MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Psychopharmacology for Anxiety Disorders

Jerrold F. Rosenbaum, M.D.
Psychiatrist-in-Chief emeritus MGH
Director, Center for Anxiety and Traumatic Stress Disorders
Director, Center for Neuroscience of Psychedelics
Stanley Cobb Professor of Psychiatry, HMS

Disclosure Regarding Financial Interests and Affiliations: September 2020

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

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

Terran Biosciences, Advisor

The Real Odin, Advisor

Anxiety

- Pleiomorphic
- Universal
- Ubiquitous
- Pathological when chronic, severe, associated with maladaptive behavior
- Shortens and impairs lives

Anxiety

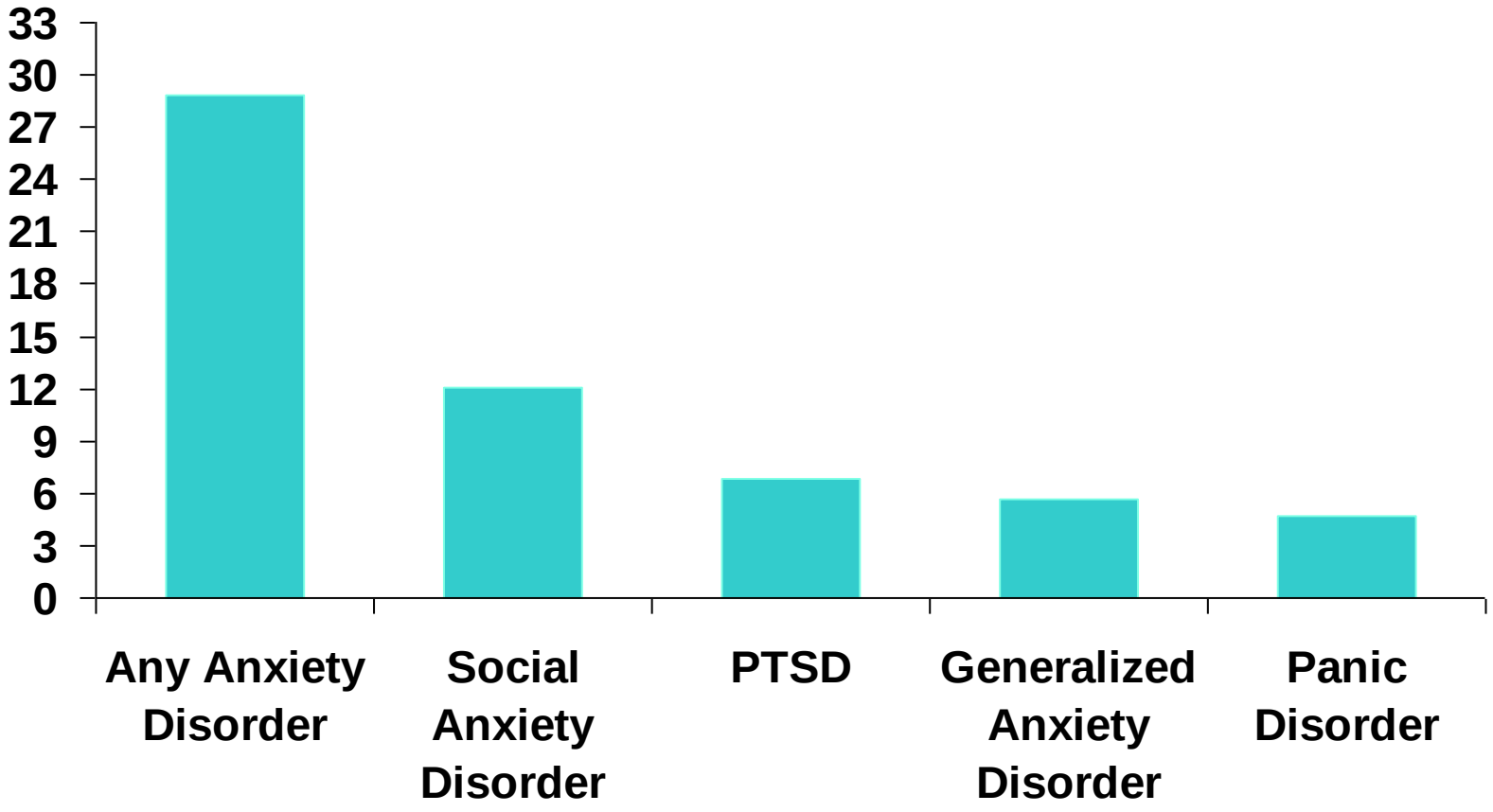
- Symptom
- Disorder
  - e.g. DSM 5
- Comorbidities
  - Psychiatric
  - Medical
  - Iatrogenic

The Nature of Anxiety

- Cognitive, physiological, behavioral and emotional symptoms/distress
- Each represent a point of therapeutic intervention
- Psychological and pharmacological approaches
  - Advantages and synergies

Anxiety Disorders Are Common:

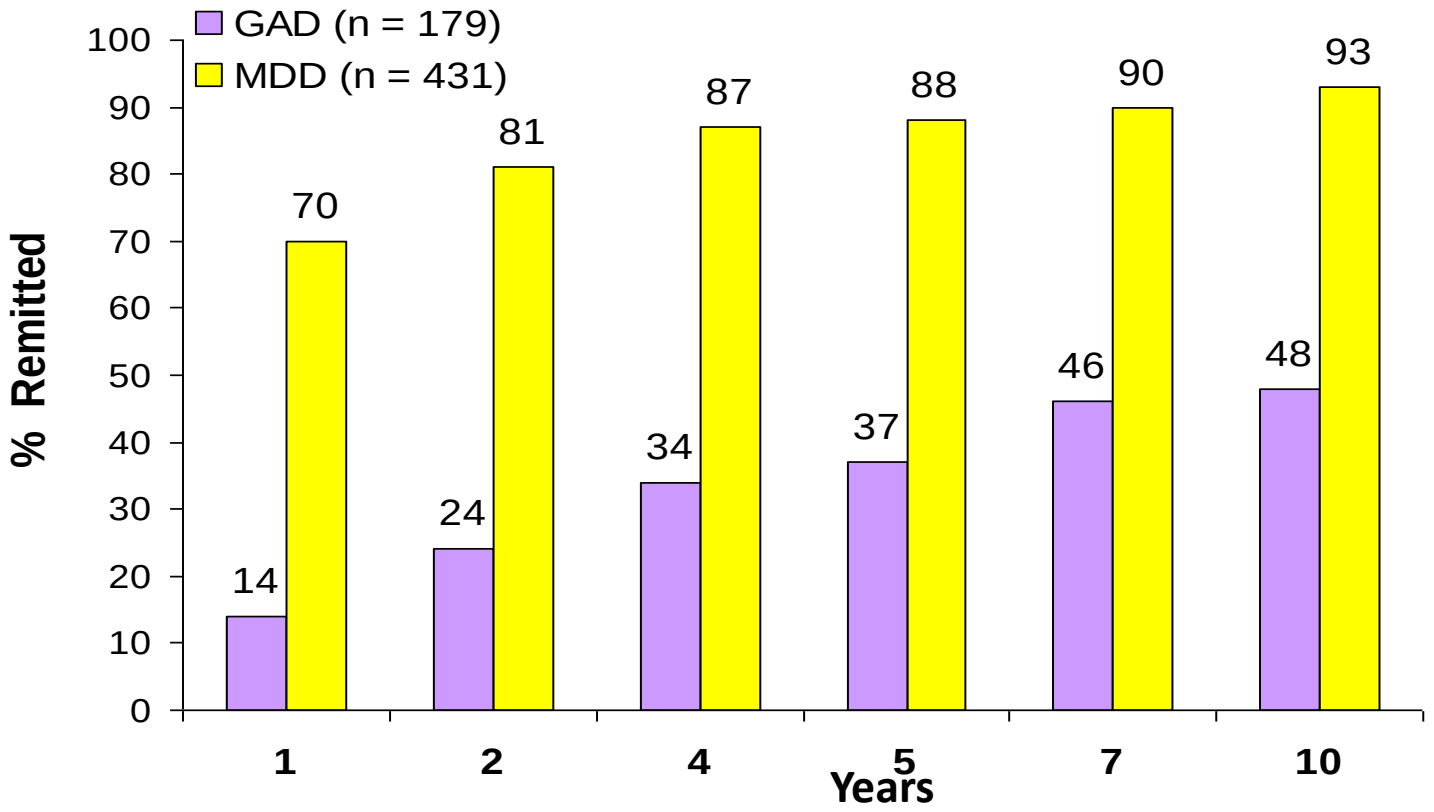
National Comorbidity Survey Replication



Kessler et al. *Arch Gen Psychiatry*. 2005;62:593-602

Anxiety Disorders are 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

RDoC Domains for Anxiety Disorders: Negative Valence

Potential Threat (Anxiety)

- distant/ambiguous or uncertain threat in future
- worry, rumination, anticipatory or conditioned fear
- social and performance anxiety, nervousness, anxiety sensitivity

Acute Threat (Fear)

- Protection from perceived near term danger
- Interoceptive or external threat cued acute threat responding

Sustained Threat

- prolonged adaptation to exposure to real or imagined internal or external threat
- Avoidance, emotion dysregulation, vigilance
- Chronic stress responses

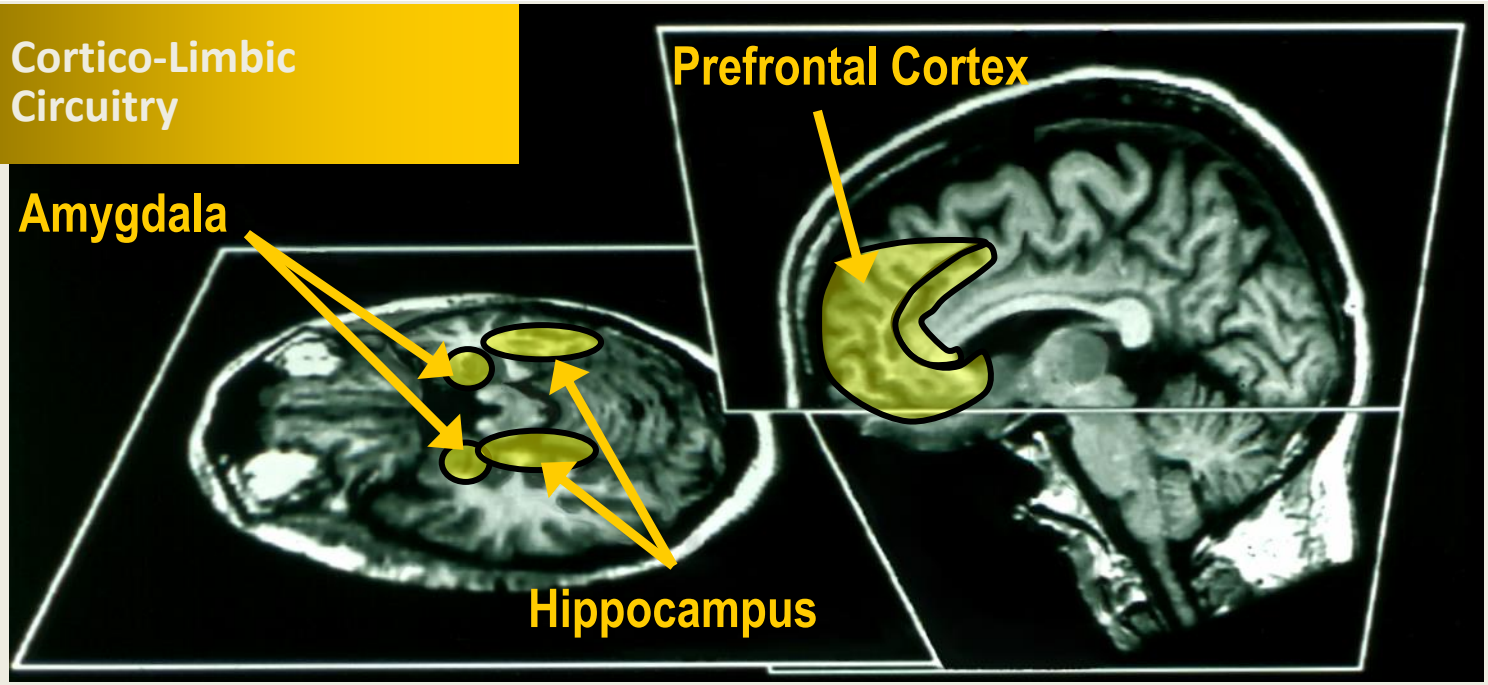
NIMH RDoC Website

Evolutionary Links to Anxiety

- Dysregulated Fear Circuitry generally thought as underlying biology or dysregulated
- Autoimmune analogy
  - BZD analogous to prednisone?
  - Sentinel vs. Warrior

Panic: Classic Neurocircuitry Model “false alarms”

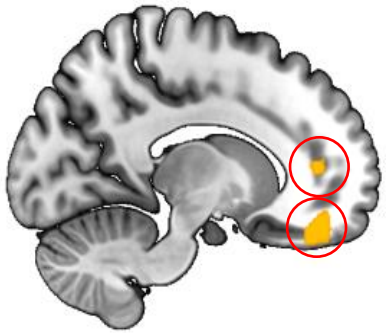
- **Amygdala: Drives autonomic and emotional responses**
- **Hippocampus: Evaluates threat contexts (safe/unsafe)**
- **Prefrontal Cortex (PFC): Regulates limbic responses of amygdala and hippocampus (“top down”)**



Slide Created by Karleyton Evans, MD.
Adapted from Rauch, et al. *CNS Spectrums*. 1998;3(suppl 2):30-34.

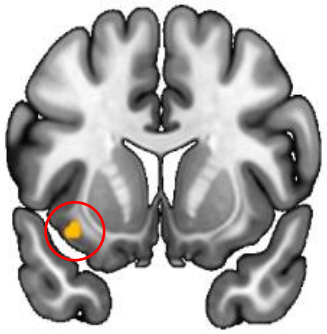
Deficits in vmPFC during Extinction Recall Across Anxiety Disorders Increase with Number of Disorders

rACC & vmPFC



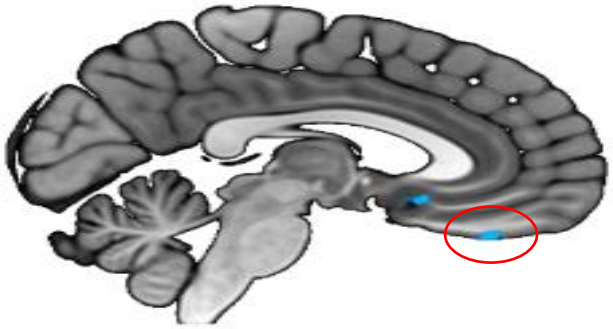
HC > Anx

Insula



HC > Anx

vmPFC



1 > 2-4

Marin et al , Milad JAMA Psychiatry 2017

Key Biology of Anxiety Disorders (I)

- **Stress Response Systems, Neuroendocrine & Immunologic Responding**: HPA Axis, glucocorticoids, CRF, catecholamines; inflammatory responses (eg IL6, CRP); oxytocin/estrogen/testosterone

- **Neurotransmitters & receptors**: e.g., GABA, serotonin, noradrenergic, glutamate (e.g., NMDA R); ?orexin, PACAP & NPY neuropeptides*

- **Key brain regions and neurocircuitry**: eg amygdala, hippocampus, mPFC, insula, dorsal ACC, hypothalamus, locus coeruleus (pons)

- **Brain networks and connectivity**: e.g., executive control (e.g., top down emotion regulation deficits, conscious worry/catastrophizing), salience (drives attn. and hyper-reactivity to interoceptive and external threat cues), and default mode (memory, extinction, emotion reg.)

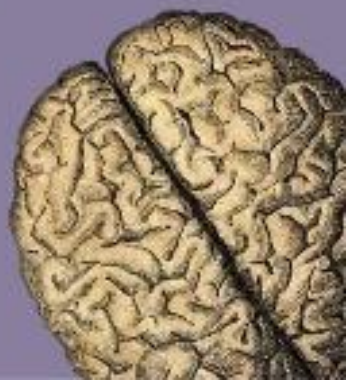
*PACAP= Pituitary adenylate cyclase activating polypeptide (PACAP, gene *Adcyap1*) ; NPY= Neuropeptide Y

DSM-5 reorganized Anxiety Cluster

DSM-5 Disorders

Anxiety Disorders

- Separation Anxiety Disorder
- Selective Mutism
- Specific Phobia
- Social Anxiety Disorder (Social Phobia)
- Panic Disorder
- Panic Attack (Specifier)
- Agoraphobia
- Generalized Anxiety Disorder
- Substance/Medication-Induced Anxiety Disorder
- Anxiety Disorder Due to Another Medical Condition
- Other Specified Anxiety Disorder
  Unspecified Anxiety Disorder



www.slideshare.com, SMR Grey

Key Biology of Anxiety Disorders (II)

- **Genetic contributions**: increased familial transmission (including twin studies), some candidate genes (e.g., *5HTTLPR* & val158met polymorphisms, *RGS2* variant, and *FKBP5*), GWAS early hits, emerging epigenetics (e.g., oxytocin genes and SAD)

  → less clear genetic predictors of treatment response

- **Physiology/autonomic dysregulation**: psychophysiologic hyper-reactivity (e.g., skin conductance, heart rate), reduced heart rate variability, and CO2 respiratory hypersensitivity (panic)

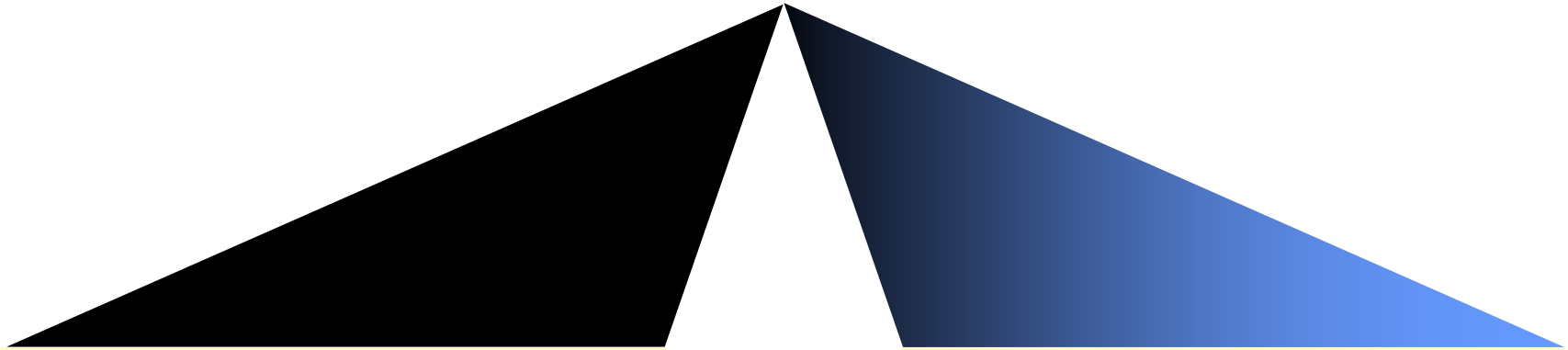
- **Temperament and biological risk factors interacting with environmental exposures**

- **Fear conditioning and extinction learning**

- **Emotion dysregulation and avoidance**

- **Microbiome?**

Anxiety Disorder Treatment Options



PSYCHOSOCIAL
- Exposure
- Cognitive Behavioral
- Meditation/Mindfulness
- Other psychotherapies

PHARMACOLOGICAL
- Antidepressants
- Benzodiazepines
- "Antipsychotics"
- Adrenergic Blockers
- Other

Psychopharmacology of Anxiety

- The list of what never is used or never works for anxiety may be shorter than a list of potential therapeutic agents with some support of efficacy
- Holy Grail remains 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 received over 90 million Rx's for BZDs

Anxiolytic Need

- Normalize those born anxious
- Relieve anxious distress to allow a normal life
- Premedicate for phobic situations
- Emergency prn use
- Treatment comorbid anxiety in multiple psychiatric, neurologic, and meical conditons
- Transient situational crises

Medications for Anxiety Disorders

The largest unsatisfied Market!

Antidepressants

- Serotonin Selective Reuptake Inhibitors (SSRIs)
- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
- Other Newer Antidepressants
- Tricyclic Antidepressants (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)

Benzodiazepines

Other Agents

- Azapirones
- Beta blockers
- Anticonvulsants
- Atypical Antipsychotic
- Other ”GABA” ish

SSRI and SNRI Antidepressants First Line for Anxiety Disorders

- Safety and lack of misuse concerns
- Efficacy for comorbid depression
- General efficacy across all persisting anxiety states
- Start low, go slow, but go”
  - start citalopram 10 mg, sertraline 25 mg, venlafaxine 37.5 mg
  - Minimize early exacerbation of anxiety and overlapping side effects, but MAY NEED HIGHER DOSES
  - Remember cranzac and applezac?
- Challenges: discontinuation syndromes, initial activation, insomnia, sexual dysfn, GI effects, weight gain
- Augmentation/Mitigation : benzodiazepines, beta-blocker, other

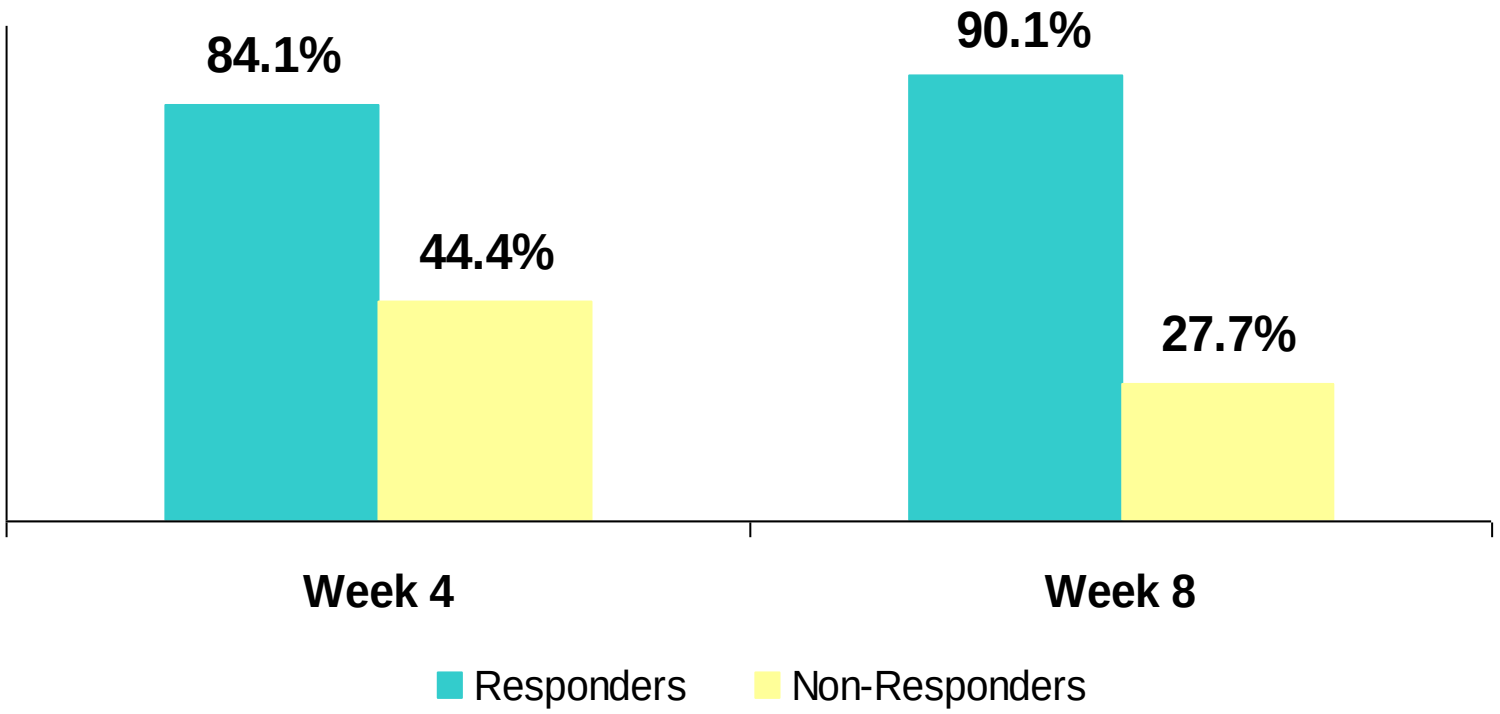
SSRIs and SNRIs for SAD

- Multiple RCTs support safety and efficacy of SSRIs (e.g., sertraline, paroxetine, escitalopram) and SNRI class (e.g., venlafaxine XR)
- Considered first-line pharmacotherapy
- SSRI effect sizes range: -0.03 to 1.2*
- Data suggest continued improvement with longer periods treatment (e.g., LSAS at 6 months)

  → Still requires "exposure": May take time to return to avoided situations

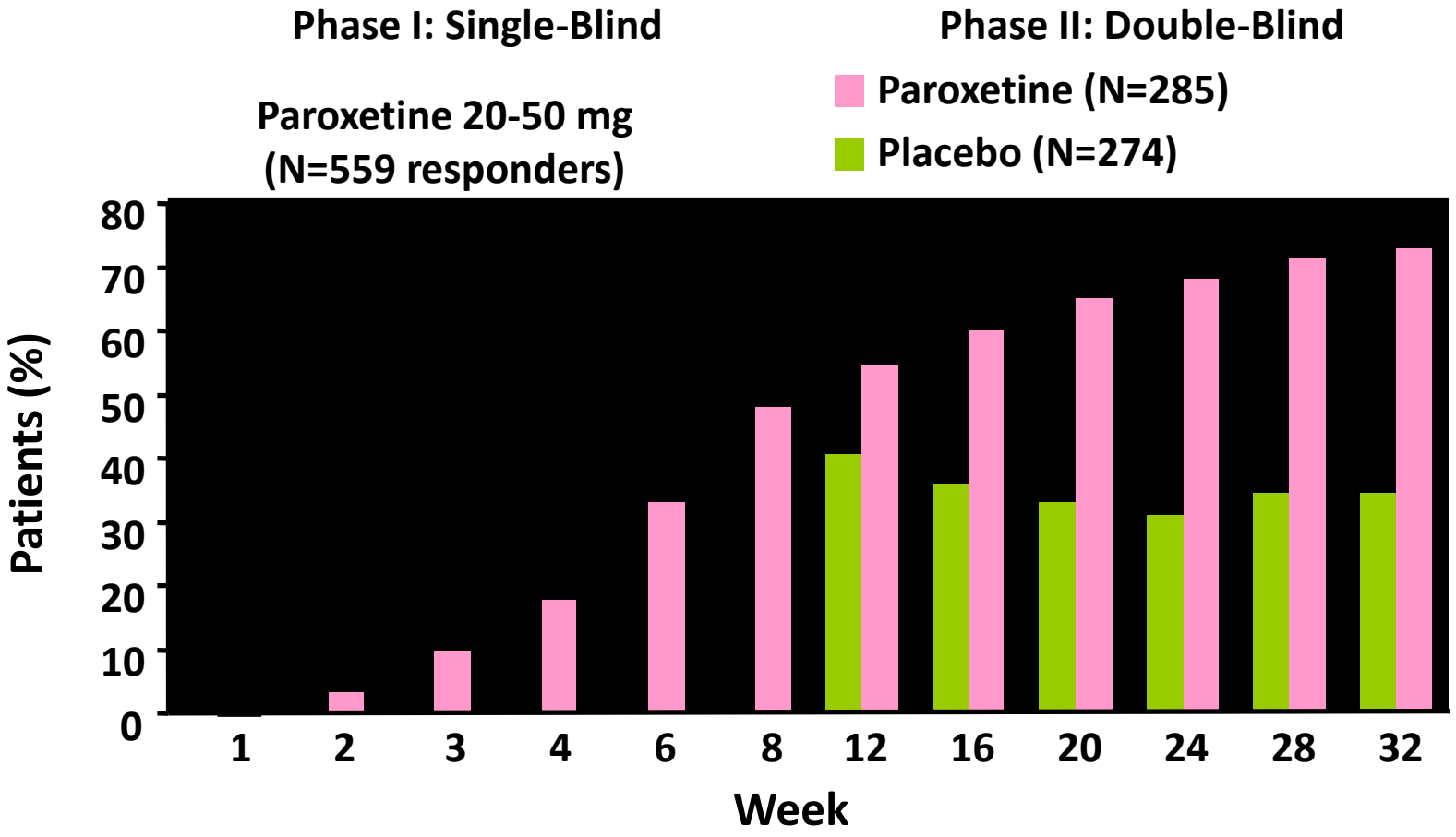
*Hedges. J Psychopharmcol. 2006; e.g., Stein MB et al. Psychopharmacology. 2005; Leibowitz. J Clin Psych. 2003; Kasper. Br J Psych. 2005.

Response to SSRI in SAD at 12 Weeks Given Response at 4 and 8 Weeks



Stein DJ et al. J Clin Psychiatry. 2002;63:152-5.

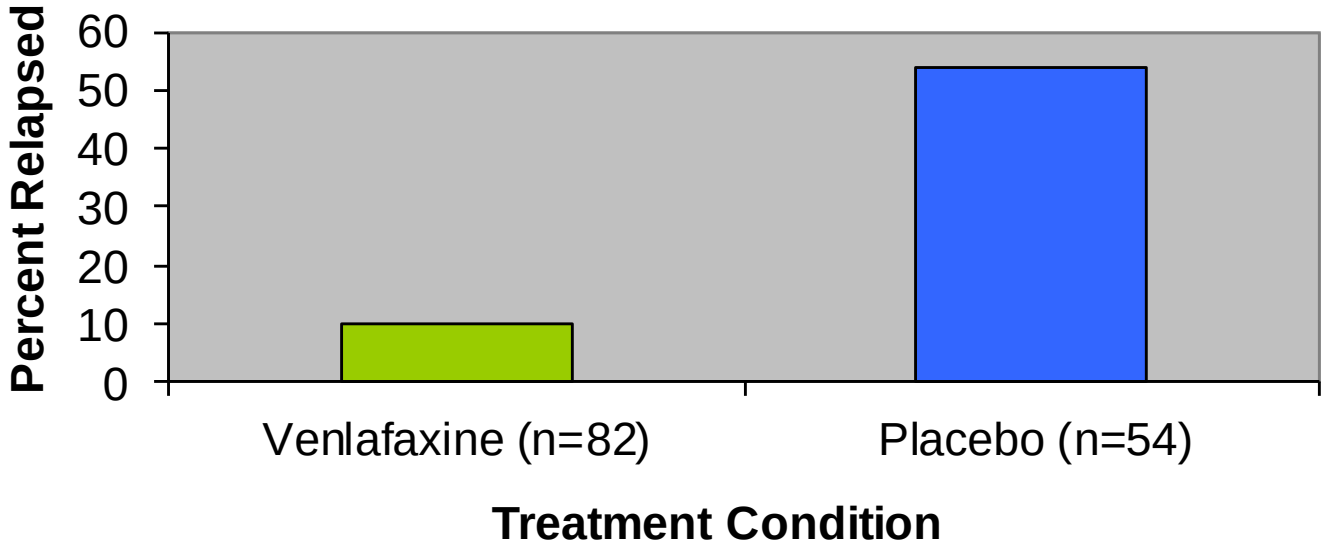
GAD:
Remission Rates Increase with Long-Term Treatment



*p<0.01 vs. placebo; LOCF dataset; Remission defined as HAM-A ≤7;
Stocchi F et al. J Clin Psychiatry, 2003; 64:250-258

Antidepressants & GAD: Support for 12 months+ to reduce relapse rate

Percentage Relapsed after 12 months: 6 months Open-Label Venlafaxine, followed by 6 months Double-Blind Venlafaxine or Placebo



NOTE: **Clinical recommendations at least one year after response prior to d/c effective meds; reflect on this when thinking about BZD guidelines**

*p < .001 vs. placebo

Rickels K et al. Arch Gen Psychiatry. 2010;67:1274-81

Duloxetine and Adult Generalized Anxiety: Meta-analysis 7 RCTs (n=2674)

- SNRI: dosing 30 to 120/d *(no evidence 120>60 GAD)* vs placebo over 9 to 15 wks

- Duloxetine efficacy:
  - Mean difference HAMA reduction **3.34 points** (4 studies)
  - RR=1.48 Response (50% HAMA reduction, 6 studies)
  - RR=1.60 Remission (HAMA<=7 or CGIS 1 or 2, 6 studies)

FDA indication GAD
Zhang et al . 2016

Vortioxetine and GAD: Meta-analysis 4 short-term RCTs (n=1677)

- 5HT reuptake inhib., 5HT3R antag. & 5HT1R agonism
- Vortioxetine 5mg or 2.5 - 10mg/day flexible dose (n=1068) vs placebo (n=609) for 8 weeks

→Greater HAMA reduction with vortioxetine but variable response and remission

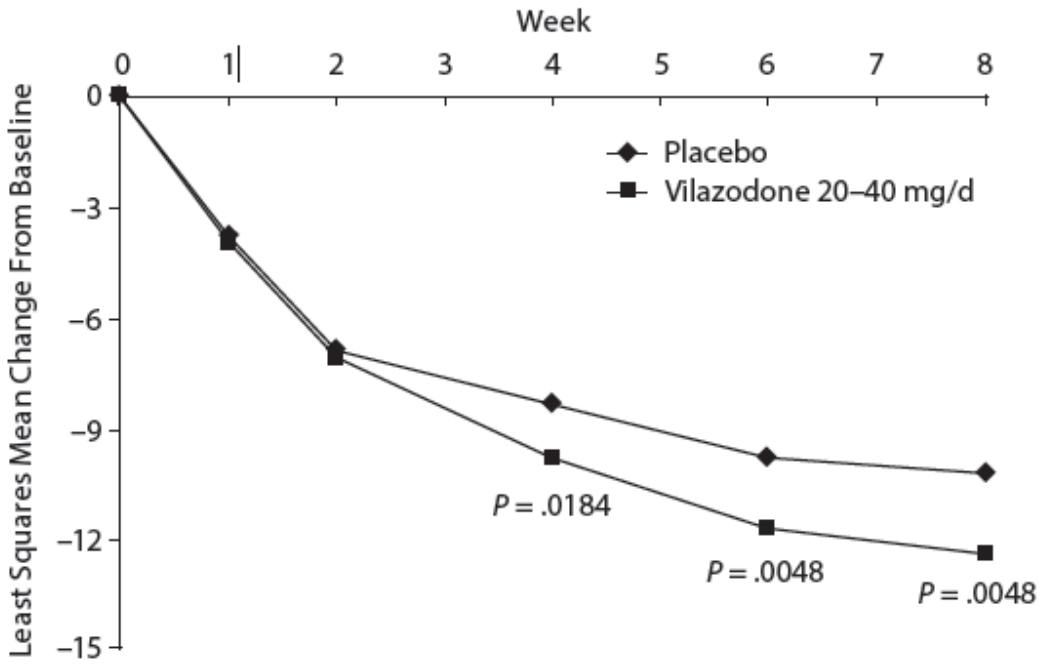
→Small effect sizes (SMD= -0.118) but greater with more severe GAD (HAMA>25: SMD 1.221)

This information concerns a use that has not been approved by the US FDA.

Pae et al . J Psychiatric Res 2015

Short Term Efficacy of Vilazodone for GAD (n= 400 RCT)

Figure 2. HARS Least Squares Mean Change by Week (modified ITT population, MMRM)[a]



[a]*P* values are for vilazodone 20–40 mg/d versus placebo.
Abbreviations: HARS = Hamilton Anxiety Rating Scale, ITT = intent to treat, MMRM = mixed-effects model for repeated measures.

AEs > placebo: nausea, diarrhea, dizziness, fatigue, sexual dysfunction

Durgam S et al. J Clin Psychiatry. 2016;77:1687-94 (comparable prior RCT: Gommoll et al 2015).

Tricyclic Antidepressants

- Efficacious but less rarely used due to side effect profile (e.g., cardiovascular, anticholinergic) and lethality in overdose
- Imipramine: most RCT data in panic
- 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)

Bakker A et al. *Acta Psychiatrica Scand*. 2002.

This information concerns a use that has not been approved by the US FDA.

Potential Benefits of Benzodiazepines

- Effective
- Rapid onset of therapeutic effect
- Well-tolerated
- Rapid dose adjustment feasible
- Can be used “PRN” for situational anxiety
- Reduces early antidepressant-induced unpleasant activation
- Meta-analyses (e.g. GAD*) suggest:

  →greater effect size than serotonergic antidepressants
  → greater effect higher HAMA baseline scores & shorter studies

*Gomez et al Exp Op Pharmacother 2018; Gale et al J Psychopharm 2019

Potential Drawbacks of Benzodiazepines

- Sedation, cognitive, and psychomotor impairment
- Interaction with alcohol
- Physiologic dependence with ongoing therapy
- Discontinuation-related difficulties: TAPER VERY SLOWLY
- Potential for abuse in predisposed individuals
- Less effective for comorbid depression
- *May interfere with CBT exposure component
- Lethality when co-prescribed or ingested in combination with opiates, alcohol

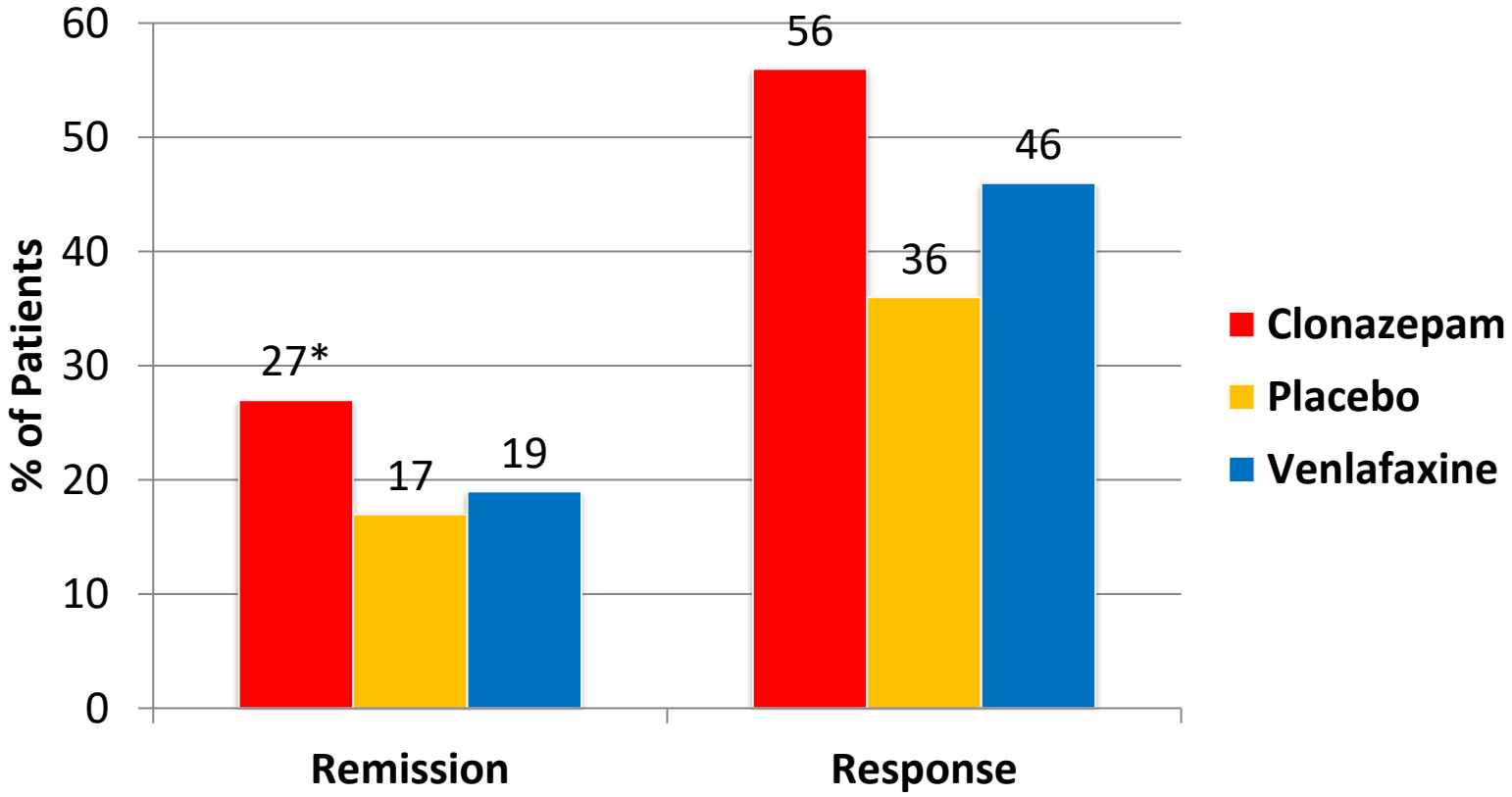
Benzodiazepine Use in Panic Disorder: Is Less More?

- Disadvantages PRN use:
  - Decreases opportunity to learn self-efficacy with exposure

    → Potentially reduces efficacy of CBT
  - Focuses attention on need for rescue
  - Lowers threshold for panic if leave home without it
  - Potential for excessive use and abuse
  - PRN dosing alone does not treat persisting systems or prevent panic attacks
  - Inadequate dosing = risk without efficacy

*Westra HA & Stewart SH. Curr Pharm Design. 2002.

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:**

no evidence that long-term use of benzodiazepines frequently results in notable dose escalation

Soumerai SB et al. Psychiatr Serv. 2003;54:1006-11.

Evidence-Based Guidelines for Benzodiazepine Discontinuation in Panic: Clonazepam

- 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 benzos 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
Am J Psychiatry 177:6, June 2020

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

Optimal Dosing: APA Panic Guidelines 2009

	Starting and Incremental Dose (mg/day)	Therapeutic Dose (mg/day)
SSRIs		
Citalopram	10	20-40
Escitalopram	5-10	10-20
Fluoxetine	5-10	20-40
Fluvoxamine	25-50	100-200
Paroxetine	10	20-40
Paroxetine CR	12.5	25-50
Sertraline	25	100-200
SNRIs		
Duloxetine	20-30	60-120
Venlafaxine ER	37.5	150-225
Benzodiazepines		
Alprazolam	0.75-1.0	2-4
Clonazepam	0.5-1.0	1-2
Lorazepam	1.5-2.0	4-8

MASS

Stein MB et al. Practice Guideline for the Treatment of Patients with Panic Disorder. American Psychiatric Association. 2009.

BZD Prescribing Guideline

Table. Gourlay's Original 10 Universal Precautions[5]
1. Make a Diagnosis with Appropriate Differential
2. Psychological Assessment Including Risk of Addictive Disorders
3. Informed Consent
4. Treatment Agreement
5. Pre- and Post-Intervention Assessment of Pain Level and Function
6. Appropriate Trial of Opioid Therapy +/– Adjunctive Medication
7. Reassessment of Pain Score and Level of Function
8. Regularly Assess the "Four A's" of Pain Medicine
9. Periodically Review Pain Diagnosis and Comorbid Conditions, Including Addictive Disorders
10. Documentation

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:
  - Social phobia
  - Panic
  - Depression
  - Sexual dysfunction
- Dosing: 30-60 mg/d

This information concerns a use that has not been approved by the US FDA.

Beta-Blockers

- Propranolol: 10-40 mg PO QD
- Atenolol: 50-150 mg PO QD
- Suppresses increased heart rate, tremors:
  - James Lange Theory
- Effective for discrete "performance anxiety" taken 1-2 h before event
- Propranolol meta-anal. panic (n=130), social (n=16), spec phobia (n=37) found insufficient evidence for anxiety disorders[1]
- Not effective for depression/comorbidities

This information concerns a use that has not been approved by the US FDA

[1]Steenen et al . J psychopharmacology, 2016

”Anticonvulsants” for SAD

- None “first line”
- Some RCT support for:

  - Gabapentin (900-3600 mg/d)

  - Pregabalin (at 600 mg)

  - Other anticonvulsants have demonstrated possible efficacy for SAD on the basis of open and anecdotal experience

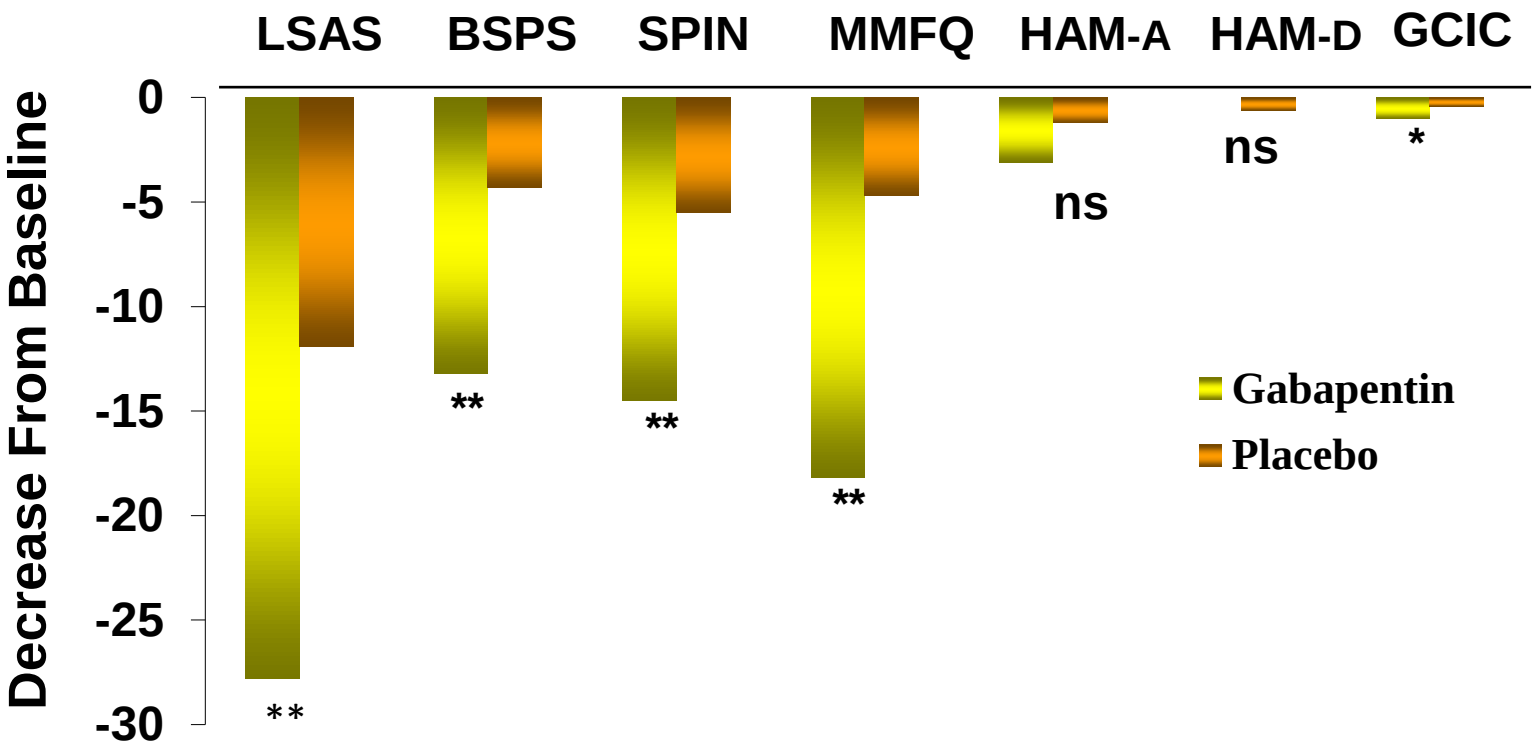
    - Valproate
    - Tiagabine

  - Negative results for Levetiracetam (3,000 mg/day)

This information concerns a use that has not been approved by the US FDA.

Pande et al. J Clin Psychopharmacol. 1999:19:341; Pande. J Clin Psychopharmacol. 2004. Feltner et al. Int Clin Psychopharmacol. 2011 26;213-220

Gabapentin in Social Anxiety Disorder: 14 weeks 900-3600mg/d (N=69)

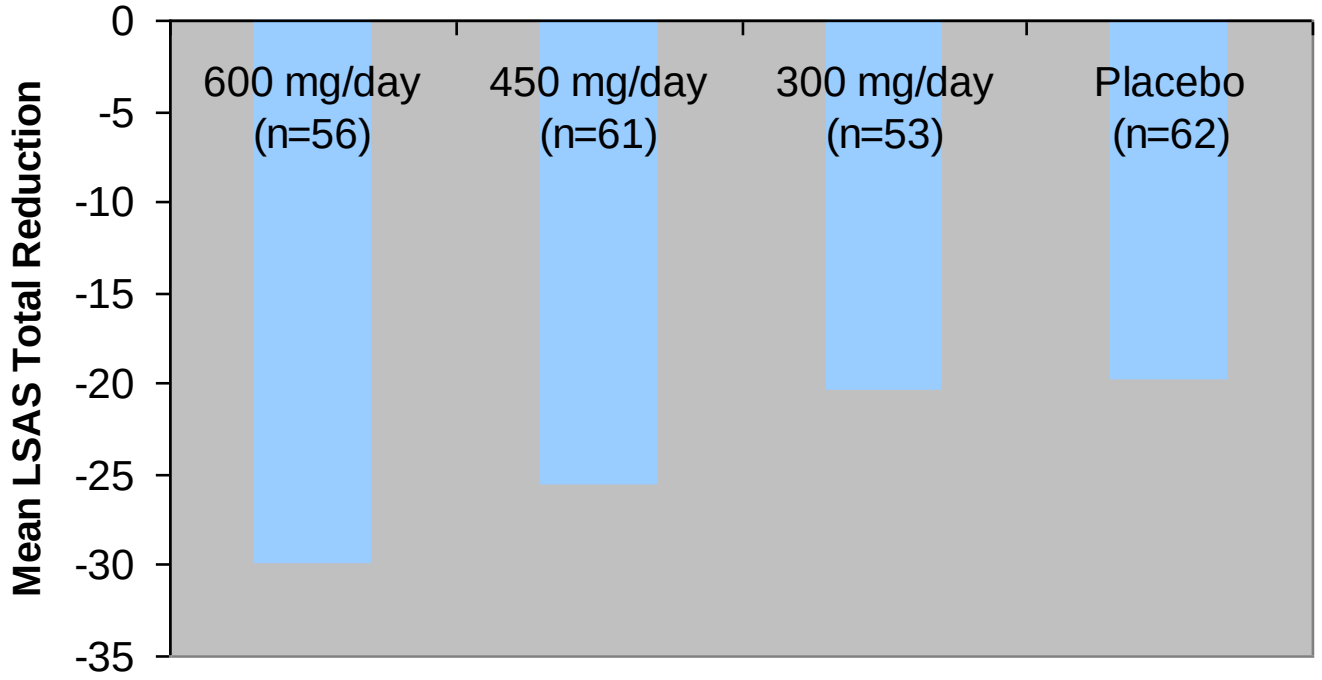


(Pande 1999)

** P<0.01 vs placebo
* P<0.05 vs placebo
ns = not significant

This information concerns a use that has not been approved by the US FDA

Pregabalin 600mg reduces LSAS compared to placebo Social Anxiety



*p<.01 vs. placebo

PGB administered TID

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

Evidence for Pregabalin (300-600mg) in GAD: *Note not FDA approved GAD*

1. Four week RCT 300mg (n=89; -12.2), 450mg (n=87; -11.0), and 600mg (n=85; -11.8) **all superior (p<0.05) to placebo** (n=85; -8.4) **but not Alprazolam** (n=88; -10.9)

2. Eight week RCT: 300-600mg (n=121) : PGB greater HAMA reduction by **day 4** vs. placebo (-5.3 vs. -3.4, p<0.01) and Venlafaxine XR (-2.9; p<.01):

3. Refractory GAD 150-600mg PGB (n=180) or placebo (n=176) **after partial response (<50% responder rate) 8-week flexible dose SSRI or SNRI**

→ **PGB greater HAMA reduction than placebo** (-7.6 vs. -6.4; p<0.05)

4. N=106 12 week RCT **POST BENZO TAPER**

- After 8-52 weeks BZD tx, stabilized on alprazolam for 2-4 weeks
- Once stable, 25% benzodiazepine taper per week while randomized to 300-600mg PGB (n=56) or placebo (n=50).
- → **PGB greater reduction in HAMA v. placebo (-2.5 vs. +1.3; p <0.001) at LOCF.**
- → **However, high drop-out in both PGB (47%) and placebo (63%) groups.**

1. Rickels K et al. Arch Gen Psychiatry. 2005;62:1022-30.
2. Kasper S et al. J Psychopharmacol. 2009; 24:87-96.
3. Rickels K et al. Int Clin Psychopharmacol. 2012;27:142-50.
4. Hadley SJ et al. J Psychopharmacol. 2012;26:461-70.

This information includes uses that have not been approved by the US FDA.

Atypical Antipsychotics: for Refractory Anxiety?

- Especially for complex comorbidity:
  → e.g. bipolar disorder and anxiety
- Better side effect and safety profiles than typicals
- Weight gain and metabolic syndrome
- When keen to avoid BZDs and others prone to misuse in SUD or at risk populations
- Low doses of quetiapine are popular for sleep and anxiety

Krystal et al JAMA. 2011 Aug 3;306(5):493-502.

This information concerns a use that has not been approved by the US FDA.

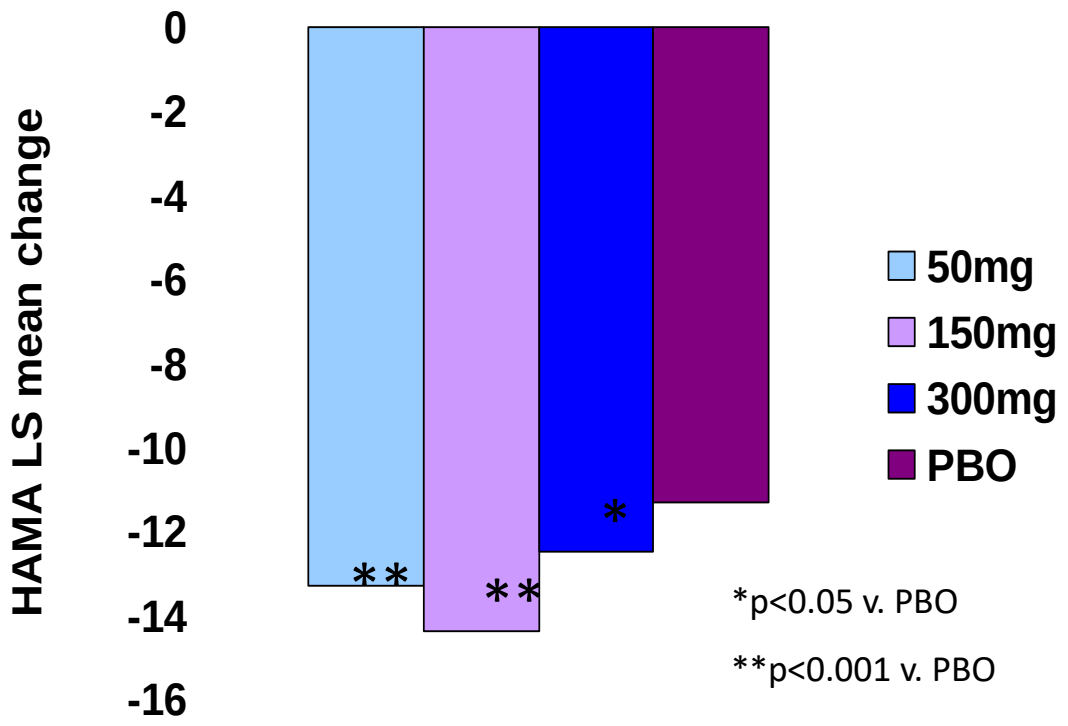
Pooled analysis of 3 RCTs Week 8 Quetiapine XR for GAD

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

- 50mg (n=438)
- 150mg (n=654)
- 300mg (n=425)

- All doses greater reduction HAMA than placebo (n=654).

➢ 2nd Meta-anal (Maneeton et al 2016) reported only 50 and 150 more effective than placebo, but **comparable response rate (62%) to SSRIs (60%) & NNT vs placebo response = 9**



Stein DJ et al. Human Psychopharm. 2011;26:614-28.

This information concerns a use that has not been approved by the US FDA.

Second Generation Antipsychotics (SGAs) for Uncomplicated and Refractory GAD: Meta-analysis

- 4 RCTs (n=1383) of SGA monotherapy vs. placebo
  - 150mg/day quetiapine higher response and remission, including greater decrease in HAMA score, vs. placebo
    - however, greater risk of all-cause discontinuation and weight gain

- 5 RCTs (n=912) of SGA augmentation vs. monotherapy vs. placebo for refractory GAD
  - SGA augmentation no different than placebo in response or remission rates
    - greater risk of all-cause discontinuation

This information concerns a use that has not been approved by the US FDA.

Lalonde CD, Lieshout RJ. *J Clin Psychopharm.* 2011; 31(3): 326-333

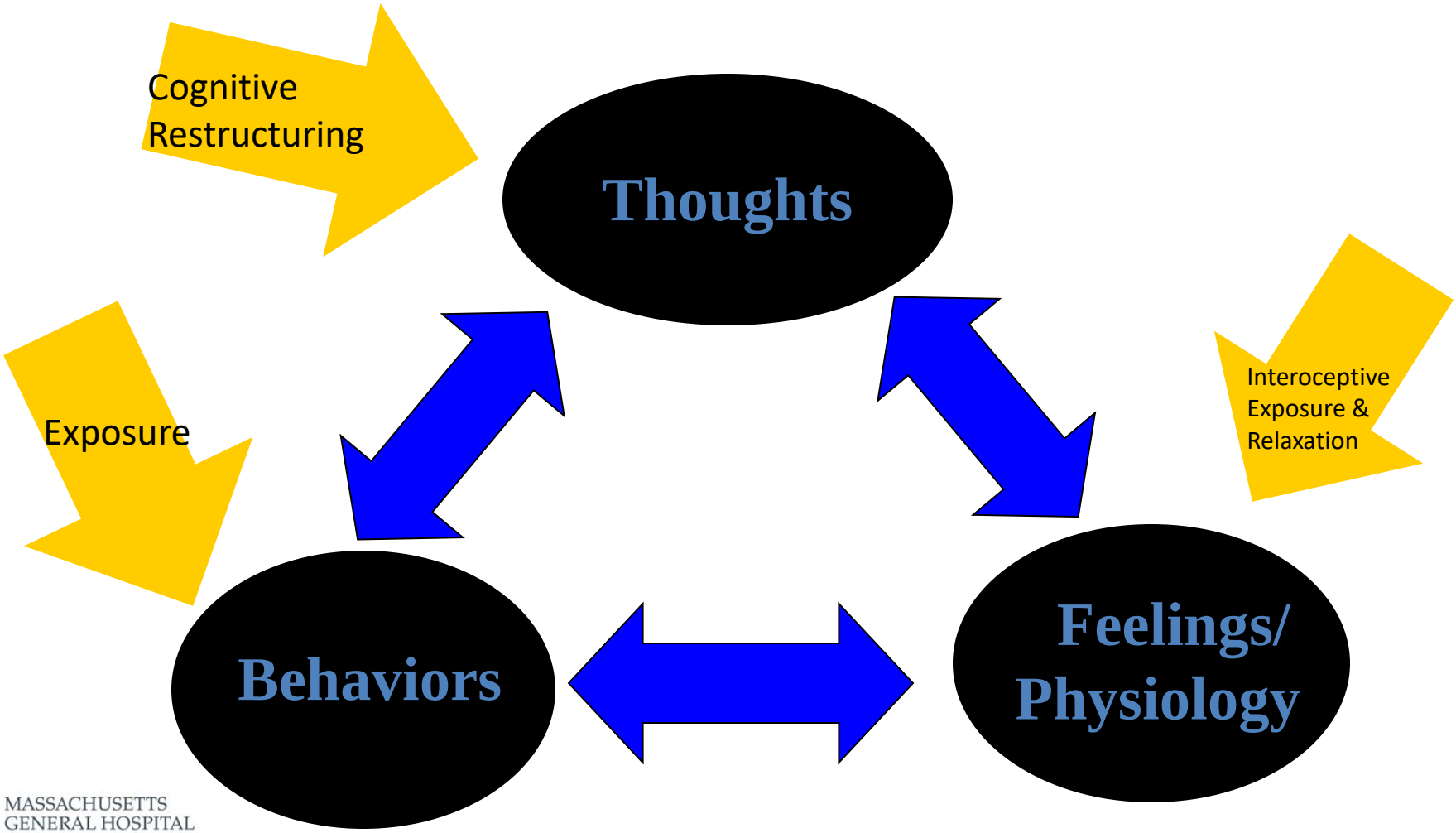
Social Anxiety and Pharmacotherapy Meta-analysis (n = 52 studies)

Pooled effect sizes for pharmacotherapy trials by drug category

Drug Category (Type)	Pooled Effect Size (*g*)	No. Studies
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
NK1 (Gr205171)	0.46	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

Broad Range First Line CBT and Psychotherapies Anxiety Disorders

- **CBT**: core cognitions and/or exposure with targets specific to diagnoses:
  - **All**: psychoeducation, self monitoring
  - **GAD**: Worry exposure and metacognitive beliefs, emotion regulation and relaxation
  - **Panic**: Cognitive restructuring anxiety and somatic 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 packages

e.g. Barlow & Farchione, 2017; Mennin et al., 2018; Hayes et al. 2011; Andrews et al. 2018

3 Phase RCT for SSRI-Refractory Panic

- 6 weeks open-label sertraline flexible dosed to 100 mg/day (n=46)
  - 20.5% achieved remission
- 6 weeks
  - 1) increased SSRI dose or
  - 2) continued SSRI + placebo

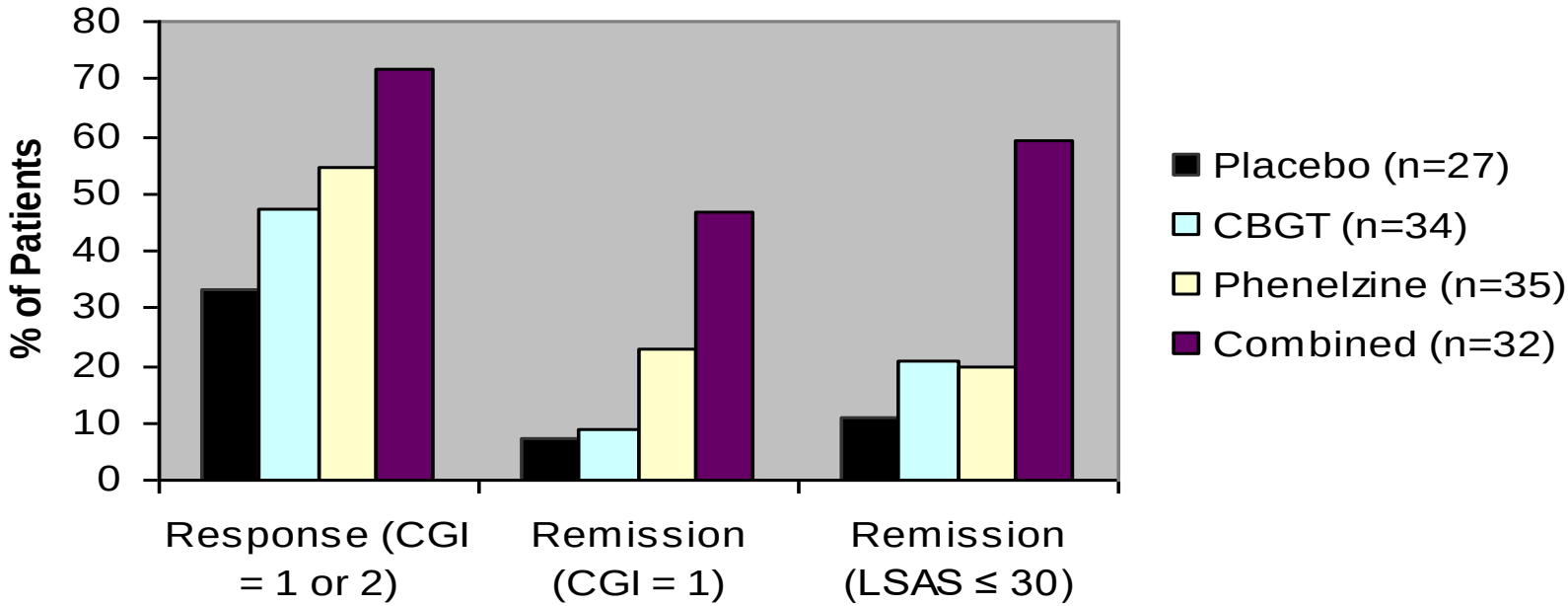
No greater benefit with increased SSRI dose:? Too early

- 12 weeks
  - Added CBT or
  - SSRI optimization + clonazepam

No difference between added CBT and clonazepam

Simon et al. J Clin Psychiatry. 2009:70:1563-1570

Combined Phenelzine 60-90mg/d and CBGT superior to monotherapies and placebo in Social Anxiety Disorder



*p<.01 vs. placebo: CBGT= Cognitive Behavioral Group TherapyNote: study initiated 1995 when best data SAD was with MAOIs

Recent study with internet CBT SAD and escitalopram also greater effect combined vs iCBT plus placebo (Gingnell et al 2016)

Blanco et al. Arch Gen Psychiatry. 2010 67:286-295

Extinction Learning with Pharmacotherapy: D-Cycloserine

- Rather than anxiolysis, use pharmacotherapy to enhance the effects of exposure – putative memory enhancers
- Fear extinction (safety learning) mediated by NMDA receptor activity in the basolateral amygdala
- Some positive but mixed data DCS anxiety disorders
- Meta-analysis 21 trials (n=1047) w anxiety/OCD/PTSD: significant small augmentation effect at endpoint (d=0.25) but not follow up
- Success of exposure session may moderate effect

e.g., Ressler et al., 2004; Richardson et al., 2004; Hofmann et al. 2006; Otto et al 2010; Hofmann 2012; Smits et al 2103; Leyfer et al 2018; Pyrkosch et al 2018; Mataix-Cols et al 2017

Integrating CBT into Pharmacotherapy:

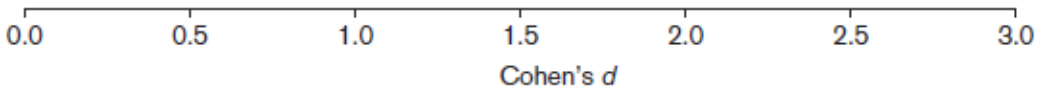
Always Provide and Encourage

- 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

Panic, Social, & GAD Meta-Analysis RCTS

Fig. 2

Treatment	*n*	*d*
SNRIs	23	2.25
Benzodiazepines	42	2.15
CBT + drug	16	2.12
SSRIs	62	2.09
TCAs	15	1.83
Relaxation	17	1.36
CBT/exposure, individual	93	1.30
Pill placebo	111	1.29
CBT, group	18	1.22
Psychodynamic therapy	5	1.17
Non-face-to-face therapies	34	1.18
Psychological placebo	16	0.83
Waiting list	50	0.20



Bandelow B et al. Int Clin Psychopharmacol. 2015;30:183-92.

Novel Mechanisms of Action

- Endocannabinoid receptor antagonists
  - MAGL and FAAH
- Psychedelics
  - LSD
  - Psilocybin
- Neurosteroids and novel GABA receptor antagonists

Complementary Pharmocotherapy

- **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
- V**alerian** Root: sedative
- **Mezembrine:** (Zembrin) (e.g. CalmZ 1-4 q day)
- **Chamomile:** (e.g. 500 mg TID)

Anxiety Disorders Management

- Exercise, mindfulness, diet, walks in nature
- Evaluate medical/psychiatric/substance comorbidity
- RCT data suggest comparable efficacy for SSRIs, SNRI, 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
- Mixed support combining CBT and meds first line (BZDs may interfere with CBT, esp. as prn)
- → plan to attempt slow taper if start BZDs to determine lowest necessary dose, e.g. zero if possible
- Encourage exposure to avoided situations for all