Pharmacotherapy of Anxiety Disorders: Update on Panic, GAD and Social Anxiety Disorder

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Disclosure Regarding Financial Interests and Affiliations: September 2017*
*24 months to this date

**Research Grants:** American Foundation for Suicide Prevention, Department of Defense, Highland Street Foundation, NIH, Janssen

**Equity:** *Spouse:* G1 Therapeutics, Gatekeeper
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

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
Generalized Anxiety Disorder (GAD)

- Daily Worry and Nervousness ≥ 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)
Social Anxiety Disorder – DSM 5 Criteria

A. Fear or anxiety about social situations involving possible scrutiny by others
B. Fear of acting in a way (or showing anxiety symptoms) that will be negatively evaluated
C. The social situations almost always provoke fear or anxiety
D. The social situations are avoided or endured with intense fear/anxiety
E. Fear/anxiety out of proportion to actual threat and to sociocultural context
F. Persistent; lasts ≥ 6 months
G. Causes clinically significant distress or impairment
H. Not due to physiological effects of substance or medical condition
I. Not better explained by symptoms of another mental disorder
J. If another medical condition present, fear/anxiety/avoidance is clearly unrelated or excessive

Specify if Performance only: if fear restricted to speaking or performing in public

( American Psychiatric Association 2013)
Panic Disorder

- Recurrent “out of the blue” panic attacks
  - Physical and cognitive acute fearful symptoms
  - Commonly become situationally linked
- At least one attack with ≥ 1 month:
  - Persistent concern about additional attacks
  - Worry implications of panic attack or consequences
  - Significant change in behavior
- No medical cause
- With or without agoraphobia
Agoraphobia

– Fear of being in a place where escape might be difficult (or embarrassing), or where help might not be available if panic attack

– *Typical fears*: crowds, lines, shops, drive, bridges, tunnel, train, bus, plane, outside home alone, hot enclosed places, haircuts

– Situations avoided or endured with distress, or only with a companion
DSM-5 reorganized Anxiety Cluster

*PTSD, etc., now in separate category*

### “Trauma- and Stressor-Related Disorders”

<table>
<thead>
<tr>
<th>Disorder Name</th>
<th>Used To Be In (DSM-IV-TR)</th>
<th>Now In (DSM-5)</th>
</tr>
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<tbody>
<tr>
<td>Reactive Attachment Disorder</td>
<td>“Disorders Usually First Diagnosed in Infancy, Childhood and Adolescence”</td>
<td>“Trauma and Stressor-Related Disorders”</td>
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<td>Disinhibited Social Engagement Disorder</td>
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<tr>
<td>Acute Stress Disorder</td>
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<td>“Trauma and Stressor-Related Disorders”</td>
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<td>Adjustment Disorders</td>
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Human Anxiety Disorders

<table>
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<tr>
<th>Primarily Fear</th>
<th>Primarily “Anxiety”</th>
<th>Other</th>
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<tbody>
<tr>
<td>Panic Disorder</td>
<td>Generalized Anxiety D.O.</td>
<td>OCD</td>
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<tr>
<td>Specific Phobia</td>
<td>Anxiety D.O. due to Medical</td>
<td>OCD-related</td>
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<td>Social Phobia</td>
<td>Anxiety D.O. due to Substances</td>
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<tr>
<td>PTSD</td>
<td>Separation Anxiety D.O.</td>
<td></td>
</tr>
</tbody>
</table>

However, from research, and often treatment, perspectives, we still see some overlaps.

Krueger (1999) Arch Gen Psych, 56(10): 921-;
Vollengergh et al., (2001) Arch Gen Psych, 58(6): 597-603
PANIC ATTACK:

"All of a sudden I felt dizzy, my legs gave out on me, and I couldn't catch a breath. It felt like someone was choking me. I could feel my heart was beating too fast and I was terrified I was dying. I knew I had to get away before I lost it."

**Symptoms:**
- Increased heart rate
- Chills, hot flushes
- Nausea / abdominal distress
- Shortness of breath
- Expressions of fear
- Chest discomfort
- Sweating
- Lightheadedness / faint
- Choking sensation
- Fear of dying / losing control

**PANIC ATTACK = ‘Fear Attack’ in Fear-related Disorders**

- Lateral hypothalamus: heart rate, blood pressure, bradycardia, ulcers
- Dorsal vagal N.: panting, respiratory distress
- Parabrachial N.: arousal, vigilance, attention
- Basal forebrain: increased startle response
- Retic. Pontis Caudalis: freezing, social interaction
- Paraventricular N.: corticosteroid release
The Human Amygdala and Fear

ETKIN & WAGER, 2007
Deficits in vmPFC during Extinction Recall Across Anxiety Disorders Increase with Number of Disorders

Marin et al JAMA Psychiatry 2017
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
• 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 to 1.2*
- Data suggest continued improvement with longer periods treatment (e.g., LSAS at 6 months)
  → May take time to return to avoided situations

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

Week 4: 84.1% Responders, 44.4% Non-Responders
Week 8: 90.1% Responders, 27.7% Non-Responders

GAD:
Remission Rates Increase with Long-Term Treatment

*\( p < 0.01 \) vs. placebo; LOCF dataset; Remission defined as HAM-A \( \leq 7 \); Stocchi F et al. J Clin Psychiatry, 2003; 64:250-258
Duloxetine and Adult Generalized Anxiety: Meta-analysis 7 RCTs (n=2674)

- SNRI: dosing 30 to 120/d (no evidence 120>60 GAD)
- Duloxetine 30 to 120mg/day 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)
- Greater discontinuation due to AEs but not overall
  - Concerns liver function and ETOH; typical AEs nausea/Headache/dry mouth /fatigue/ insomnia/ dizziness/ constipation
  - Note: range of pain indications including fibromyalgia

FDA indication GAD
Zhang et al. 2016
Vortioxetine and Generalized Anxiety: Meta-analysis 4 short-term RCTs (n=1677)

- 5HT reuptake inhibition, 5HT3R antagonism & 5HT1R agonism
- Vortioxetine (n=1068) vs placebo (n=609) adult GAD with 5mg or 2.5 - 10mg/day flexible dose
- 8 weeks signif greater HAMA reduction vortioxetine but variable study findings for response and remission and some heterogeneity
- Small effect sizes (SMD= -0.118) but greater more severe GAD (HAMA>25: SMD 1.221)
- Nausea and dizziness > placebo but no difference study discontinuation overall (AE & lack efficacy)

- Initial anxiety worsening (initiate with “test” dose - e.g., 10 mg/d imipramine)

This information concerns a use that has not been approved by the US FDA (Trintellix FDA for MDD).
Short Term Efficacy of Vilazodone for GAD (n= 400 RCT)

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

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

\(^a\)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.

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)

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
Potential Drawbacks of Benzodiazepines

- Sedation, cognitive, and psychomotor impairment
- Interaction with alcohol
- Physiologic dependence with ongoing therapy
- Discontinuation-related difficulties
- Potential for abuse in predisposed individuals
- Not effective for comorbid depression
- May interfere with Cognitive Behavioral Therapy 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

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

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*

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

Nardi et al, J Clin Psychopharmacol, 2010:30:290-293
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
• Recent propranolol metaanal. panic (n=130), social (n=16), spec phobia (n=37) found insufficient evidence for anxiety disorders¹
• Not effective for depression/comorbidities
• Decreases physiologic symptoms of arousal, not emotional experience of anxiety

¹Steenen 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 (Gabitril)
  - Negative results for Levetiracetam (3,000 mg/day)

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

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

Decrease From Baseline

** 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

![Chart showing LSAS reduction with different doses of Pregabalin and placebo](chart.png)

- *p<.01 vs. placebo

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

PGB administered TID

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


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

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


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.


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 produced 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.
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)
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

![Graph showing relapse rates](#)

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
### Optimal Dosing: APA Panic Guidelines 2009

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Starting and Incremental Dose (mg/day)</th>
<th>Therapeutic Dose (mg/day)</th>
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<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td>10</td>
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<td></td>
<td>Escitalopram</td>
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<td></td>
<td>Fluoxetine</td>
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<td></td>
<td>Fluvoxamine</td>
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<td>Paroxetine</td>
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<td>Sertraline</td>
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<td><strong>SNRIs</strong></td>
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<td>Duloxetine</td>
<td>20-30</td>
<td>60-120</td>
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<td></td>
<td>Venlafaxine ER</td>
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<td><strong>Benzodiazepines</strong></td>
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<td>Alprazolam</td>
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<td>Clonazepam</td>
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<tr>
<td></td>
<td>Lorazepam</td>
<td>1.5-2.0</td>
<td>4-8</td>
</tr>
</tbody>
</table>

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).
Lack of Effect Baseline Severity on Pharmacotherapy Outcomes
GAD, SAD, and Panic (n = 56 RCTs)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1 (with interaction)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>β  (95% CI)</td>
<td>P</td>
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<tr>
<td>GAD</td>
<td></td>
<td></td>
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<tr>
<td>Group</td>
<td>0.31 (0.15 to 0.47)</td>
<td>0.001**</td>
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<tr>
<td>Baseline</td>
<td>-0.03 (-0.15 to 0.09)</td>
<td>0.60</td>
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<tr>
<td>G x B</td>
<td>0.04 (-0.13 to 0.20)</td>
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<tr>
<td>SAD</td>
<td></td>
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<tr>
<td>Group</td>
<td>0.43 (0.29 to 0.57)</td>
<td>&lt;0.001***</td>
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<tr>
<td>Baseline</td>
<td>0.06 (-0.04 to 0.17)</td>
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<tr>
<td>G x B</td>
<td>-0.06 (-0.20 to 0.09)</td>
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<td>Panic disorder</td>
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<tr>
<td>Group</td>
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<tr>
<td>Baseline</td>
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<tr>
<td>G x B</td>
<td>0.002 (-0.10 to 0.10)</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

GAD, generalised anxiety disorder; SAD, social anxiety disorder.

a. Predictors are treatment group, baseline severity and their interaction (GxB).

*P < 0.05, **P < 0.01, ***P < 0.001.

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

<table>
<thead>
<tr>
<th>Drug Category (Type)</th>
<th>Pooled Effect Size (g)</th>
<th>No. Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI (Paroxetine, Fluvoxamine, Sertraline, Fluoxetine, Citalopram, Escitalopram)</td>
<td>0.44</td>
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<tr>
<td>SNRI (Venlafaxine ER)</td>
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<tr>
<td>MAOI (Phenelzine, Moclobemide)</td>
<td>0.36</td>
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<tr>
<td>MAO-A (Brofaromine)</td>
<td>0.60</td>
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<tr>
<td>Benzodiazepines (Clonazepam, Alprazolam)</td>
<td>0.82</td>
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<td>Antipsychotics (Olanzapine)</td>
<td>0.72</td>
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<td>Anticonvulsant (Gabapentin, Pregabalin, Levetiracetam)</td>
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<td>Beta-blockers (Atenolol)</td>
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<td>Herbal (St. John's Wort)</td>
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<td>NaSSA (Mirtazapine)</td>
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<tr>
<td>NK1 (Gr205171)</td>
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# Canadian Clinical Practice Guidelines for the Pharmacotherapy of SAD

<table>
<thead>
<tr>
<th>First-Line</th>
<th>Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR</th>
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<td>Second-Line</td>
<td>Alprazolam, bromazepam, citalopram, clonazepam, gabapentin, phenelzine</td>
</tr>
<tr>
<td>Third-Line</td>
<td>Atomoxetine, bupropion SR, clomipramine, divalproex, fluoxetine, mirtazapine, moclobemide, olanzapine, selegiline, tiagabine, topiramate</td>
</tr>
</tbody>
</table>

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
### Adjunctive therapy

**Third-Line:** aripiprazole, buspirone, paroxetine, risperidone  
**Not recommended:** clonazepam, pindolol

### Not recommended

Atenolol*, buspirone, imipramine, levetiracetam, propranalol*, quetiapine

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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

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Katzman et al. BMC Psychiatry 2014; 14(Suppl 1):S1
CBT Model of Anxiety Disorders
How enhance outcomes?

Thoughts

Cognitive Restructuring

Exposure

Behaviors

Feelings/Physiology

Interoceptive Exposure & Relaxation
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
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**
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*

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

*p<.01 vs. placebo: CBGT= Cognitive Behavioral Group Therapy

Note: 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
Combined CBT and Pharmacotherapy: Panic

• RCT (n=251) of 12 weeks sertraline (n=62), pill placebo (n= 62), self-administered CBT (sCBT) plus placebo (n=64), or sCBT plus sertraline (n=59)

• sertraline + self-administered CBT superior to both sertraline monotherapy and placebo/SCBT at 12 and 24 weeks for fear of bodily sensations

• Not significantly different on other measures

→ however, only combined treatment differed placebo panic measures despite known efficacy

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 (Mao et al 2016) good tol. and effect: responders (n=93) randomized to 26 wks (15% relapse vs. 25% placebo switch)  

P=0.047 for interaction

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

• Kavalactones = active agents
• Probably GABA-ergic
• RCT / 1 run in week (PCB) / 6 weeks
• 120-240mg kavalactones vs. PCB
• ITT data from n=58

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

Sarris et al. 2013

Change in HAMA

Total sample (n=58)
Pure GAD subgroup (n=26)

Kava
Placebo

p=0.046
p=0.02
Anxiety Disorders Management

- Provide psychoeducation
- 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)
  - MAOIs refractory only
- Anticipate side-effect sensitivity
- Mixed support combining CBT and meds first line (Ads as benzos may interfere CBT, esp. prn)
- \( \rightarrow \) anticipate plan to d/c meds if start together
- Encourage return to avoided situations for all
Stress and Antidepressant Effects on Hippocampal Neurogenesis and Atrophy

Control | Stress | Antidepressant