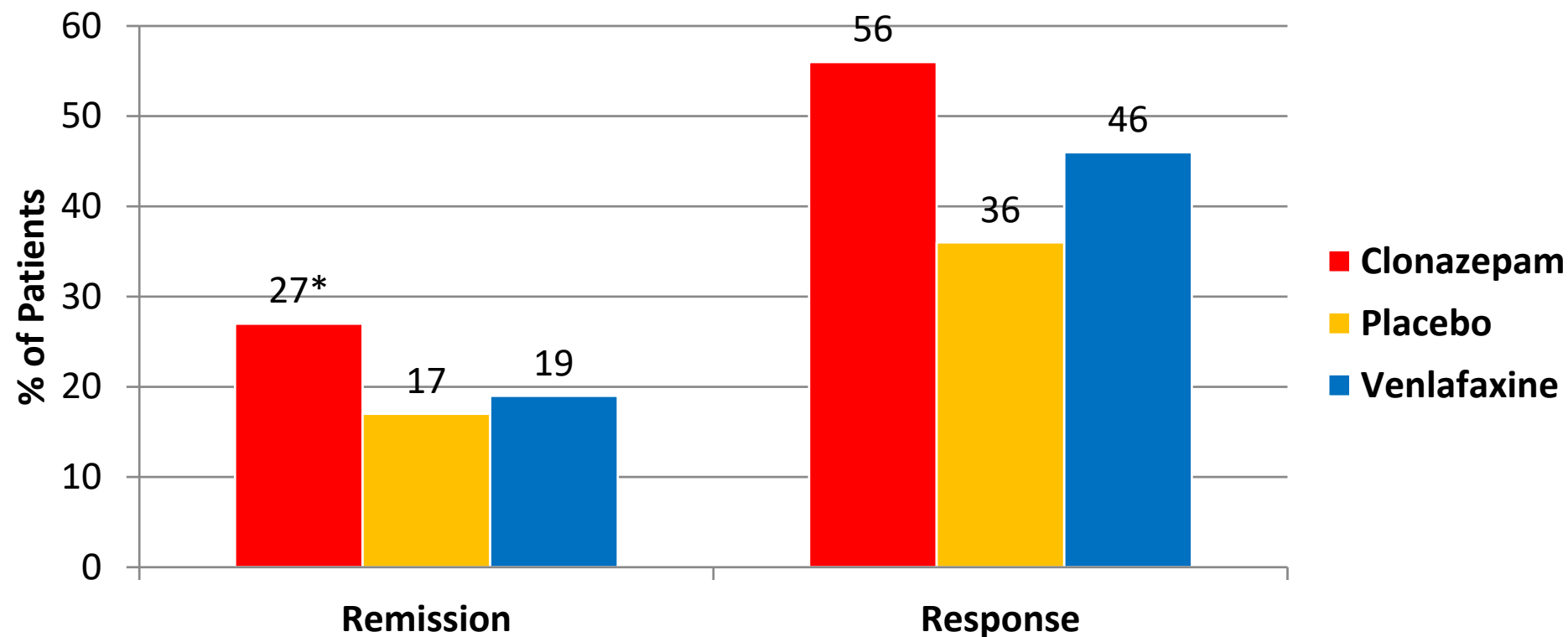
Drawbacks of Benzodiazepines

- Initial sedation, cognitive and psychomotor impairment with initiation or dose escalation
- Additive with alcohol; dangerous with opiates
- Physiologic dependence with chronic therapy
- Discontinuation-related difficulties: need to taper slowly
- Potential for abuse in substance users; ~7 % will misuse
- Less effective for comorbid depression
- May interfere with CBT exposure learning

Benzodiazepine Use in Panic Disorder

- Frequently underdosed as PD patients may be sub-sensitive
- Decreases opportunity to learn self-efficacy with exposure, potentially reducing efficacy of CBT
- Focuses attention on need for rescue
 - Lowers threshold for panic if leave home without it
- PRN dosing alone does not prevent persisting symptoms or prevent panic attacks
- Mean dose of clonazepam in pivotal study for PD was 2.7 mg/day

Clonazepam Augmentation of Sertraline vs. Switch to Venlafaxine for Refractory SAD



*greater drop in LSAS severity ($p=0.020$) and disability ($p=0.0028$) vs. Placebo

Remission = LSAS score ≤ 30

Response = LSAS score ≤ 50

Pollack, et al. *Am J Psychiatry*. 2014;171:44-53.

Long-Term Use of Benzodiazepines and Dose Escalation

- Study of 2440 Medicaid patients (80% using benzodiazepines ≥ 2 years)
- Analysis for escalation to high dosage (≥ 20 mg/day diazepam or equivalent for elderly; ≥ 40 DMEs per day for younger patients)
- Results
 - Median daily dosage remained constant at 10 DMEs during 2 years of continuous use
 - Incidence of escalation to a high dosage was 1.6%
- Conclusion: *Does not support concern that long-term use of benzodiazepines frequently results in dose escalation*

Benzodiazepine Discontinuation in Panic Disorder:

- Clonazepam minimum 3 years and in remission >1 year
- Mean dose at start 2.7 mg/d
- Decreased by 0.5 mg/2-week period until 1 mg/day
- Then tapered 0.25 mg/week
 - 68.9% of the 73 patients free of medication after 4 months tapering, with additional 19% after 3 more months
 - Most discontinuations symptoms were mild
 - Improvement in PD and quality of life maintained during taper and follow-up
 - *Supports very slow taper*
 - *However, cumulative relapse rates whether BZD or antidepressant Rx were high post-discontinuation at 6 year follow-up (89% of n=76) though lower with clonazepam than paroxetine**

Nardi, et al. *J Clin Psychopharmacol*. 2010;30:290-293.

Freier, et al. *J Clin Psychopharm*. 2017;37:4.

Benzodiazepines: A Perspective

- As with most of our therapeutics, we lack long-term studies comparing outcomes of anxiety disorder patients on benzodiazepines with those on alternative pharmacologic, behavioral, or even no treatment.

COMMENTARY

Benzodiazepines: A Perspective

Jerrold F. Rosenbaum, M.D.

A week after the mandate for all to shelter at home in Massachusetts, I received this message from a severely ill disease-phobic patient (who was working remotely with her behavioral medicine psychologist to reduce her disabling fears): “I am very thankful I have lorazepam at home with me these days! I am trying hard not to take it and am putting forth great effort on what I am thankful for each day.”

I confess that some of the most gratifying memories in my career had to do with benzodiazepines. In the early 1980s, there was a woman with agoraphobia in Beacon Hill who, after being given alprazolam and the support of a visiting

My work turned to focus on the antecedents of anxiety and the potential for early recognition and interventions to limit lifelong disability (4). As others have also reported, roughly one in six individuals appear to be born predisposed to develop uncomfortable physiological and behavioral responses that predispose to fearful behaviors, and in some cases this predisposition evolves into recurrent or lifelong social anxiety and other mood and anxiety disorders (5). Behavioral interventions help many young individuals (6). For others, as adults, when given an adequate prescription of a benzodiazepine in a regimen avoiding interdose rebound, their

- <https://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.2020.20040376>

Am J Psychiatry. 2020 June;177:6.

Buspirone

- **“Not a benzodiazepine”**
- **Non-sedating**
- **“Everything you want in an anxiolytic except...”**
- **Indicated for generalized anxiety; possible antidepressant effects at higher doses.**
- **Potentially useful as AD augmentation:**
- **Dosing: 30-60 mg/d as monotherapy, lower as augmentation**

Beta-Blockers

- **Propranolol: 10-40 mg PO QD**
- **Atenolol: 50-150 mg PO QD**
- **Lowers heart rate, reduces tremors:**
 - **James Lange Theory**
- **Effective for discrete “performance anxiety” taken 1-2 hours before event**
- **Propranolol meta-analysis: panic (n=130), social (n=16), specific phobia (n=37) found insufficient evidence for anxiety disorders¹**
- **Not effective for depression/comorbidities**

¹Steenen, et al. *J Psychopharmacology*. 2016.

Gabaergic “Anticonvulsants” for SAD

- RCT support for:
 - Gabapentin (900-3600 mg/d)
 - Recent concern raised about long-term risk for dementia
 - Pregabalin (200-600 mg)
 - Other anticonvulsants have demonstrated possible efficacy for SAD on the basis of open and anecdotal experience
 - Valproate
 - Tiagabine
- Negative results for Levetiracetam (3,000 mg/day)
- Concern re association of gabapentin with dementia

Pande, et al. *J Clin Psychopharmacol*. 1999;19:341.

Pande, *J Clin Psychopharmacol*. 2004.

Feltner, et al. *Int Clin Psychopharmacol*. 2011 26;213-220.

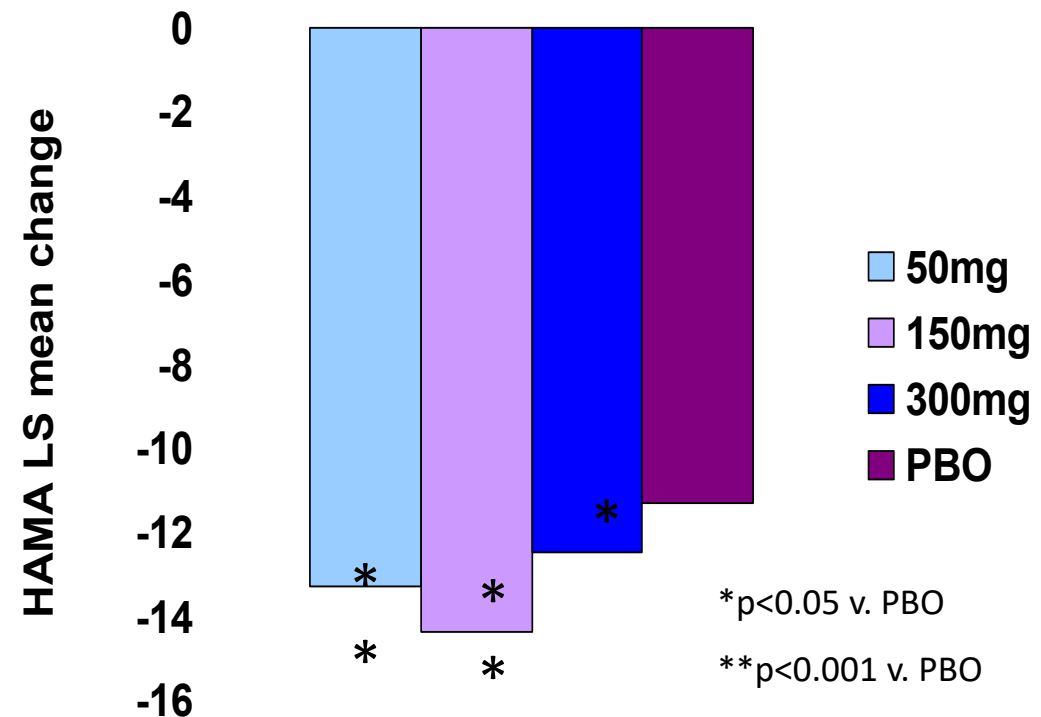
Second Generation Antipsychotics: for Refractory Anxiety?

- Especially for complex comorbidity:
 - e.g., bipolar disorder and anxiety
- Monitor for weight gain and metabolic syndrome
- ? Preferred for those prone to misuse in SUD populations
- Low doses of quetiapine are popular for sleep and anxiety

Pooled analysis of 3 RCTs: Quetiapine XR for GAD

Three, 8-week RCTs of Quetiapine XR (from Bandelow 2010, Khan 2011, Merideth 2012)

- 50 mg (n=438)
- 150 mg (n=654)
- 300 mg (n=425)
- All doses greater reduction HAMA than placebo (n=654).
- Meta-analysis reported only 50 and 150 more effective than placebo



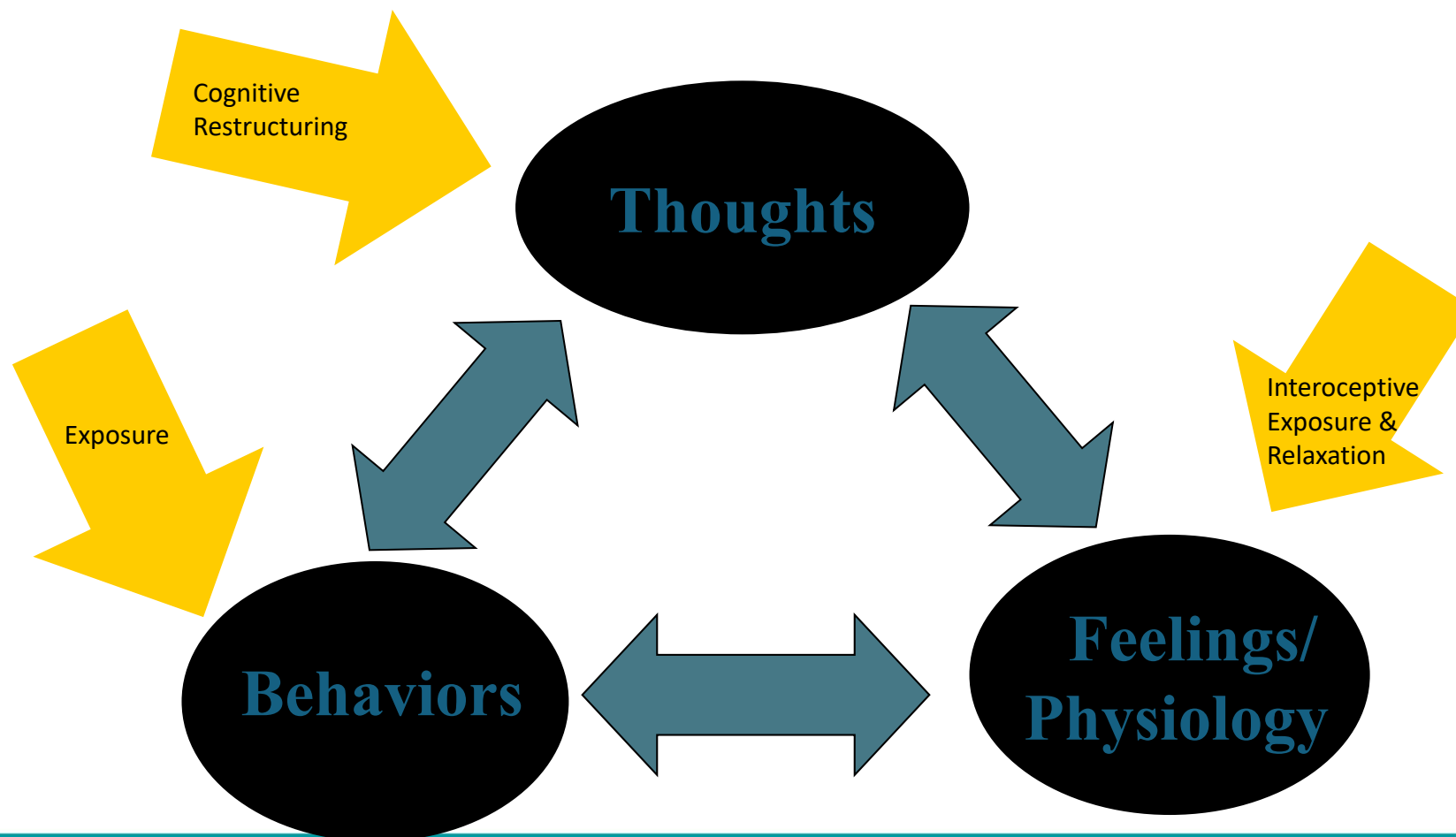
Social Anxiety and Pharmacotherapy Meta-analysis (n = 52 studies)

Pooled effect sizes for pharmacotherapy trials by drug category		
<u>Drug Category (Type)</u>	<u>Pooled Effect Size (g)</u>	<u>No. Studies</u>
SSRI (Paroxetine, Fluvoxamine, Sertraline, Fluoxetine, Citalopram, Escitalopram)	0.44	26
SNRI (Venlafaxine ER)	0.45	5
MAOI (Phenelzine, Moclobemide)	0.36	9
MAO-A (Brofaromine)	0.60	6
Benzodiazepines (Clonazepam, Alprazolam)	0.82	2
Antipsychotics (Olanzapine)	0.72	1
Anticonvulsant (Gabapentin, Pregabalin, Levetiracetam)	0.21	5
Beta-blockers (Atenolol)	0.08	1
Herbal (St. John's Wort)	-0.07	1
NaSSA (Mirtazapine)	0.13	1

Curtiss J, et al. *Exp Opin Pharmacother*. 2017;18:243-251.

CBT Model of Anxiety Disorders

How Enhance Outcomes?



CBT: Pros and Cons

- **Advantages**
 - It works
 - Lower relapse rate than medication when discontinued
 - Most people like it
 - Time-limited
 - Overall low price
 - Few side effects
 - Apps and on-line
- **Disadvantages**
 - More time intensive to administer than medication
 - Limited provider availability
 - More effort for patient than taking medication
 - Variable third-party coverage
 - Not all patients willing/able
 - Initially “too anxious”
 - Severe or comorbid disorders

Psychotherapies for Anxiety Disorders

- CBT: Targets cognitions and/or exposure to targets specific to diagnoses:
 - All: psychoeducation, self monitoring
 - GAD: Worry exposure and metacognitive beliefs, emotion regulation and relaxation
 - Panic: Cognitive restructuring anxiety and somatic (anxiety) sensitivity, and catastrophizing, interoceptive and situational exposure, agoraphobic avoidance
 - SAD: Cognitive restructuring and exposures to reduce social fears and avoidance
- Unified protocol for anxiety disorders (Barlow and colleagues)
- Growing support: internet based CBT protocols (alone or supported) potentially comparable and increases access (e.g., panic meta $g=1.31$)
- Growing integration: motivational interviewing, mindfulness, and acceptance based approaches (e.g., ACT)
- Psychodynamic therapy

Novel Treatments for Anxiety Disorders: Emerging Therapeutic Landscape

Mechanism	Representative Agents	Lead Indications	Development Stage
Psychedelic therapies	DT120 ODT (Definium)	GAD, MDD	Phase III
	MM120 (MindMed)	GAD	Phase III
	CYB003 (Cybin)	MDD, anxiety symptoms	Phase III (MDD)
	BPL-003 (Beckley/ATAI)	TRD, anxiety disorders planned	Phase II
	GH001 (GH Research)	TRD, anxiety potential	Phase II
Pherines (chemosensory neuroactive compounds)	PH94B (fasedienol, Vistagen)	Acute SAD	Phase III
Psychoplastogens (non-hallucinogenic)	Delix DLX series	Anxiety, depression	Preclinical/IND-enabling
	Transcend programs	PTSD, anxiety	Early clinical
Glutamatergic modulation	Osavampator (NBI-1065845)	MDD, cognitive symptoms	Phase II
	AMPA PAMs	Anxiety/MDD	Early clinical
Orexin modulation	Seltorexant	Depression with insomnia; anxiety potential	Phase III (MDD)
	Daridorexant	Anxiety-related insomnia	Approved insomnia
GABA-A neuroactive steroids	Multiple compounds	GAD	Early clinical
Novel GPCR targets	TAAR1, V1a antagonists, M1/M4 modulators	Anxiety spectrum	Phase I-II

Integrating CBT into Pharmacotherapy

Always Provide and Encourage

- **Information on anxiety**
 - Role of maladaptive thoughts in escalating the anxiety cascade
- **Exposure**
 - Encouraging step-by-step exposure to feared and avoided situations and sensations
- **Use of CBT techniques instead of PRN medication**

Complementary and Alternative

- **Lavendar:** Silexan Capsules 80 mg: Five studies with N= 524 receiving silexan 80 mg and N=121 taking silexan 160 mg. Silexan 160 mg resulted in greater decline of HAMA compared to silexan 80 mg, placebo [-2.20 (-4.64, 0.24)] and paroxetine [-1.24 (-5.34, 2.85)]. Silexan 80 mg was equivalent in response to paroxetine. Scientific Reports | (2019) 9:18042 | <https://doi.org/10.1038/s41598-019-54529-9>
- **Valerian Root:** Sedative
- **Sceletium Tortuosum:** (mesembrine or Zembrin) (e.g., CalmZ ?dose)
- **Chamomile:** (e.g., 500 mg TID)
- **CBD**
- **St. Johns Wort**

Anxiety Disorders Management

- Exercise, meditation/mindfulness, diet, walks in nature
- Evaluate medical/psychiatric/substance comorbidity
- RCT data suggest comparable efficacy for SSRIs, SNRIs, TCAs (except SAD, PTSD), BZDs (except PTSD), and CBT
 - SSRI/SNRIs and CBT are considered first line due to long-term safety and broad efficacy
 - Longer acting high potency benzos optimal (not for PTSD)
- Anticipate side-effect sensitivity with ADs
- Mixed support combining CBT and meds first line (BZDs may interfere with CBT, esp. as prn)
 - plan slow taper with BZDs to determine lowest necessary dose, e.g., zero if possible
- Encourage exposure to avoided/phobic situations always