New Developments in the Treatment of Social Anxiety Disorder

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Clinical Importance of Social Anxiety Disorder (aka Social Phobia)

- Highly prevalent (early onset and chronic)
- Significant social and occupational disability
- Risk factor for depression, alcohol abuse, suicide
- Treatments available, but underutilized

History of SAD Diagnosis

1960s–1970s
   - “Dissection” of phobias by Marks
1970s–1980s
   - Performance anxiety and β-blockers
   - DSM-III introduces diagnosis of “social phobia”
1980s
   - Commonality with atypical depression → MAOI testing
   - Broadening of Dx in DSM-III-R (Generalized Type, “SAD”)
2010s
   - DSM-5: Subtype changed—Generalized to “Performance Type”

Prevalence of Common Psychiatric Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lifetime Prevalence</th>
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<tbody>
<tr>
<td>Major depressive disorder</td>
<td>17.1%</td>
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<tr>
<td>Alcohol dependence</td>
<td>14.3%</td>
</tr>
<tr>
<td>Social anxiety disorder</td>
<td>13.3%</td>
</tr>
<tr>
<td>Postsynaptic hyperactivity</td>
<td>7.8%</td>
</tr>
<tr>
<td>Generational anxiety disorder</td>
<td>8.1%</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>3.3%</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>3.2%</td>
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</tbody>
</table>

MIAO = monoamine oxidase inhibitor; SAD = social anxiety disorder.

DSM-5 SAD

- Fear of scrutiny in social or performance situations
- Fear that behavior/anxiety will → negative evaluation eg, embarrassment, rejection, offending others
- Exposure usually provokes anxiety
- Avoids or endures with intense anxiety
- Fear is excessive for situation and sociocultural context
- Clinically significant distress or impairment
- If secondary to medical condition, fear is excessive

SAD Subtypes

- Performance (aka Discrete, Nongeneralized)
  - Limited to performance situations
  - Most commonly related to public speaking
  - Social interactions spared
- Generalized (DSM-III-R to DSM-IV): Anxiety in most social situations
  - Most impairment
  - Most comorbidity
  - Most studied

Beyond *DSM* Criteria: Additional Clinical Features of SAD

- **Cognitive**
  - Self-consciousness, feelings of scrutiny
  - Fear of negative evaluation ("She won’t like me")
  - Social inferiority ("I won’t measure up")

- **Physiological**
  - Blushing, sweating, tremor/twitching, freezing
  - Panic attacks may occur (only social situations)

- **Behavioral**: Avoidance, poor eye contact, passive

Symptoms in Relation to Feared Events

- **Anticipatory Anxiety** (e.g., persons may worry for hours to weeks before a feared event)

- **Situational Anxiety** – Physical and/or cognitive symptoms

- **Post-Event Processing** – Persons may repeatedly critique their social performance, often accompanied by depressed mood

Age of Onset of SAD in Community

SAD: Educational and Occupational Impairment in Community

- *Impairment (%) refers to percentage of change in wages and percentage point changes in probabilities of college graduation and having a technical, professional, or managerial job.

Complications of SAD

Elevated rates of secondary

- Major depression (15%–20%)
- Alcohol dependence (20%–30%, OR = 2.8)

Many patients only seek treatment after developing a complication

Potential for Suicidal Ideation in SAD

*With any DSM-III major disorder.*

Based on a subset of persons in the Epidemiologic Catchment Area study, which assessed rates and risks of psychiatric disorders based on a probability sample of > 18,000 adults aged ≥ 18 years.

Clinical Inquiry RE: SAD
You Need to Ask
• What situations are uncomfortable? Offer list...
• What do you fear in those situations?
• Do you experience physical symptoms of anxiety?
• What situations do you avoid?
• What situations are comfortable for you?
• What is this problem preventing you from doing?

Differential Diagnosis of Social Fear and Avoidance
• Panic Disorder – Unexpected panic attacks
• Agoraphobia – Fear crowds due to fear of panic
• Generalized Anxiety Disorder – Social fears are only part of broader worries
• Depression – Loss of interest in social activities
• Psychosis – Social avoidance due to fear of harm
• Autistic Spectrum – Impaired relatedness even with closest others

Embarrassing Medical Conditions and SAD
• Social anxiety common in essential tremor, stuttering, hyperhidrosis, disfigurement, obesity, etc.
• In DSM-5 diagnosed as SAD if anxiety is excessive
• Stress-Diathesis Model relevant
• SAD treatments may be useful

Some Models of SAD
• Genetic/Developmental: Behavioral Inhibition
• Evolutionary: Excessive focus on status rather than affiliative mode → automatic submissive behavior
• Cognitive-Behavioral (attention bias to social threat, fear of negative evaluation, avoidance → failure to extinguish fears)
• Neurobiological
  – “Fear” circuitry: Amygdala reactivity/Prefrontal inhibition
  – Self-referential processing (posterior midline, DMN)
  – Dopamine, serotonin, GABA, glutamate
  – HPA axis; sympathetic activation in performance type
  – Oxytocin/social trust and reward?

Rationale for CBT in SAD
• Fear is maintained by
  – Phobic Avoidance
    • Limits chance to disprove fears, gain skills
    • Reinforces fears, increases symptoms
  – Negative Cognitions
    • Biased, unhelpful, “automatic”
    • Increase symptoms, avoidance
    • Block habituation, even if exposure occurs

Evidence for Efficacy of CBT in SAD
• > 30 RCTs (including wait list control studies) support efficacy
• Meta-analysis of rigorously controlled trials (n = 7): Effect size Hedges’ g = .66
• In RCT comparisons to medications, equivalent or better than SSRIs in 2 trials, somewhat less efficacious than phenelzine in 2 trials
• Persistence of benefit after treatment discontinuation is greater than that of medications

CBT = cognitive-behavioral therapy
DMN = default mode network; GABA = gamma-amino butyric acid; HPA = hypothalamic-pituitary-adrenal.
RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor.
CBT Methods for SAD

- Develop Hierarchy of Feared Situations
- Identify Maladaptive Cognitions, Safety Behaviors
- Develop
  - Adaptive Cognitions
  - External Focus
  - Adaptive Goal Setting
- Exposure through role-playing and homework

Cognitive Restructuring

- Identify automatic negative thoughts
- Treat AT as hypothesis, dispute it
- Negative thoughts are questioned systematically and more helpful “rational response” developed
- The rational response should be brief, believable, and helpful in reducing anxiety

If I approach her, I’ll stammer and get rejected
“Even if I’m anxious, I can start a conversation” or “I’ll feel good if I give it a try”

Exposure

- Prepare by reviewing rationale and addressing fears
- Begin with easier situations
- Set modest, achievable goals, eg, approach 1 stranger at party and contribute ≥ 3 questions or comments to the conversation
- Use rational response in role-plays and exposure assignments
- Manage post-event processing by limiting focus to whether goal was achieved

New Developments in CBT for SAD

- Focus on problematic emotion regulation and metacognitions (cognitions about thinking) that may underlie maladaptive social cognitions
  - My worries are uncontrollable
  - My worries are dangerous
  - It’s helpful for me to replay distressing events
- Internet-delivered CBT, particularly if therapist-guided, has efficacy in SAD (21 trials)
- Virtual reality exposure therapy appears promising for SAD (3 trials)

Other Psychotherapies with Controlled Trials for SAD

- Short-term Manual-Guided Psychodynamic
  - Efficacious in several RCTs relative to wait list
  - Mixed support for efficacy equivalence to CBT
- Interpersonal: Less efficacious than CBT in 2 RCTs
- Mindfulness and Acceptance-Based Therapies
  - 9 studies, mostly uncontrolled
  - Some evidence of efficacy, but less than CBT in some studies

Psychopharmacology of SAD: RCTs

- SSRI/SNRI (> 20 RCTs)
  - Paroxetine, sertraline, venlafaxine, fluvoxamine, escitalopram*, fluoxetine*
- Benzodiazepines
  - Clonazepam*, alprazolam*
- MAOIs*
  - Phenelzine*, moclobemide)*
- Gabapentin*, pregabalin*
- Mirtazapine*
- β-blockers*
  - Atenolol*, propranolol*
**Good Pharmacotherapy Should Also Encourage Exposure**

- Encourage patient to enter feared situations as tolerated
- Supplement medication with a patient workbook
- Supplement medication with public speaking practice (eg, Toastmasters)
- If inadequate response consider augmentation with CBT


**SSRIs**

- First-line medication for generalized SAD
- Best balance of efficacy/safety
- Effective for comorbid depression


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**“Relative Risk” of Response by Class of Medication Treatment for SAD**

Based on drug-placebo difference in response rate.


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**SSRI Response Rates (%)**

Based on drug-placebo difference in response rate.


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**Sertraline: 12-Week Trial**

Baseline Characteristics

<table>
<thead>
<tr>
<th>Sertraline (n=211)</th>
<th>Placebo (n=204)</th>
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</thead>
<tbody>
<tr>
<td>No. subjects ITT*</td>
<td>205</td>
</tr>
<tr>
<td>% male†</td>
<td>60</td>
</tr>
<tr>
<td>% white†</td>
<td>67</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>35</td>
</tr>
<tr>
<td>Mean duration of illness (yr)</td>
<td>21</td>
</tr>
<tr>
<td>Age at social anxiety onset (yr)</td>
<td>13</td>
</tr>
<tr>
<td>Mean LSAS score†</td>
<td>91</td>
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*ITT = intent-to-treat sample (ie, all randomized patients who took ≥ 1 dose and had ≥ 1 postrandomization efficacy evaluation). †Among randomized subjects.


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**Sertraline: Significantly Greater Response Rate vs Placebo**

### Sertraline: 96% Maintained Response in a Longer Term Continuation Trial

![Graph showing maintenance of response over weeks for sertraline and placebo groups.](image)


### Benzodiazepine Studies in SAD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/day)</th>
<th>Response Rate (CGI-I ≤ 2)</th>
</tr>
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<tbody>
<tr>
<td>Alprazolam</td>
<td>0.7-6.3</td>
<td>38%**</td>
</tr>
<tr>
<td>Bromazepam (off label)</td>
<td>21 mg</td>
<td>82%**</td>
</tr>
<tr>
<td>Citalopram (off label)</td>
<td>0.25-3.0</td>
<td>78%***</td>
</tr>
</tbody>
</table>

*P ≤ 0.01, **P ≤ 0.001*  
*Score on 11-item Generalized Social Phobia Scale (mean social phobia total score in mean score for general population = 19)*

CGI-I = Clinical Global Impressions-Improvement scale.


### Other Classes with RCTs in SAD (all off-label)

- **MAOIs**
  - Phenelzine efficacious, but high risk
- **Gabapentin and pregabalin**
  - Each moderately efficacious in a single trial
- **Mirtazapine**
  - Mixed results in 2 trials
- **β-adrenergic blockers (eg, propranolol)**
  - Ineffective for generalized SAD in 2 trials
  - Effective for performance anxiety in nonclinical samples


### An Adequate SSRI Trial in SAD

- 8 to 12 weeks of SSRI
- Similar dosing as used for depression
- No clear dose-response curve
- Acute responders benefit from 6 to 12 months maintenance treatment
- When treatment is tapered off after maintenance phase, 36% to 50% relapse in controlled trials

### Attention Bias Modification Therapies (ABMT)

- Attention to threat stimuli is excessive in SAD (eg, angry faces)
- Attention bias may drive cognitions and anxiety in SAD
- ABMT aims to shift attention from threat stimuli to neutral stimuli
- Most ABMT have been computer-based dot probe tasks
  - Threat and non-threat faces are displayed on screen
  - Dot appears behind one face
  - Instructions: Find the dot
  - If dot preferentially appears behind neutral face, task trains
- Attention to the neutral face
- Initially promising results have been replicated inconsistently across 15 RCTs (effect size = .27)


### A Novel Promising ABMT: Gaze-Contingent Music Reward Therapy

- Computer-based therapy
- Novel in that it rewards attention to non-threat
- Presents stimuli with 12 face matrix (threat and non-threat)
- Gaze is tracked in real time
- Visual Attention to Non-threat Faces in matrix is rewarded with music
- Large effect size in first RCT

Neuroscience-Informed Approaches: Example of Glutamate and Fear Learning

- NMDA Glutamate receptors in amygdala and hippocampus are involved in fear extinction
- Fear extinction
  - Learning that a previously feared stimulus is now safe
  - Seems impaired in phobias, PTSD
  - Believed to be key to process of exposure therapy
- D-cycloserine, glutamate NMDA receptor partial agonist, enhances extinction in animal models


D-cycloserine Treatment to Enhance Exposure Therapy

- Clinical trials of DCS given immediately before or after exposure exercises in CBT
  - Goal: To enhance learning of safety
  - Some positive results across anxiety disorders
  - Overall effects, however, have been small
    (Effect size $d = .25$ across anxiety disorders)
- Optimal dosage and timing unclear


Treatment Options Overview

- Consider subtype, comorbidity (e.g., MDD, EtOH)
- Consider CBT first (long-term efficacy and safety advantage)
- SSRIs, venlafaxine
- Off-label medications
  - Clonazepam
  - Gabapentin, pregabalin
  - Mirtazapine, MAOIs
  - PRN β-blockers, benzodiazepines (for performance type SAD)
- Alternative psychotherapies: Mindfulness, psychodynamic

MDD = major depressive disorder.

How well can a person disabled by social anxiety disorder perform after treatment?

D-cycloserine.

Zack Greinke was best pitcher in American League in 2009, after return from disability due to SAD (self-disclosed)

Recovery is Possible