MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Psychopharmacology of Anxiety Disorders

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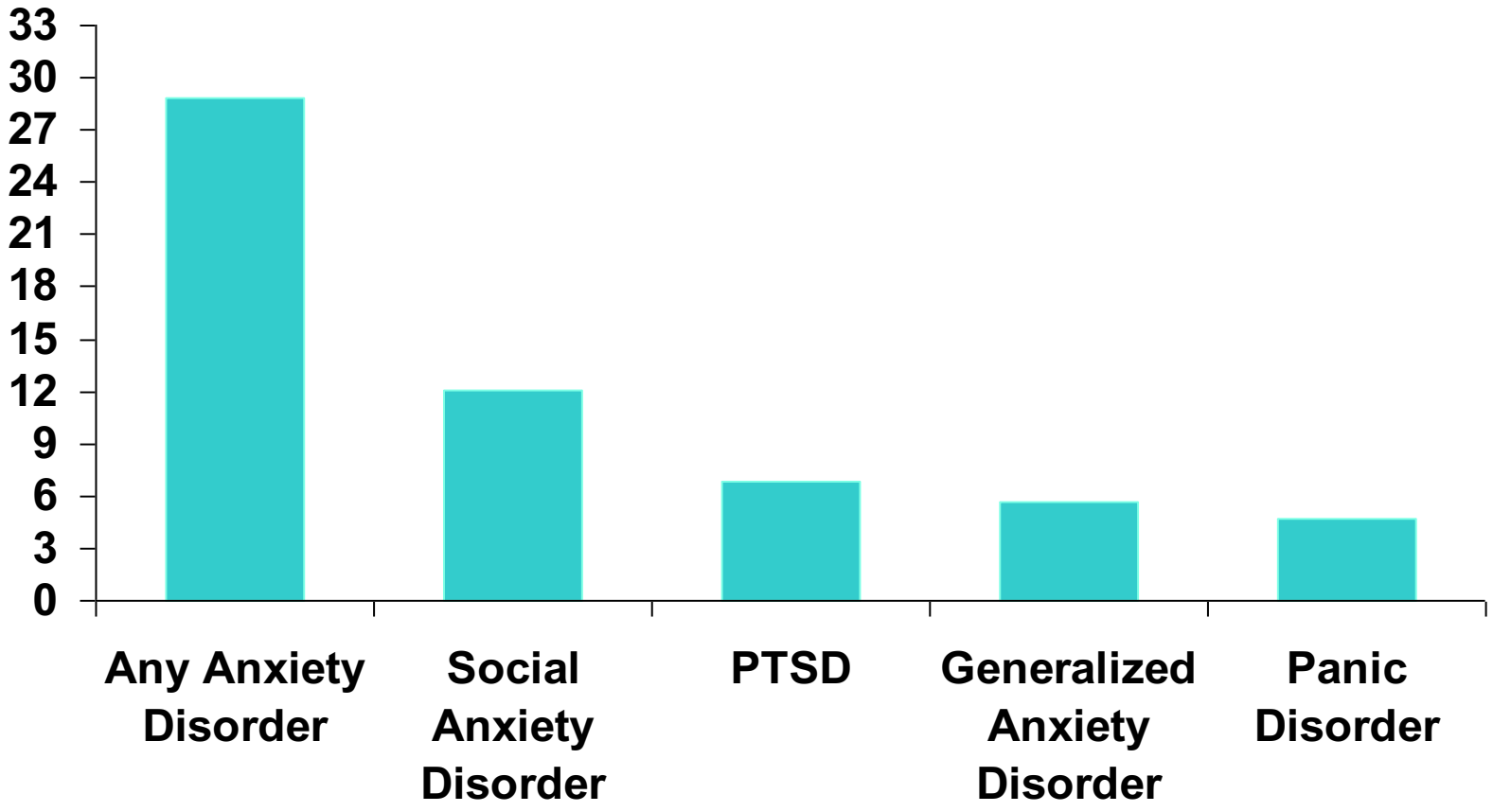
Disclosure Regarding Financial Interests and Affiliations: September 2020

Equity: Psy Therapeutics, LLC (co-founder)
Terran Biosciences, Advisor
Odin, Advisor

Anxiety Disorders Are Common:

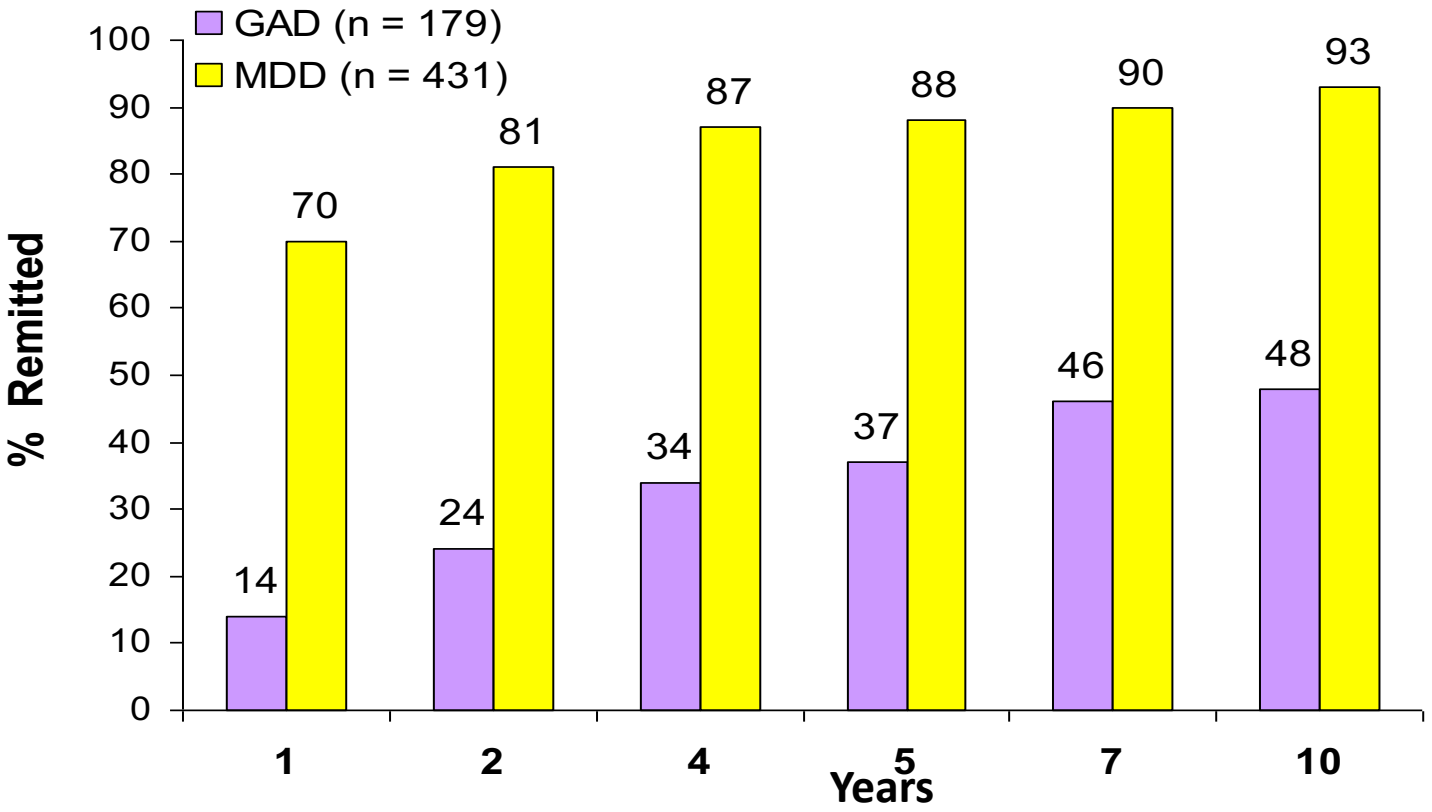
National Comorbidity Survey Replication



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

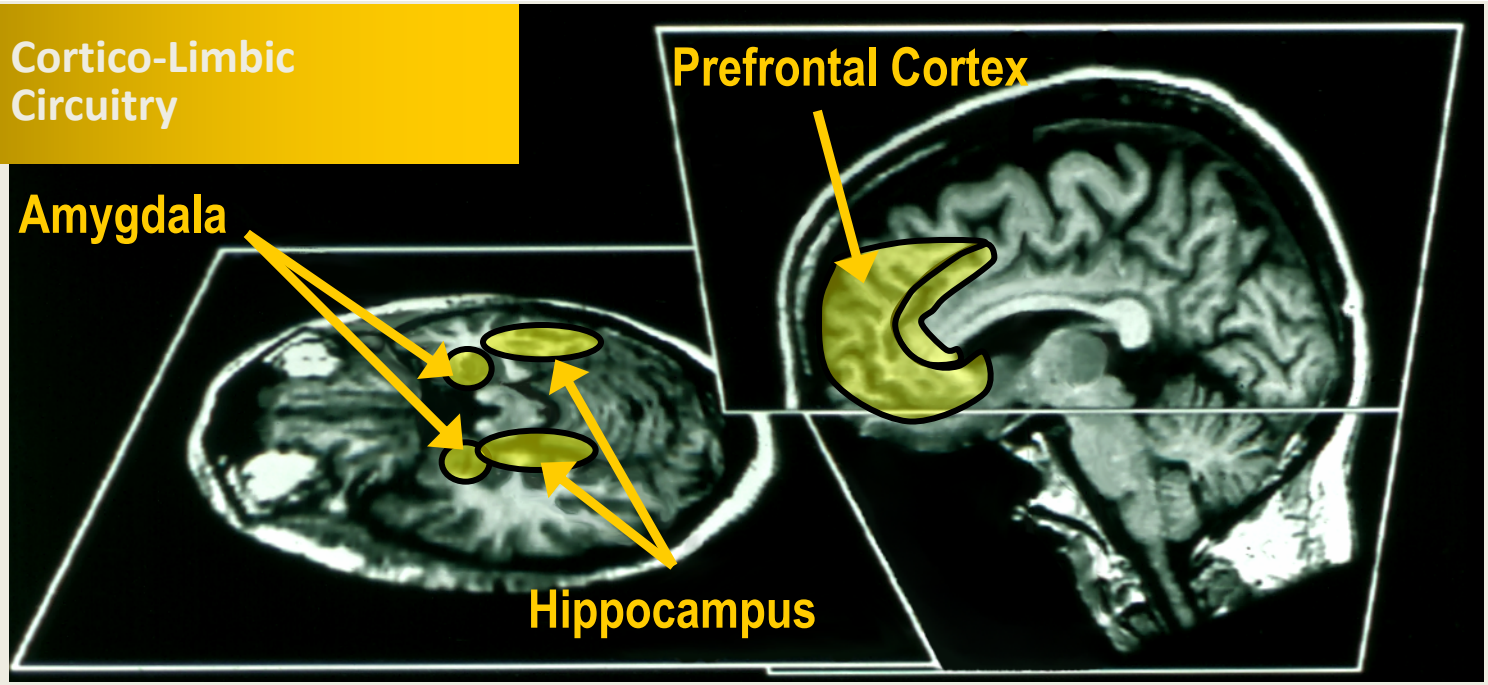
Sustained Threat

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

NIMH RDoC Website

Panic: Classic Neurocircuitry Model “false alarms”

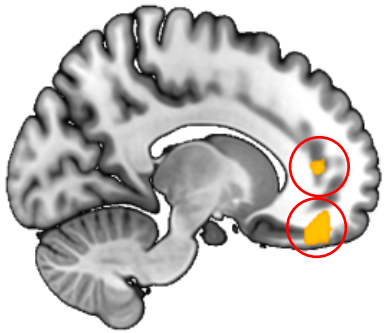
- **Amygdala: Drives autonomic and emotional responses**
- **Hippocampus: Evaluates threat contexts (safe/unsafe)**
- **Prefrontal Cortex (PFC): Regulates limbic responses of amygdala and hippocampus (“top down”)**



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

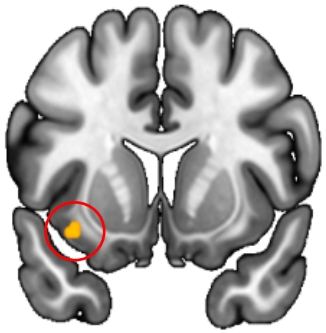
Deficits in vmPFC during Extinction Recall Across Anxiety Disorders Increase with Number of Disorders

rACC & vmPFC



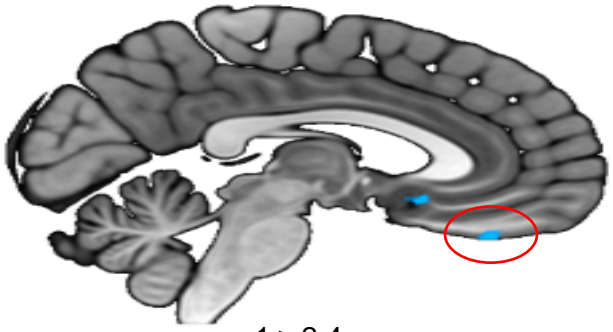
HC > Anx

Insula



HC > Anx

vmPFC



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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.)

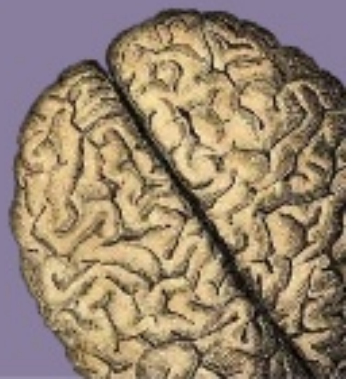
*PACAP= Pituitary adenylate cyclase activating polypeptide (PACAP, gene *Adcyap1*) ; NPY= Neuropeptide Y

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

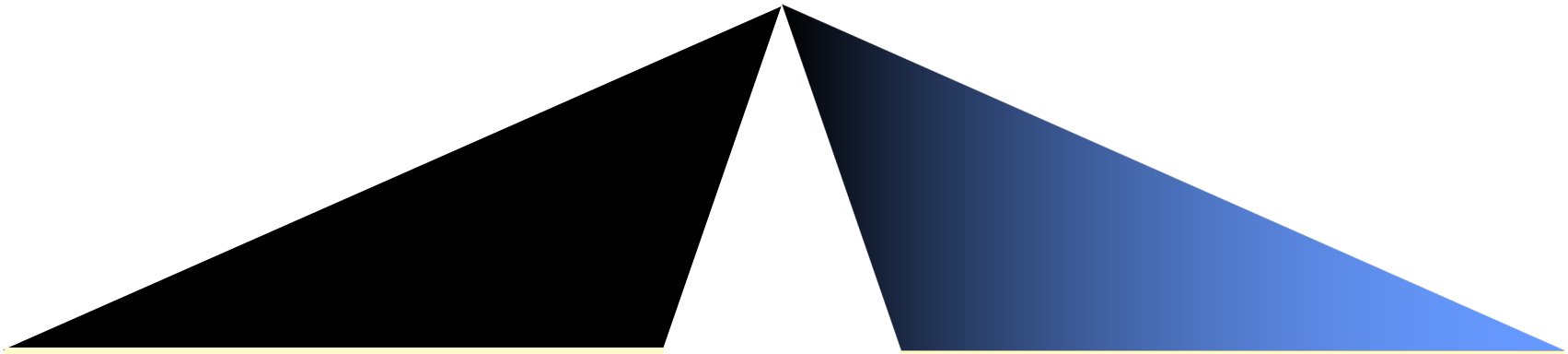


www.slideshare.com, SMR Grey

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 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-Based
- Cognitive Behavioral Therapy
- Other psychotherapies
- Relaxation/mindfulness

PHARMACOLOGICAL

- SSRIs/SNRIs
- Benzodiazepines
- Mood Stabilizers
- Antipsychotics
- Adrenergic Blockers
- Sleep agents

Medications for Anxiety Disorders

- Antidepressants
  - Serotonin Selective Reuptake Inhibitors (SSRIs)
  - Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
  - Atypical Antidepressants
  - Tricyclic Antidepressants (TCAs)
  - Monoamine Oxidase Inhibitors (MAOIs)
- Benzodiazepines
  - High Potency Benzodiazepines
  - Low Potency Benzodiazepines
- Other Agents
  - Azaspirones
  - Beta blockers
  - Anticonvulsants
  - Atypical Antipsychotics

SSRI and SNRI Antidepressants First Line for Anxiety Disorders

- Due to safety and tolerability and broad efficacy
- No clear within-class efficacy differences anxiety disorders
- 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
- Lack abuse but serotonin withdrawal, initial activation, insomnia, sexual dysfn, GI, weight gain
- AUGMENTATION STRATEGIES: Adjunctive benzodiazepine, beta-blocker, anticonvulsant

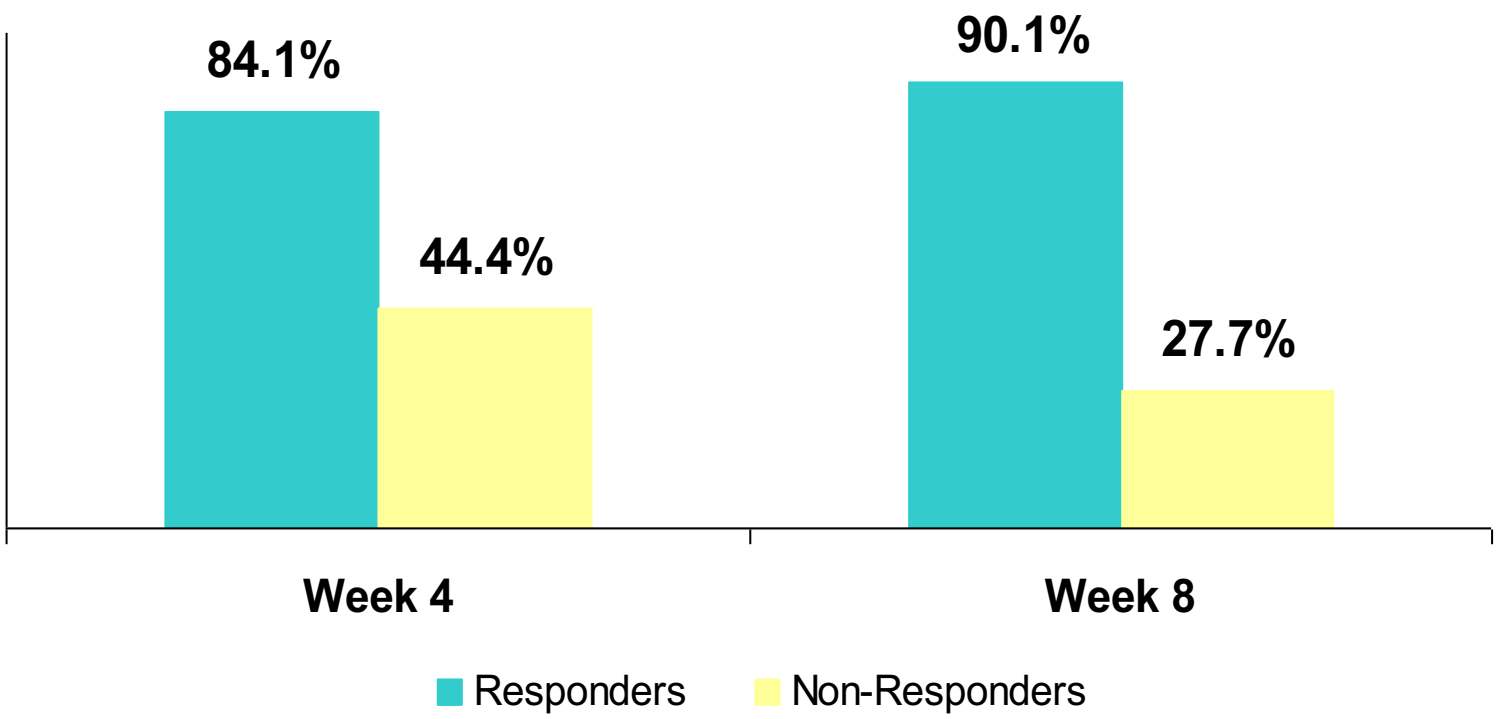
SSRIs and SNRIs for SAD

- 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 to1.2*
- Data suggest continued improvement with longer periods treatment (e.g., LSAS at 6 months)

  → May take time to return to avoided situations

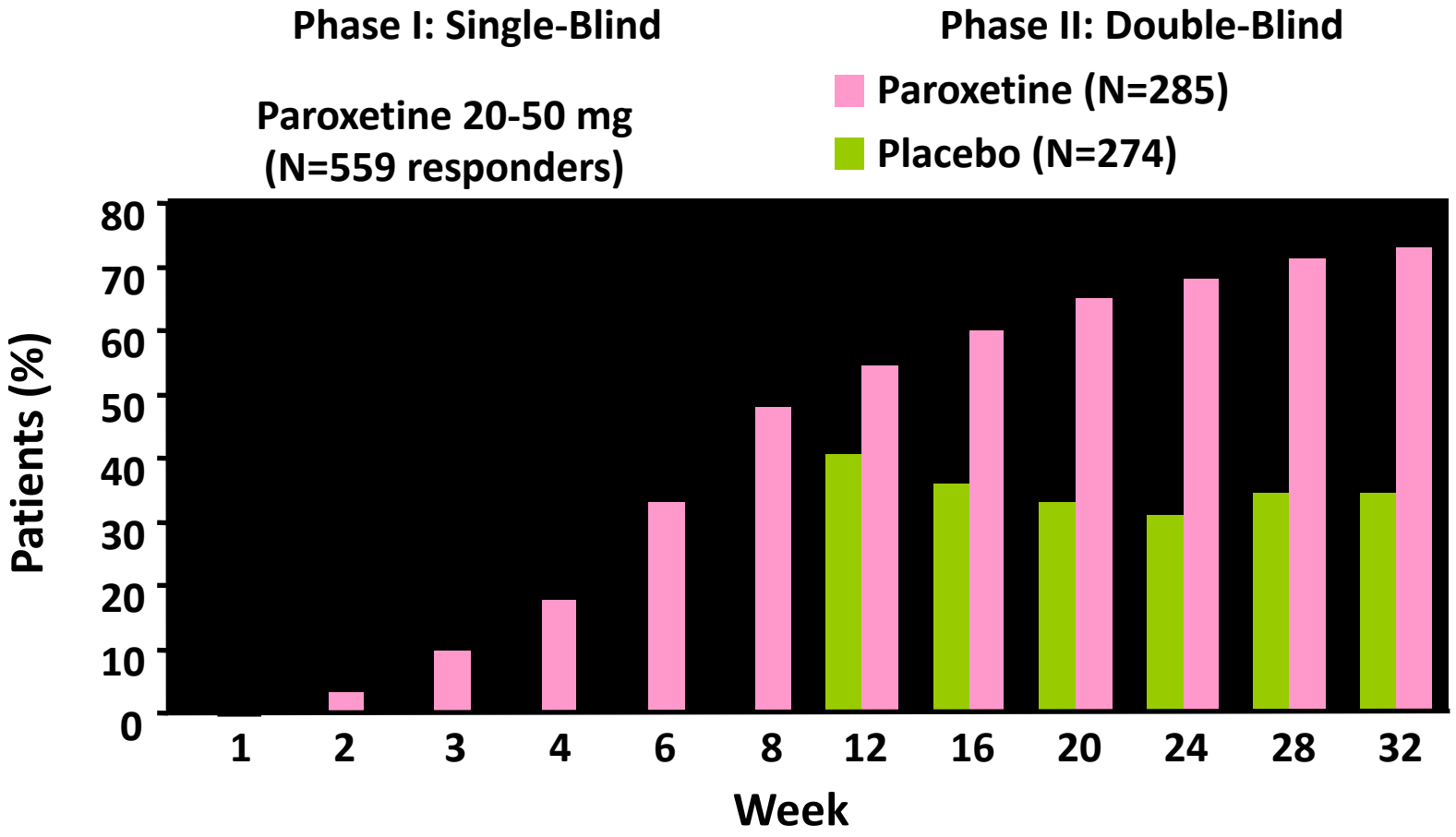
*Hedges. J Psychopharmcol. 2006; e.g., Stein MB et al. Psychopharmacology. 2005; Leibowitz. J Clin Psych. 2003; Kasper. Br J Psych. 2005.

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.

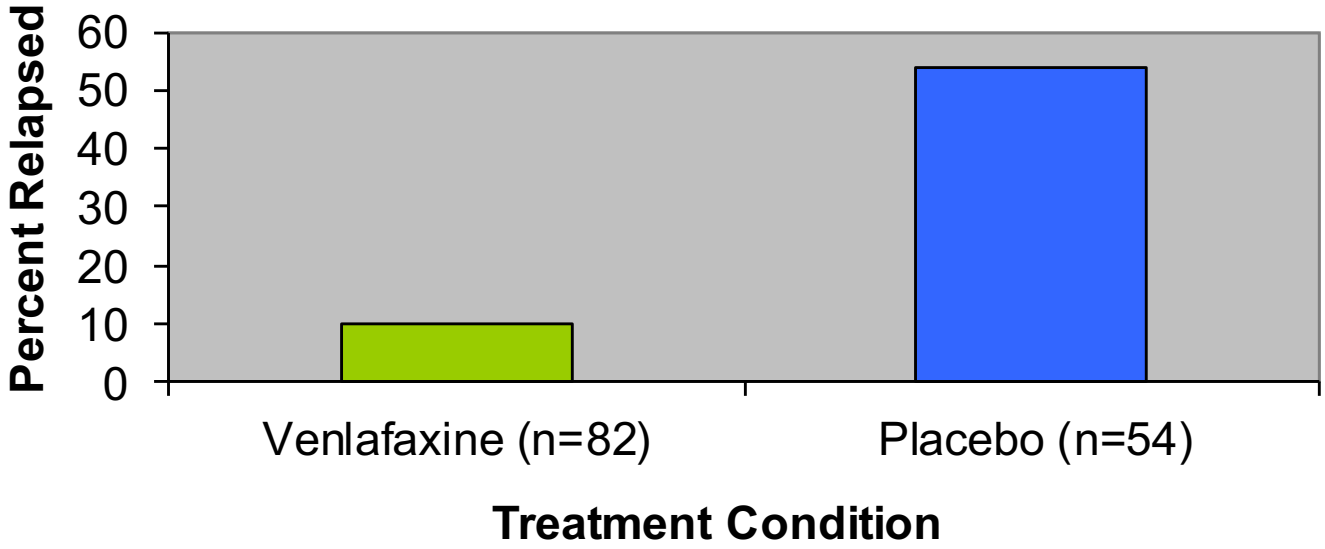
GAD:
Remission Rates Increase with Long-Term Treatment



*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**

*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

- Signif. greater 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

→ signif greater HAMA reduction vortioxetine but variable response and remission /heterogeneity

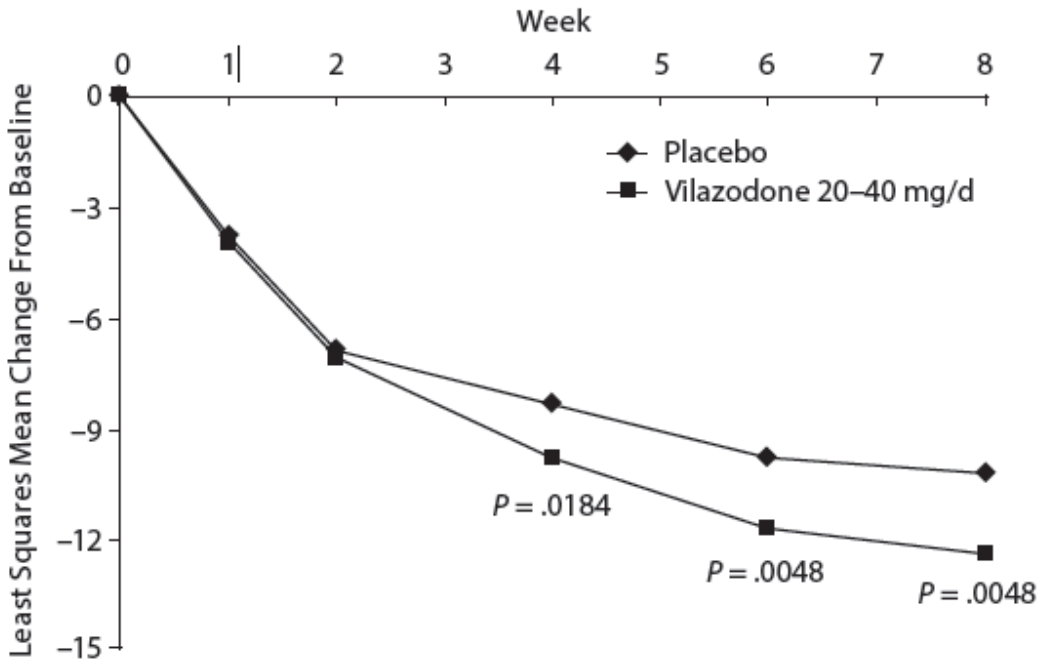
- Small effect sizes (SMD= -0.118) but greater more severe GAD (HAMA>25: SMD 1.221)
- Some recommendations 3rd line treatment given mixed results (eg Van Ameringen et al in press)

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 and Anxiety

- No longer first line due to side effect profile (e.g., cardiovascular, anticholinergic) and lethal in overdose
- Imipramine most RCT data in panic
- No evidence lesser efficacy SSRIs/SNRIs panic but lack efficacy Social Anxiety Disorder
- No RCT refractory data but clinical SSRI augmentation
- 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 antidepressant-induced activation
- Some meta-analyses (e.g. GAD*) suggest:

  →greater effect size than serotonergic antidepressants (impact publication timeline?)

  → 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
- Not effective for comorbid depression
- *May interfere with CBT exposure component

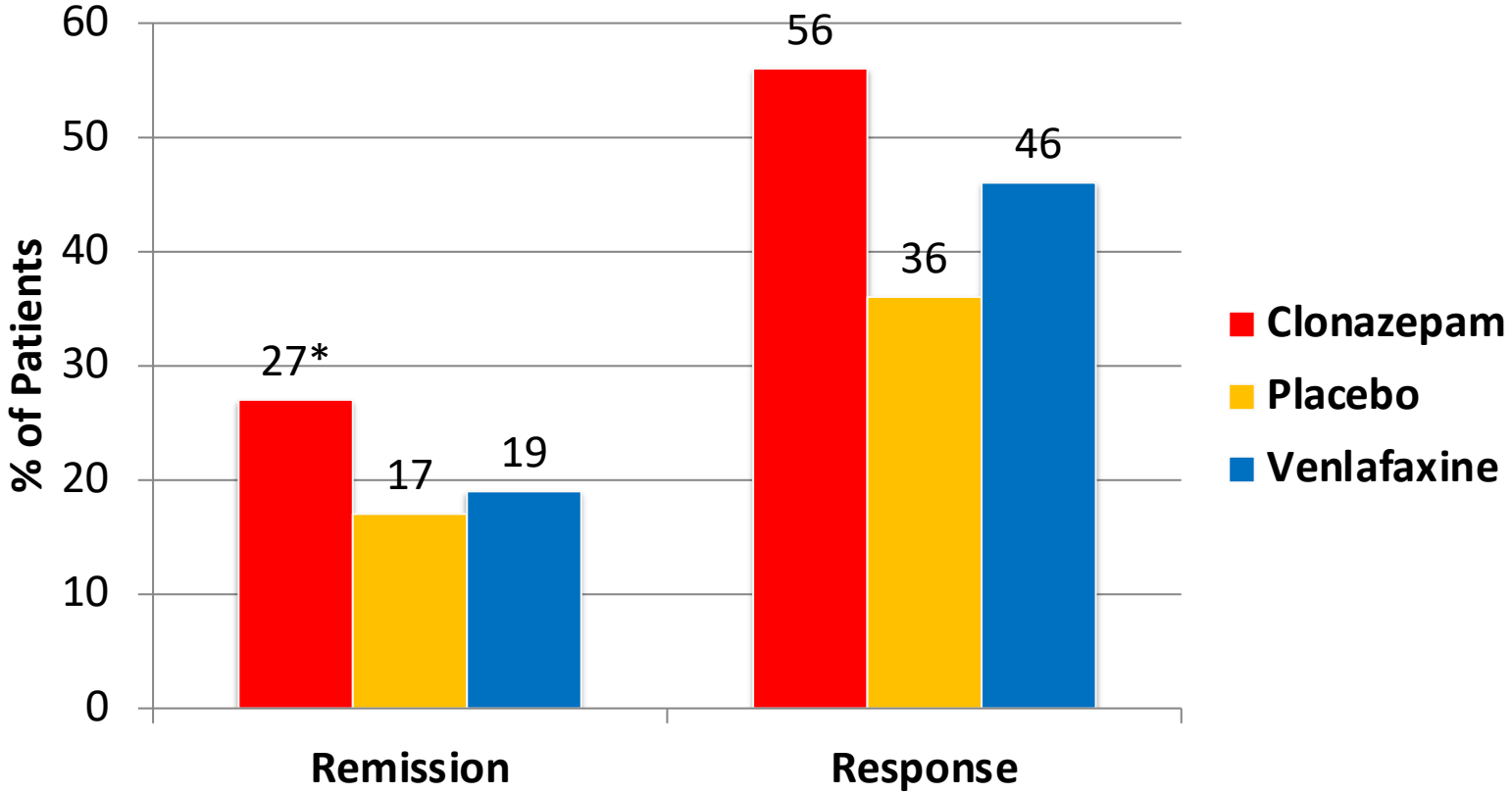
Benzodiazepine Use in Panic Disorder: Is Less More?

- Disadvantages PRN use:
  - Reinforce panic = DANGER (must abort!)

    → Greatest interference with CBT
  - Increase attention to assessment of "need"
  - Induction panic if "forget" to carry med
  - May increase liability abuse (evidence from prn vs. standing dose drug reinforcement studies*)
  - PRN dosing alone = under treatment for panic disorder
- If monotherapy, dose daily to efficacy and tolerability
  - Underdosing = risk without efficacy

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

Clonazepam Augmentation of Sertraline vs Switch 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

- 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.

Buspirone

- Non-benzodiazepine anxiolytic
- Non-sedating
- Effects on serotonin and dopamine receptors
- Indicated for generalized anxiety; weak antidepressant effects at higher doses but generally reserve milder cases or if no depression comorbidity
- Potentially useful as augmentation GAD or augment:
  - Panic
  - Social phobia
  - 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
- 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
- Decreases physiologic symptoms of arousal, not emotional experience of anxiety

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

[1]Steenen et al . J psychopharmacology, 2016

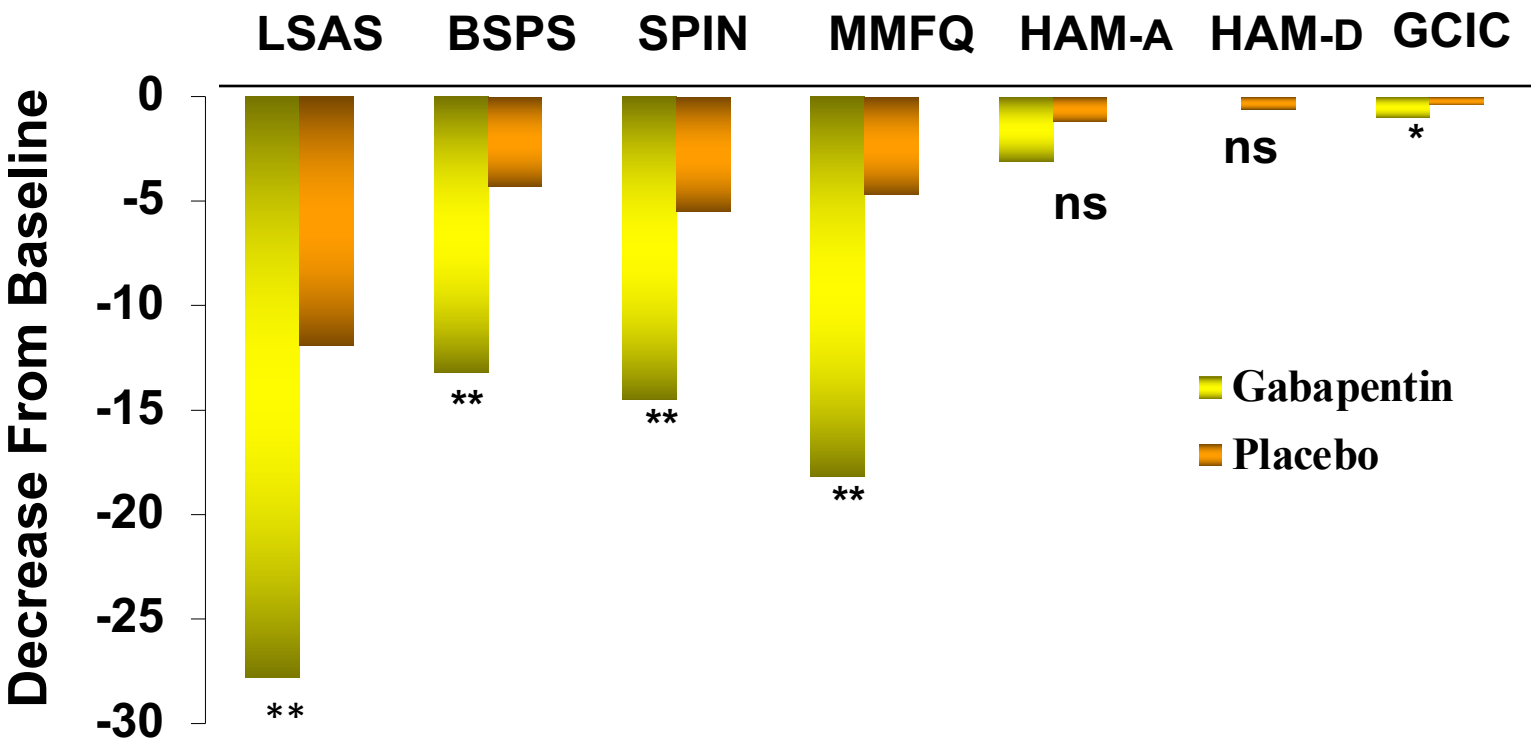
Anticonvulsants for SAD

- 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)

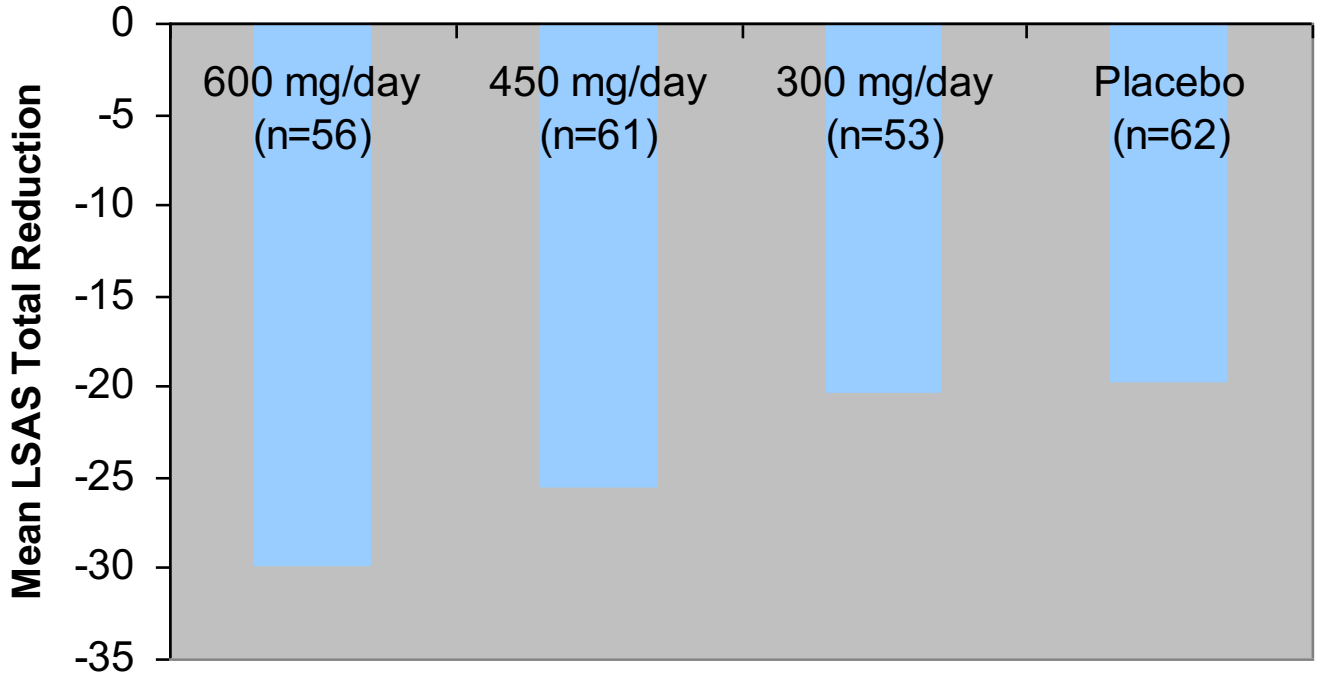


(Pande 1999)

** 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 only 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.

Atypical Antipsychotics: Role Refractory Anxiety?

- NOT a first line intervention!
- May have role for refractory patients or more complex comorbidity:
  → bipolar and anxiety
- Better side effect and safety profiles than typicals but not side effect free
- Caution re: weight gain and metabolic syndrome

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.

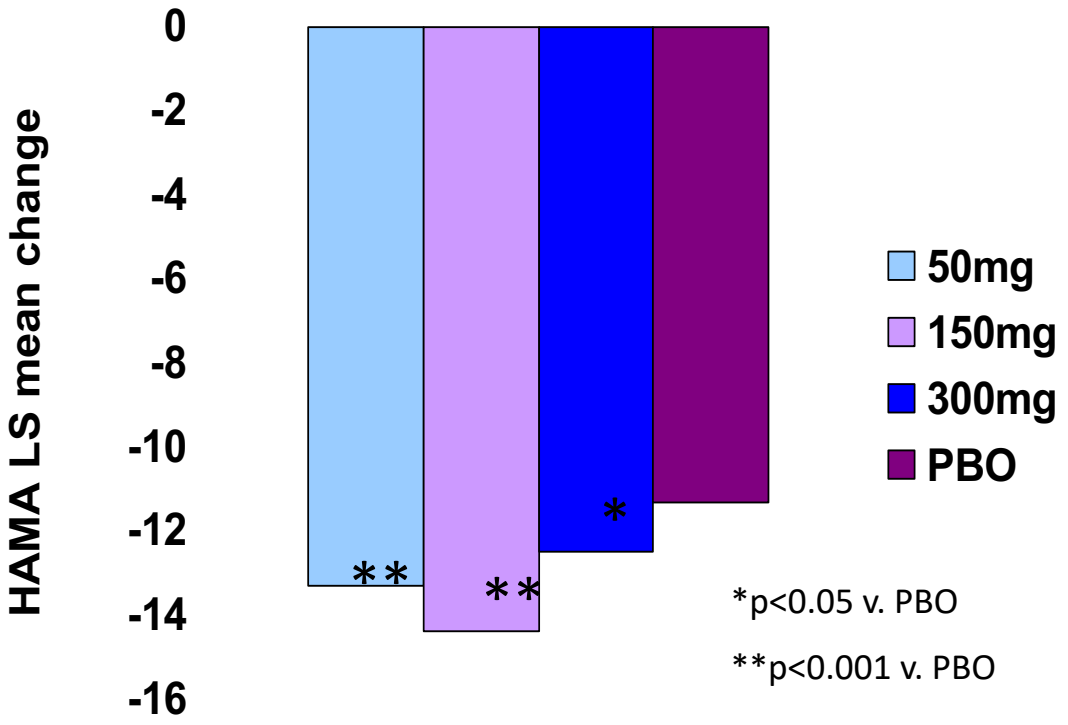
Pooled analysis of 3 RCTs Week 8 Quetiapine XR for GAD

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).

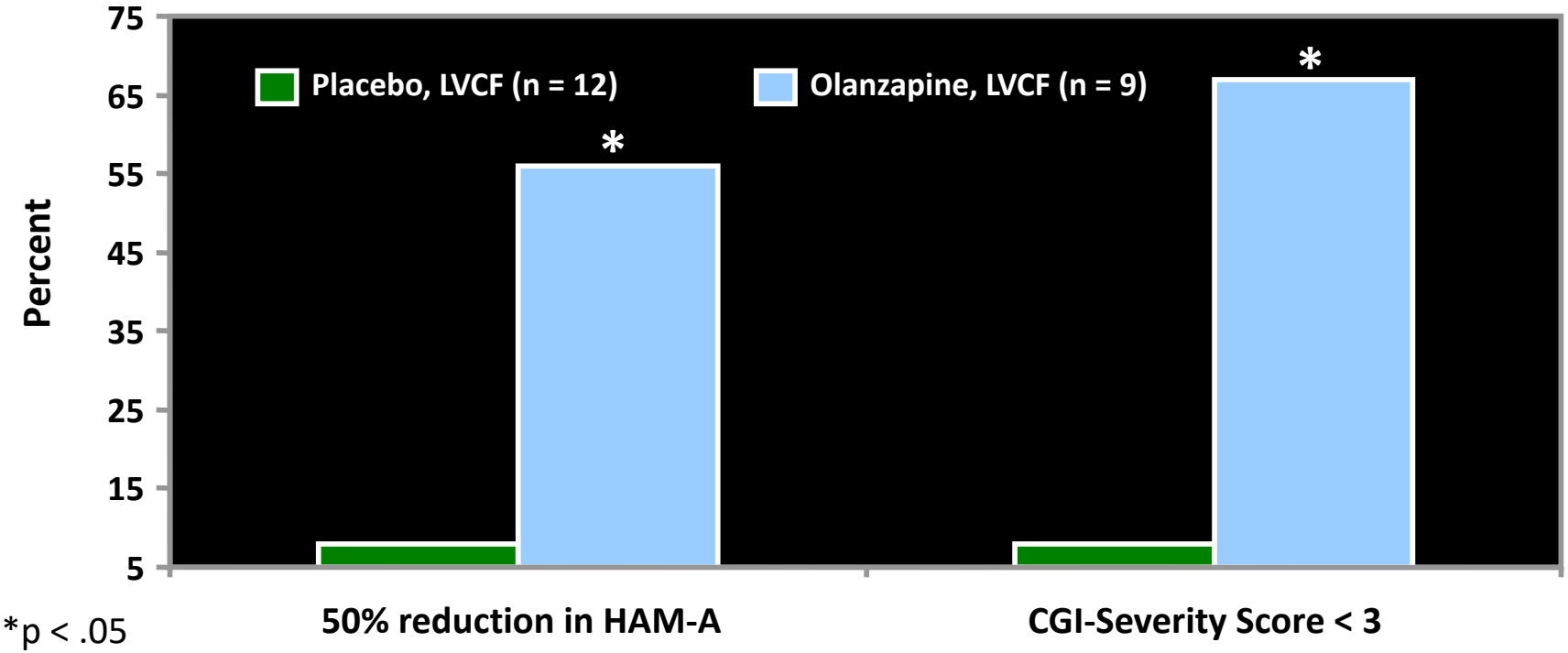
➢ 2nd Meta-anal (Maneeton et al 2016) reported only 50 and 150 more effective than placebo, but **comparable response rate (62%) to SSRIs (60%) & NNT vs placebo response = 9**



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

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

Olanzapine Augmentation of SSRIs: Support in small GAD RCT but Consider Long Term Tolerability Issues (eg Weight gain, diabetes, sedation)



*p < .05

Total n = 45. Patients with one post-randomization visit n = 21.

LVCF = last visit carried forward.

Pollack MH et al. Biol Psychiatry. 2006;59:211-15.

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

2nd Generation Antipsychotics 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

Focus on Remission: Pharmacotherapy Options for Patients Remaining Symptomatic

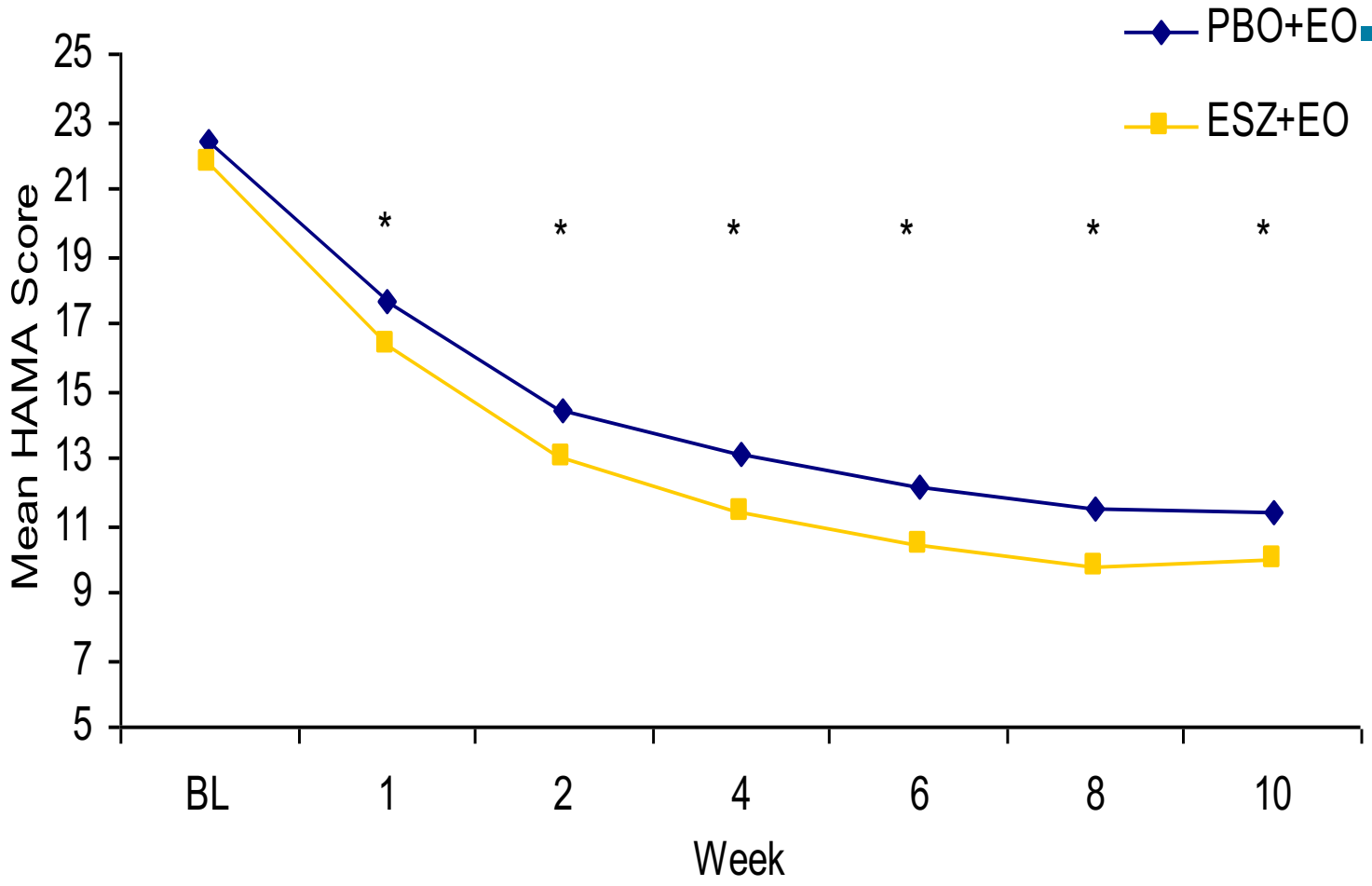
- Optimize dose, duration, and tolerability
- Augmentation
- Switch

Pharmacotherapeutic treatment regimen should reflect the adequacy of prior treatments and other patient variables (such as comorbidity)

Pharmacotherapy Augmentation: Limited Data

- Potential benefits
  - Enhance initial partial response
  - No lost time tapering
  - Combine agents differing in mechanism
- Potential downsides
  - Side-effect burden
  - Cost
  - Unclear which drug to discontinue and when

Targeted Insomnia Treatment in GAD: Escitalopram (10mg) Plus Eszopiclone (3mg) or Placebo Effect on Anxiety (HAM-A))



*p < 0.05 vs. placebo; Week 10 = end of SB placebo run-out period (N=595).

Pollack MH et al. Arch Gen Psychiatry. 2008;65:551-62.

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.

Canadian Clinical Practice Guidelines for the Pharmacotherapy of SAD

First-Line	Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-Line	Alprazolam, bromazepam, citalopram, clonazepam, gabapentin, phenelzine
Third-Line	Atomexetine, bupropion SR, clomipramine, divalproex, fluoxetine, mirtazapine, moclobemide, olanzapine, selegiline, tiagabine, topiramate

CR = controlled release; SR = sustained release; XR = extended release

Note: Although there is limited evidence for citalopram in SAD, it is likely as effective as the other SSRIs, in contrast there are negative trials of fluoxetine in SAD suggesting it may be less effective than other SSRIs

Katzman et al. BMC Psychiatry 2014; 14(Suppl 1):S1

Canadian Clinical Practice Guidelines for the Pharmacotherapy of SAD

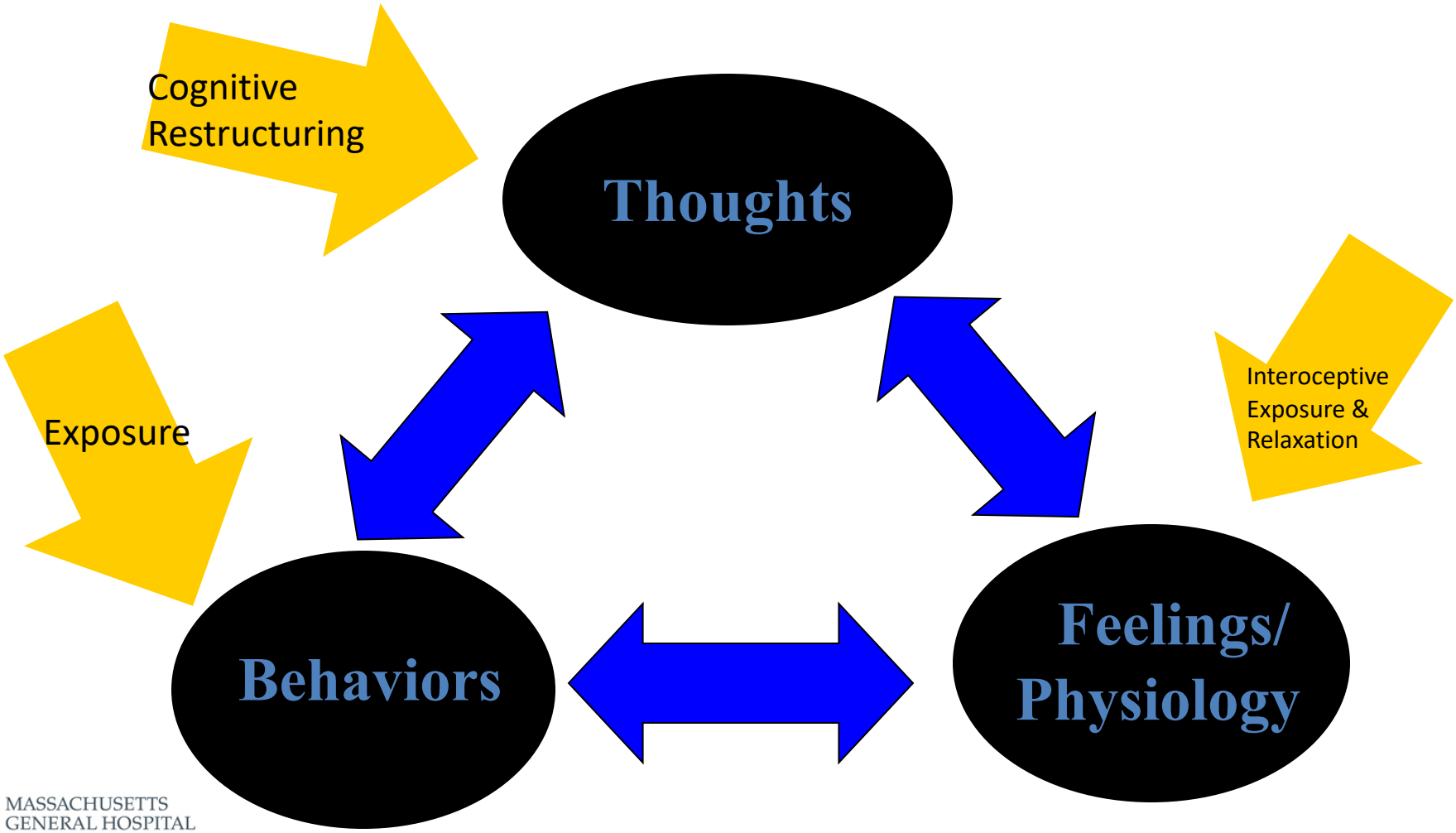
Adjunctive therapy	**Third-Line:** aripiprazole, buspirone, paroxetine, risperidone **Not recommended:** clonazepam, pindolol
Not recommended	Atenolol*, buspirone, imipramine, levetiracetam, propranalol*, quetiapine

CR = controlled release; SR = sustained release; XR = extended release

*Beta-blockers have been successfully used in clinical practice for performance situations such as public speaking

Katzman et al. BMC Psychiatry 2014; 14(Suppl 1):S1

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
- Disadvantages
  - Harder to administer than medication
  - Limited availability
  - More effort 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

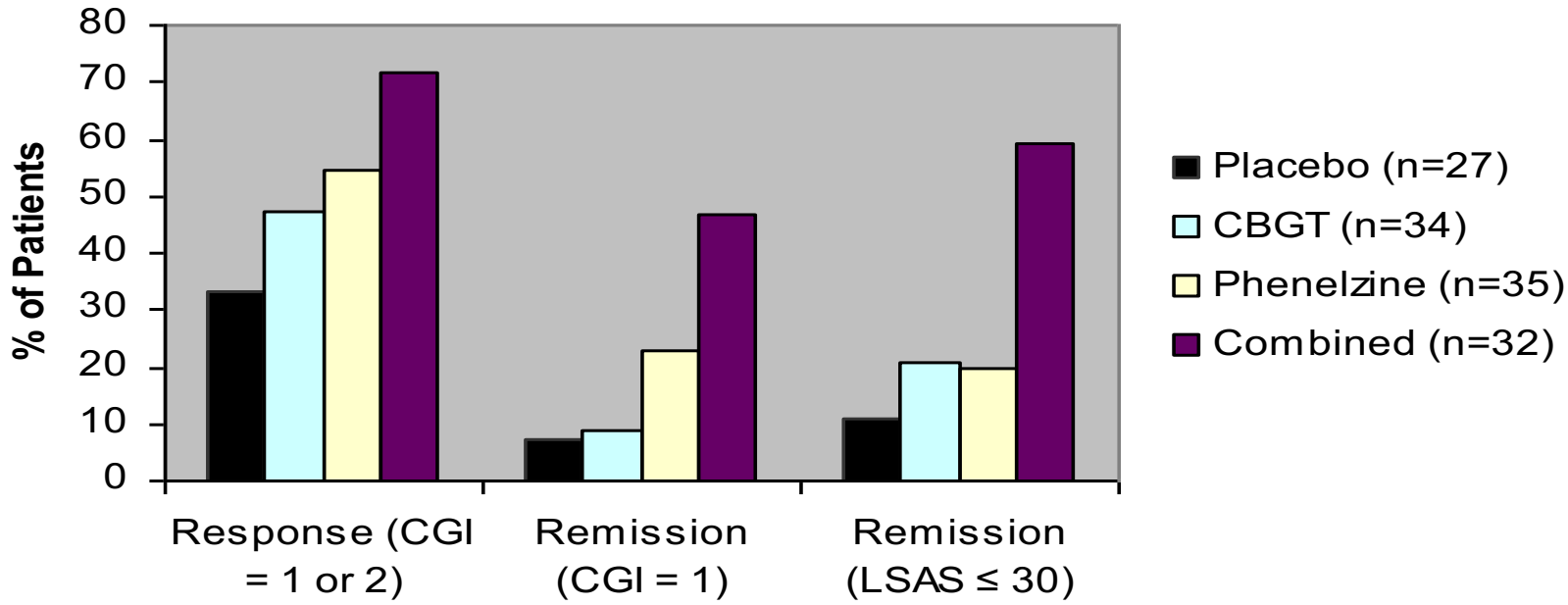
No greater benefit with increased SSRI dose:? Too early

- 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 both monotherapies and placebo: 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:

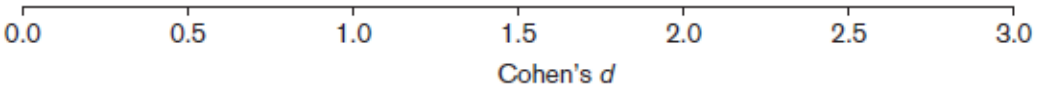
Always Provide and Encourage

- 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.

Chamomile for GAD

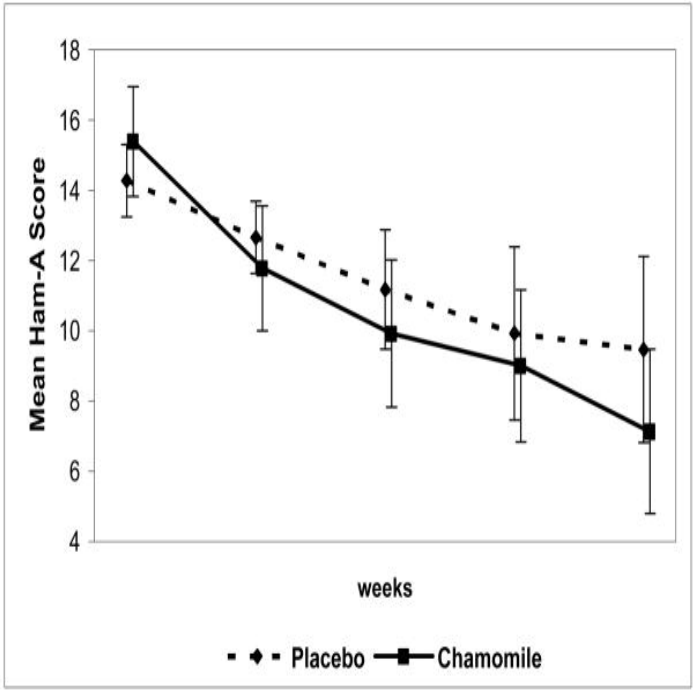
- Apigenin= active agents
- Probably GABA-ergic
- RCT / 8 weeks (ITT n=57)
- 220-1100mg chamomile (1.2% apigenin) vs. PCB

- 2nd study: 500mg TID good tol. and effect:

responders (n=93) randomized
to 26 wks (15% relapse vs.
25% placebo switch)

- Anxiety response assoc. increased

morning and diurnal slope salivary cortisol



P=0.047 for interaction

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

Amsterdam et al. 2009; Mao et al 2016; Keefe et al JPR, 2018

Lavender

- 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 score [WMD −1.14 (−1.10, 3.39)] 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.
- Overall, silexan 160 mg more significant decline in HAMA score across other comparators.
- Pharmacological effects of lavender essential oil could be attributed to the inhibition of voltage dependent calcium channels.

Scientific Reports | (2019) 9:18042 | https://doi.org/10.1038/s41598-019-54529-9

Potential targets of interest

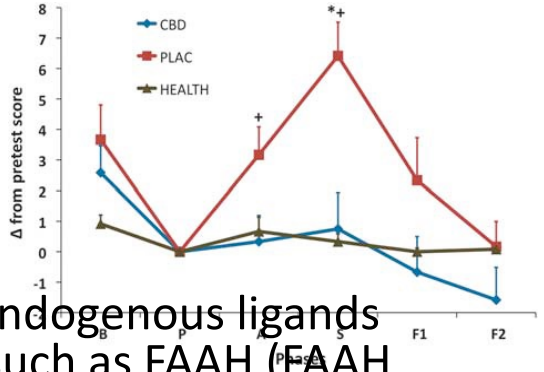
Cannabidiol (CBD) and Endocannabinoid System (vs lack MJ or THC support)

- Preclinical data: roles fear consolidation and extinction (Ganon-Elazar, 2013) and amygdala (Hill et al., 2013), and interactions endocannabinoid system w stress and HPA axis

- Cannabidiol (CBD) may have anxiolytic effects without THC's euphoric and addictive potential (Blessing 2015)

- Preliminary support anxiolysis in small RCT in SAD

CBD 600mg or placebo (n=12 each) 90min before Trier Social Stress test (Bergamaschi et al 2011)



- Ongoing research targeting: CB1 & CB2 receptors, endogenous ligands such as AEA & 2-AG, and mediators of metabolism such as FAAH (FAAH inhibition blocks stress induced reduction AEA, potentially anxiolytic: Hill et al 2017) and MAGL.

- More RCT data needed!

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

Anxiety Disorders Management

- Exercise, mindfulness, diet, time in nature
- Evaluate medical/psychiatric/substance comorbidity
- RCT data together suggest comparable efficacy for SSRIs, SNRI, TCAs (except SAD, PTSD), Benzos (except PTSD), and CBT
  - SSRI/SNRIs and CBT are first line due to side effects and broad spectrum efficacy
  - Longer acting high potency benzos optimal (but not PTSD)
- Anticipate side-effect sensitivity
- Mixed support combining CBT and meds first line (benzos may interfere CBT, esp. prn)
- → anticipate plan to d/c meds if start together
- Encourage return to avoided situations for all