



Anxiety Disorders: Differential Diagnosis and Treatment Options

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Social Anxiety Scale
(LSAS)

DSM 5 Anxiety Disorders

Panic Disorder

Agoraphobia

Generalized Anxiety Disorder

Social Anxiety Disorder

Specific Phobia

Panic Attacks

SUDDEN ONSET OF SEVERE ANXIETY

SHORTNESS OF BREATH, PALPITATIONS,
DIZZINESS, ETC.

FEAR OF “GOING CRAZY”, HAVING A
HEART ATTACK OR STROKE.

STRONG URGE TO FLEE OR SEEK URGENT
MEDICAL ATTENTION

USUALLY LAST 15-30 MINUTES

LIMITED SYMPTOM ATTACKS ARE PANIC
LIKE ATTACKS WITH FEWER SYMTPMS



Characterized by recurrent panic attacks



Followed by anticipatory anxiety- fear of having a panic attack



Followed by fear of going places or doing things where panic attacks might occur



These typically include crowded venues, bridges, tunnels, wide open spaces

Panic Disorder

Agoraphobia

Usually a consequence of having panic attacks

Fear of traveling to places where panic attacks might occur

Fear of traveling to places where access to medical attention is limited

Fear of very crowded or wide open spaces, highway driving, big bridges

Can be caused or maintained by “limited symptom attacks” rather than full panic attacks (one or two panic symptoms)

Generalized Anxiety Disorder

- ♦ Excessive anxiety and worry about a variety of topics, events or activities
- ♦ The worry is very difficult to control
- ♦ The anxiety and worry are accompanied by at least 3 of the following:
 - ♦ edginess or restlessness,
 - ♦ fatigue, trouble concentrating,
 - ♦ irritability,
 - ♦ muscle aches or soreness
 - ♦ Insomnia
 - ♦ In clinical settings co-morbid depressive symptoms are often present

♦ Hamilton Anxiety Scale

Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe

Anxious mood Worries, anticipation of the worst, fearful anticipation, irritability.	<div>01234</div>	8 Somatic (sensory) Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.	<div>01234</div>
Tension Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.	<div>01234</div>	9 Cardiovascular symptoms Tachycardia, palpitations, pain in chest, throbbing of vessels, faint feelings, missing beat.	<div>01234</div>
Fears Fear of dark, of strangers, of being left alone, of animals, of traffic, of crowds.	<div>01234</div>	10 Respiratory symptoms Pressure or constriction in chest, choking feelings, sighing, dyspnea.	<div>01234</div>
Insomnia Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.	<div>01234</div>	11 Gastrointestinal symptoms Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.	<div>01234</div>
Intellectual Difficulty in concentration, poor memory.	<div>01234</div>	12 Genitourinary symptoms Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.	<div>01234</div>
Depressed mood Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.	<div>01234</div>	13 Autonomic symptoms Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.	<div>01234</div>
Somatic (muscular) Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.	<div>01234</div>	14 Behavior at interview Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing etc.	<div>01234</div>

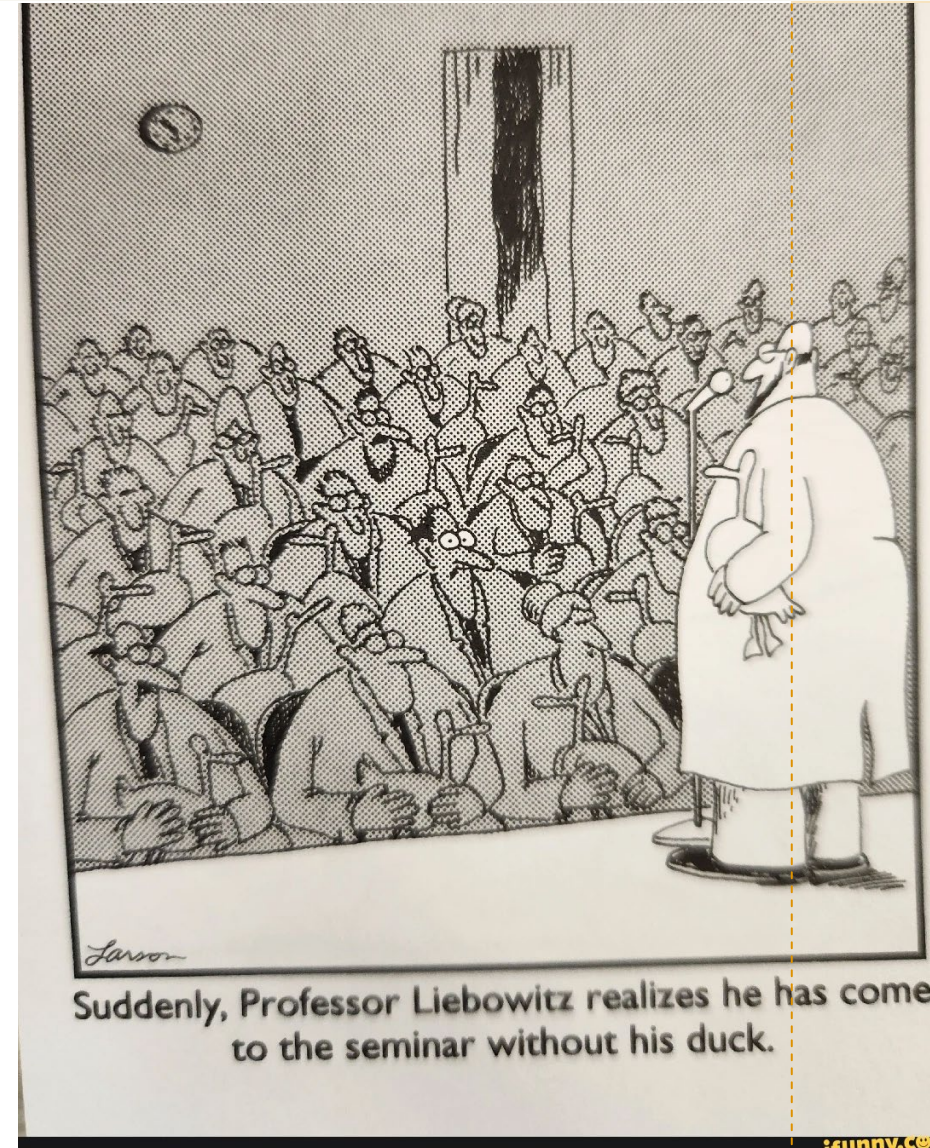
Social Anxiety Disorder (SAD)

- ♦ Fear or anxiety about specific social or performance situations due to concerns about being judged negatively, embarrassed or humiliated
- ♦ Avoidance of anxiety-producing social situations or enduring them with dread
- ♦ May be limited to only performance situations (“performance only” subtype)
- ♦ Or may involve both performance and a variety of interpersonal or social situations (in DSM 5 Social Anxiety Disorder; in DSM IV Generalized Subtype of SAD)
- ♦ SAD can be 2nd to embarrassment of having physical symptoms like a tremor if the fear and avoidance are “excessive” for that level of physical symptomatology

Symptoms of Social Anxiety

- ♦ The princess glanced in a scared way at her father's eyes, gleaming close beside her. The red patches overspread her face, and it was evident she did not understand a word, and that terror prevented her from understanding all the subsequent explanations her father offered her...
- ♦ The princess's eyes grew dim; she could see and hear nothing; she could feel nothing but the dry face of her stern father near her, his breath and the smell of him, and could think of nothing but how to escape as soon as possible from the study and to make out the problem in freedom in her own room.
 - ♦ Leo Tolstoy: War and Peace, 1865

All of us are capable
of experiencing social
anxiety



Liebowitz Social Anxiety Scale (LSAS)

- ♦ 24 item scale assesses severity and change in individuals with social anxiety disorder
- ♦ Has 13 situations related to performance anxiety- e.g. giving a speech, being observed while working, using a public bathroom, etc.
- ♦ Has 11 situations related to social interaction anxiety- e.g. going to a party where you know half the people, meeting someone you don't know, etc.
- ♦ Each situation is rated for fear / anxiety: none (0), mild (1), moderate (2) or severe (3) and for avoidance : none (0), occasionally (1-33%) (1), often (4-66%) (2) or usually (67-100%) (3).
- ♦ Not a diagnostic instrument; could have high score from depression or paranoia.

Liebowitz Social Anxiety Scale (LSAS)

Liebowitz Social Anxiety Scale (LSAS)		Fear or Anxiety		Avoidance	
		0 = None 1 = Mild 2 = Moderate 3 = Severe		0 = Never (0%) 1 = Occasionally (1-33%) 2 = Often (34-66%) 3 = Usually (67-100%)	
Items		Anxiety (S)	Anxiety (P)	Avoid (S)	Avoid (P)
1. Telephoning in public. (P)					
2. Participating in small groups. (P)					
3. Eating in public places. (P)					
4. Drinking with others in public places. (P)					
5. Talking to people in authority. (S)					
6. Acting, performing or giving a talk in front of an audience. (P)					
7. Going to a party. (S)					
8. Working while being observed. (P)					
9. Writing while being observed. (P)					
10. Calling someone you don't know very well. (S)					
11. Talking with people you don't know very well. (S)					
12. Meeting strangers. (S)					
13. Urinating in a public bathroom. (P)					
14. Entering a room when others are already seated. (P)					
15. Being the center of attention. (S)					
16. Speaking up at a meeting. (P)					
17. Taking a test. (P)					
18. Expressing a disagreement or disapproval to people you don't know very well. (S)					
19. Looking at people you don't know very well in the eyes. (S)					
20. Giving a report to a group. (P)					
21. Trying to pick up someone. (P)					
22. Returning goods to a store. (S)					
23. Giving a party. (S)					
24. Resisting a high pressure sales person. (S)					
Total Performance (P) Subscore					
Total Social (S) Subscore					
Total Anxiety & Avoidance Subscore					
Total LSAS Score					

Rater Signature: _____

Date: _____

Severity of Social Anxiety Disorder

- ♦ Total LSAS < 30: no social anxiety disorder
- ♦ Total LSAS 30-50: either performance only or mild social anxiety disorder
- ♦ Total LSAS 51-70: moderate social anxiety disorder with symptomatic distress but not much functional impairment in academic, work or social life
- ♦ Total LSAS > 70-90: marked social anxiety disorder with likely functional impairment in academic, vocational and social functioning
- ♦ Total LSAS > 90; severe social anxiety disorder with likely severe functional impairment in academic, vocational and social functioning

Specific Phobias

- ♦ Marked fear or anxiety about a specific object or situation such as:
 - ♦ flying,
 - ♦ heights,
 - ♦ particular animals,
 - ♦ blood or injections
- ♦ The particular object or situation is always avoided or endured with dread
- ♦ The fear, anxiety or avoidance is a source of significant distress or functional impairment

Conditions That Can Be Mistaken for a DSM 5 Anxiety Disorders

- ♦ Agitated Depression vs Generalized Anxiety Disorder: look for psychomotor arousal
- ♦ Obsessive Compulsive Disorder vs Generalized Anxiety Disorder: worries in GAD tend to be less specific and lack ritualistic behaviors
- ♦ Paranoia vs Social Anxiety; fear of being harmed vs fear of being embarrassed
- ♦ A person with a severe physical symptom or issue who becomes socially avoidant
- ♦ Normative shyness or introversion that is not a source of distress or impairment
- ♦ Adjustment disorder with anxiety vs generalized anxiety disorder; the former is stress related, is not associated with a prior anxiety disorder, and clears after the stressor abates

Other Issues of Differential Diagnosis

Primary affective disorder

Schizoid personality disorder

Autism spectrum disorder

Offensive form of SAD

SAD with comorbid ADHD

Body dysmorphic disorder

ASD Features Distinct from SAD

Intrusive behavior

Perseveration

Compulsions

Inability to read non-verbal cues

Invasive social behaviors

Poor impulse control

Disregard for others feelings

Standard Treatments for Anxiety Disorders

SSRIs: can treat panic disorder, agoraphobia, GAD and social anxiety disorder

SNRIs: can treat panic disorder, agoraphobia, GAD and social anxiety disorder

Tricyclics: can treat panic disorder, agoraphobia, GAD

Benzodiazepines: can treat panic disorder, agoraphobia, GAD and social anxiety disorder

Beta blockers: propranolol can treat performance only form of social anxiety disorder

SSRI Treatment of Anxiety Disorders

For panic disorder, start with low dose to not aggravate condition, e.g. 5-10 mg fluoxetine.

For social anxiety disorder, doses higher than those used for depression may ultimately be required, e.g. paroxetine 40 mg/day or more.

With social anxiety, SSRI monotherapy benefits 50-60% of patients and achieves remission in about 25%.

Dosing for GAD is similar to dosing for depression.

Benzodiazepines can augment incomplete responses to SSRIs.

SNRI Treatment of Anxiety Disorders

Similar to SSRI treatment

Panic Disorder: start low and titrate up as needed to fully block panic attacks. When correct dose is reached, unlike depression, efficacy occurs quickly.

Social Anxiety Disorder: Efficacy for venlafaxine extended release is in the antidepressant dose range.

GAD: Both venlafaxine ER and duloxetine work well in antidepressant dose range.

When treating GAD or social anxiety disorder, look for history of unexpected panic attacks which could confer heightened sensitivity to initial doses of SNRIs or SSRIs.

Fetzima not approved and not well studied in anxiety disorders.

Tricyclic Treatment of Anxiety Disorders

TCAs: imipramine, nortriptyline, desipramine, clomipramine

Work well in panic disorder; need to start low, e.g. imipramine 10 mg

Work well in GAD; dosing similar to treating depression.
Imipramine starting dose of 25 mg, aiming for 100- 300 mg day

TCAs do not seem effective in social anxiety disorder

Can monitor blood levels of TCAs; for nortriptyline, optimal dose range is

50-150 ng/ml, with less effectiveness below or above this range

Combining SSRIS and Tricyclics

- ♦ If patient is on fluoxetine or sertraline and you want to switch to SNRI, you can instead add nortriptyline, which is mostly noradrenergic.
- ♦ But fluoxetine triples co-administered nortriptyline levels while sertraline has no effect. A patient taking fluoxetine and nortriptyline who switches SSRI to sertraline will have to take much more nortriptyline to have the same level.
- ♦ Clomipramine is the most serotonergically active TCA and is effective for OCD. Adding fluoxetine has the effect of inhibiting the conversion of clomipramine to desmethylclomipramine. The metabolite is less serotonergic and less helpful for OCD. But be mindful of possible serotonin syndrome toxicity- restlessness, confusion, sweating, diarrhea, fever, muscle rigidity.

Newer Antidepressants for Anxiety

Vilazodone- 20-40 mg/ day found useful for GAD and for social anxiety disorder

Desvenlafaxine- 50-100 mg/ day found helpful for social anxiety disorder

Vortioxetine- SSRI like plus direct effect on 5HT receptors. Seems effective in GAD and social anxiety disorder at 10-20mg/ day range

Placebo controlled trial of vortioxetine in patients with MDD and social anxiety disorder: Responder rate on CGI-I was 50% on drug and 30% on placebo at 12 weeks. Depression symptoms responded more quickly than social anxiety (Liebowitz et al, Depression and Anxiety, 2017.)

Other Medications for Anxiety Disorders

Buspirone: limited effectiveness in GAD; used as augmentation

Pregabalin and gabapentin can be helpful for GAD and social anxiety disorder

Hydroxyzine: Used at times when avoiding benzodiazepines

MAOIs: Useful in social anxiety disorder and atypical depression, where interpersonal hypersensitivity are prominent

Oxytocin has been studied in social anxiety disorder and generalized anxiety disorder with inconclusive results

D-cycloserine (DCS) has been studied as an augmentation for CBT in anxiety disorders also with inconclusive results

Investigational Medications for Anxiety Disorders

- ♦ Cannabidiol with and without THC being studied for anxiety disorders.
- ♦ Other psychedelics such as psilocybin and LSD also being studied for anxiety and depression.
- ♦ Fatty acid amide hydrolase (FAAH) inhibitors affect the endocannabinoid system. A study in social anxiety disorder was not successful.
- ♦ Ulotaront, a trace amine associated receptor 1 (TAAR1) agonist with 5HT1A agonist activity is being studied for GAD, as well as schizophrenia and adjunctively for MDD.
- ♦ An alpha 7 nicotinic acetylcholine receptor partial agonist and an alpha 7 nicotinic acetylcholinergic receptor negative allosteric modulator both failed to separate from placebo on their primary outcome measures in public speaking studies of social anxiety disorder but are continuing to be studied.

Public Speaking Challenge (PSC) Studies

Subjects screened for social anxiety disorder and minimum level of severity.

Subjects taught to rate immediate level of anxiety on Subjective Units of Distress (SUDS) scale: 0=none, 30=mild, 60=moderate, 90=severe, 100=worst ever.

Challenge involves giving 5 minute speech in front of small audience with minute by minute ratings of anxiety level.

One design: single challenge where subjects are pretreated with test medication or placebo on double blind basis

Another design: first challenge- all subjects pretreated with placebo single blind; next week those with high SUDS scores get second challenge with drug or placebo on double blind basis.

Fasedienol (PH94B) in Social Anxiety Disorder

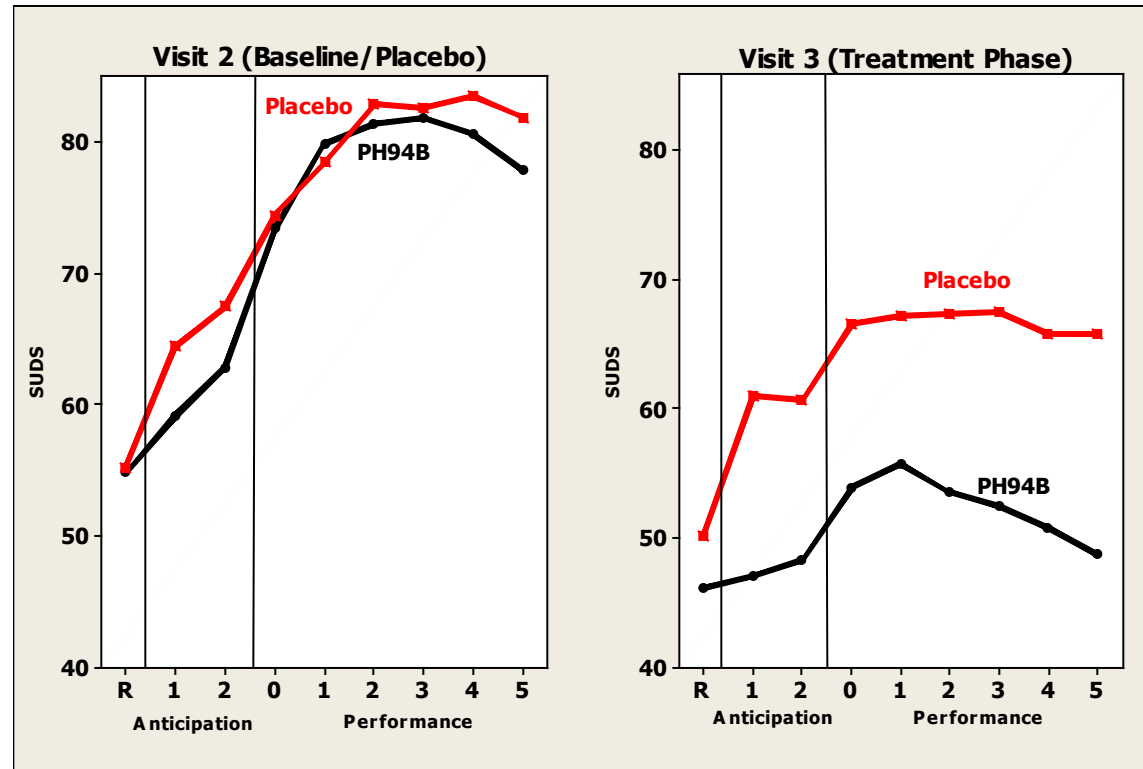
Investigational drug in a synthetic neuroactive steroid nasal spray that acts in microgram doses on nasochemosensory receptors in the midline of the nose.

Phase 2 trials were positive in a study using public speaking and social interaction challenges as well as a 4 week real world double blind crossover trial of PRN use.

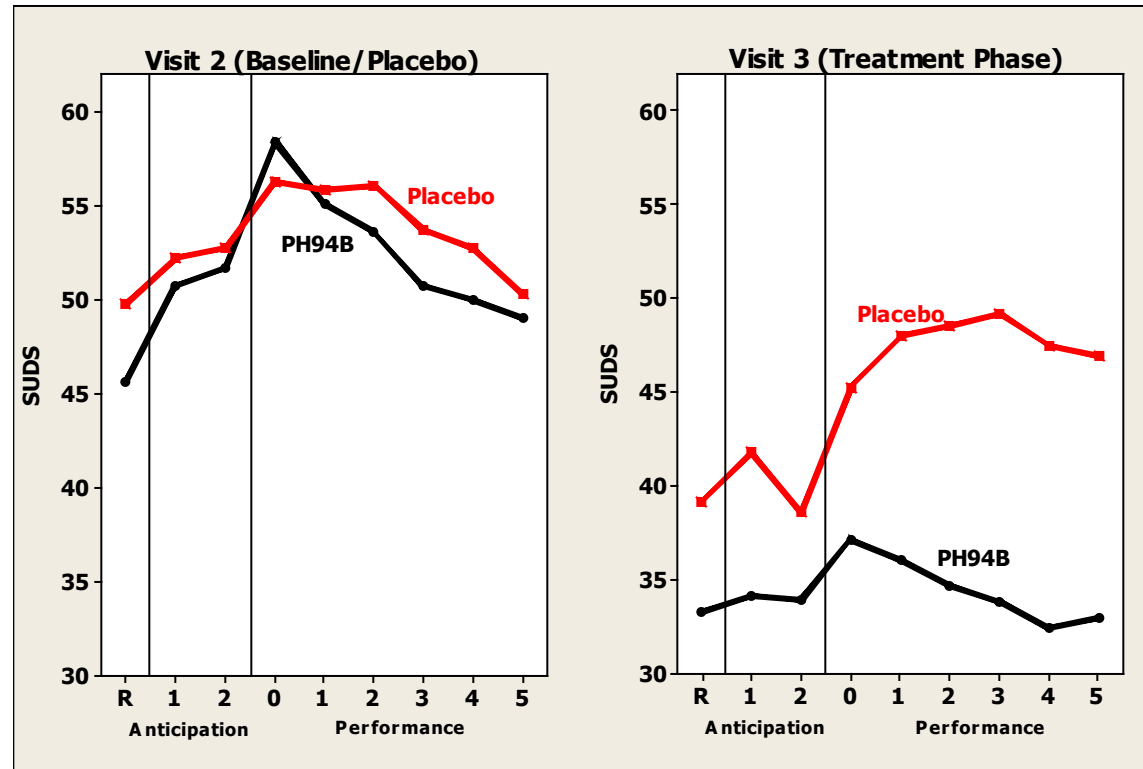
The first phase 3 trial using just a public speaking challenge failed but in a second trial fasedienol significantly separated from placebo.

If further trials are successful, fasedienol could be used as a stand alone treatment, an adjunct to other medications or a supplement to CBT.

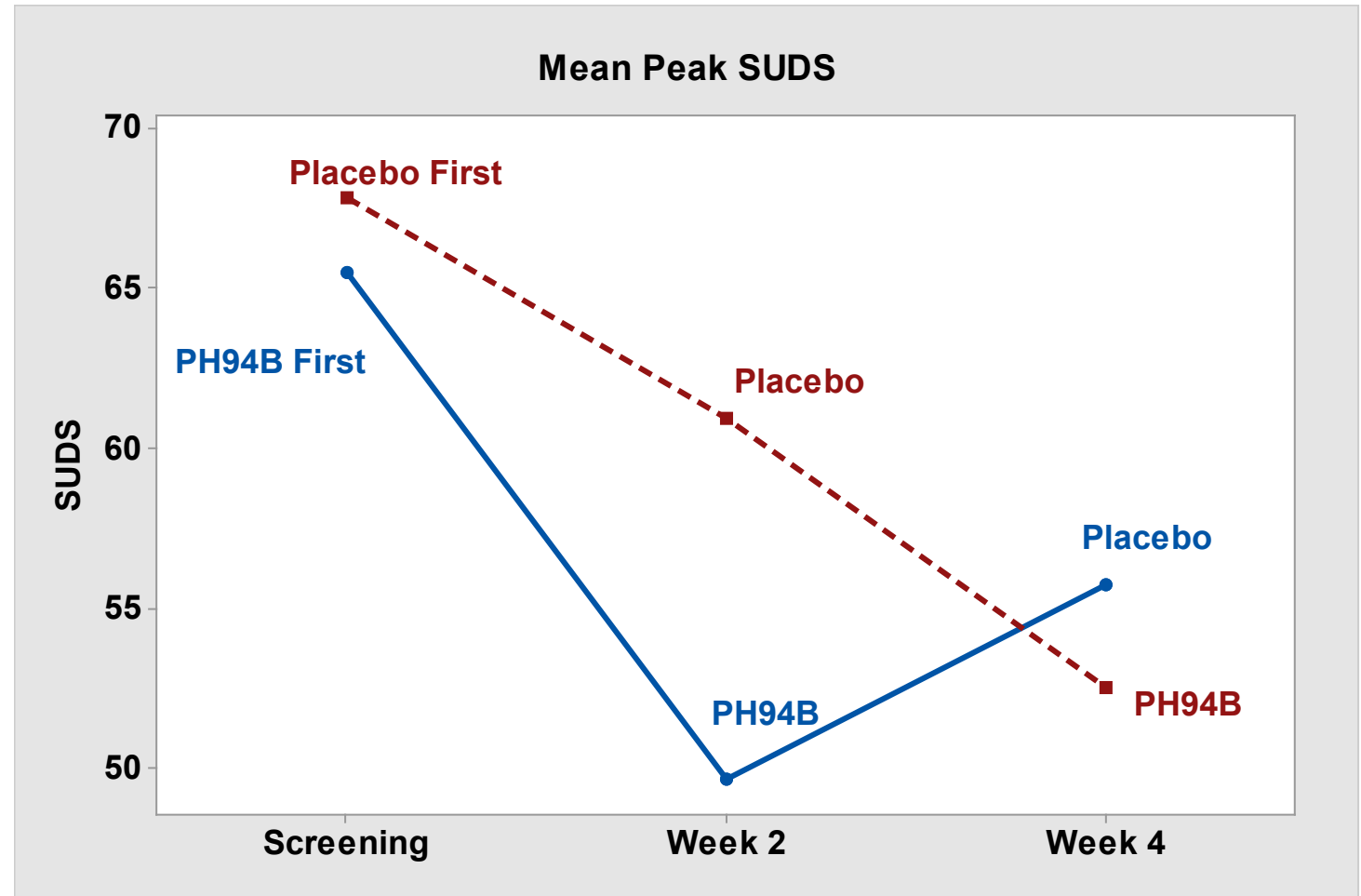
SUDS Ratings: Public Speaking Challenge of PH94B vs Placebo



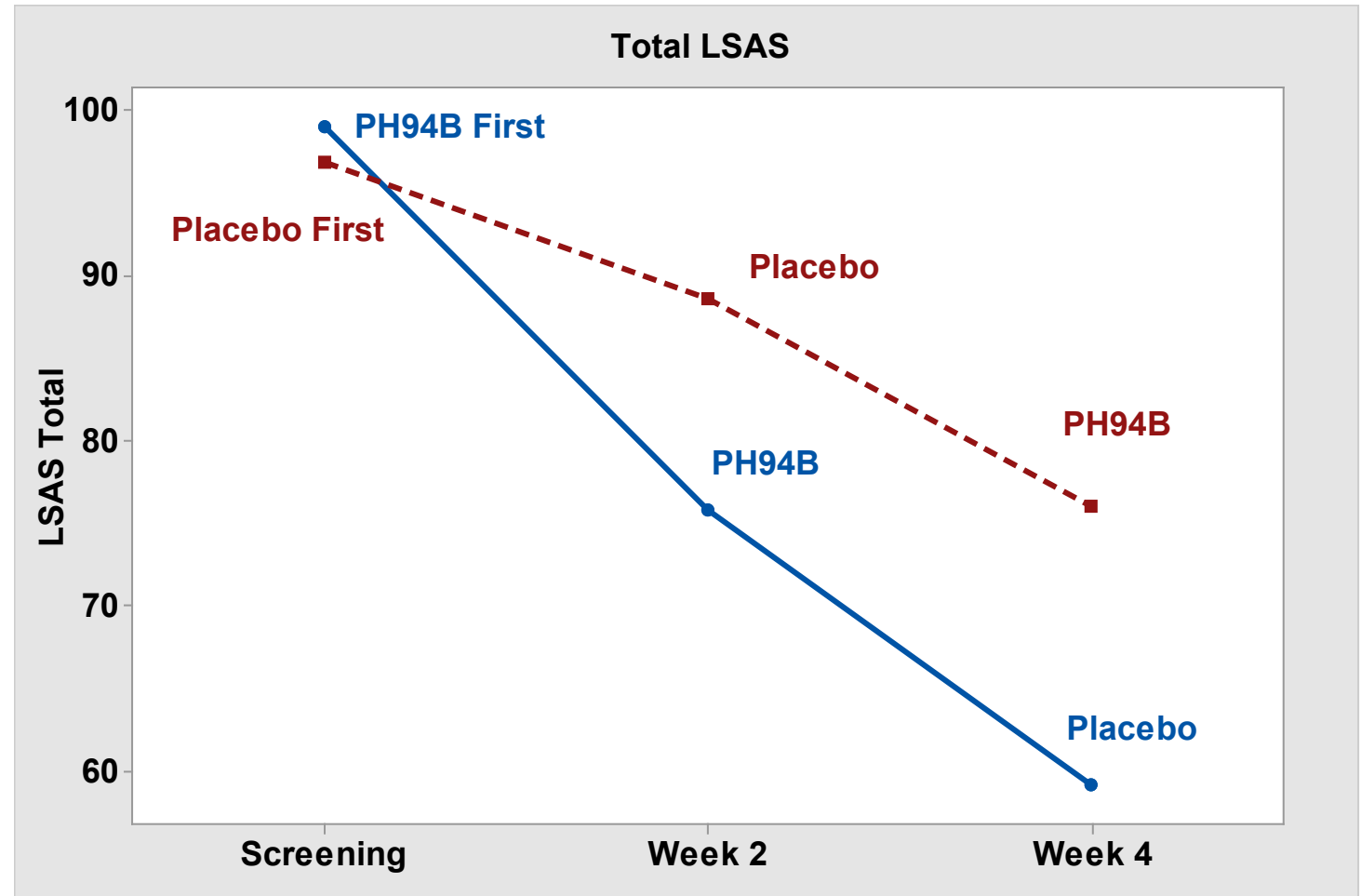
SUDS Ratings: Social Interaction Challenge of PH94B vs Placebo



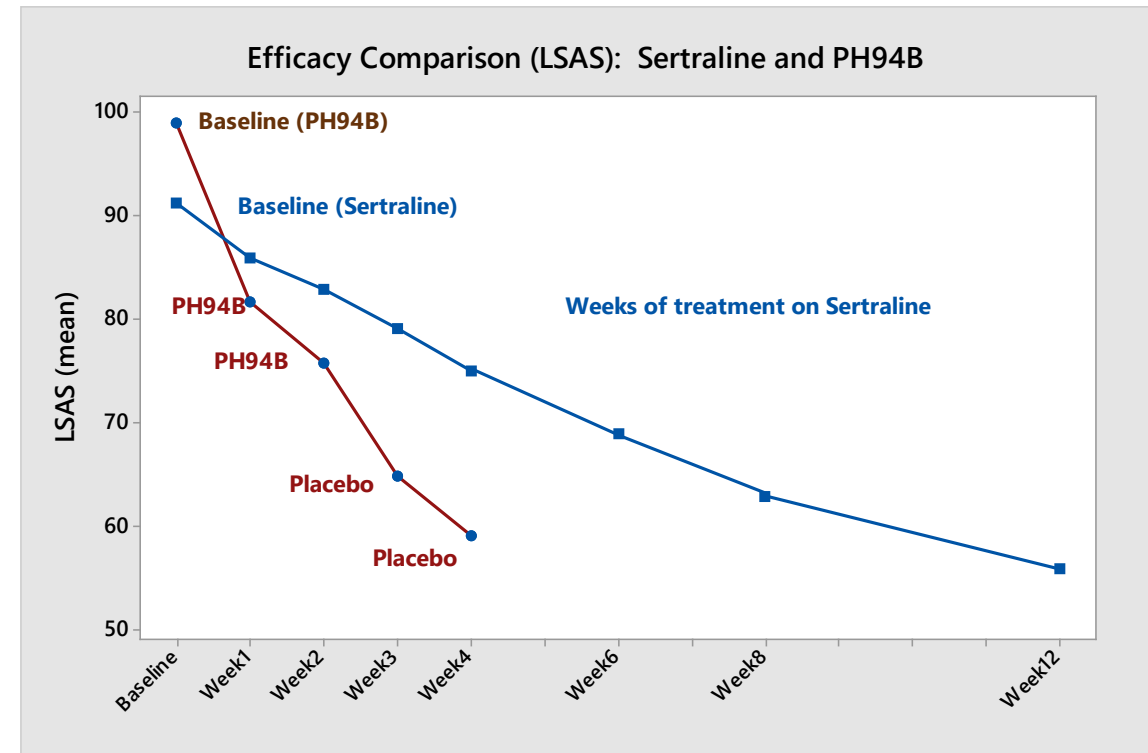
SUDS Rating: 4 week crossover trial of PH94B vs placebo



LSAS Rating: 4 week crossover trial of PH94B vs Placebo

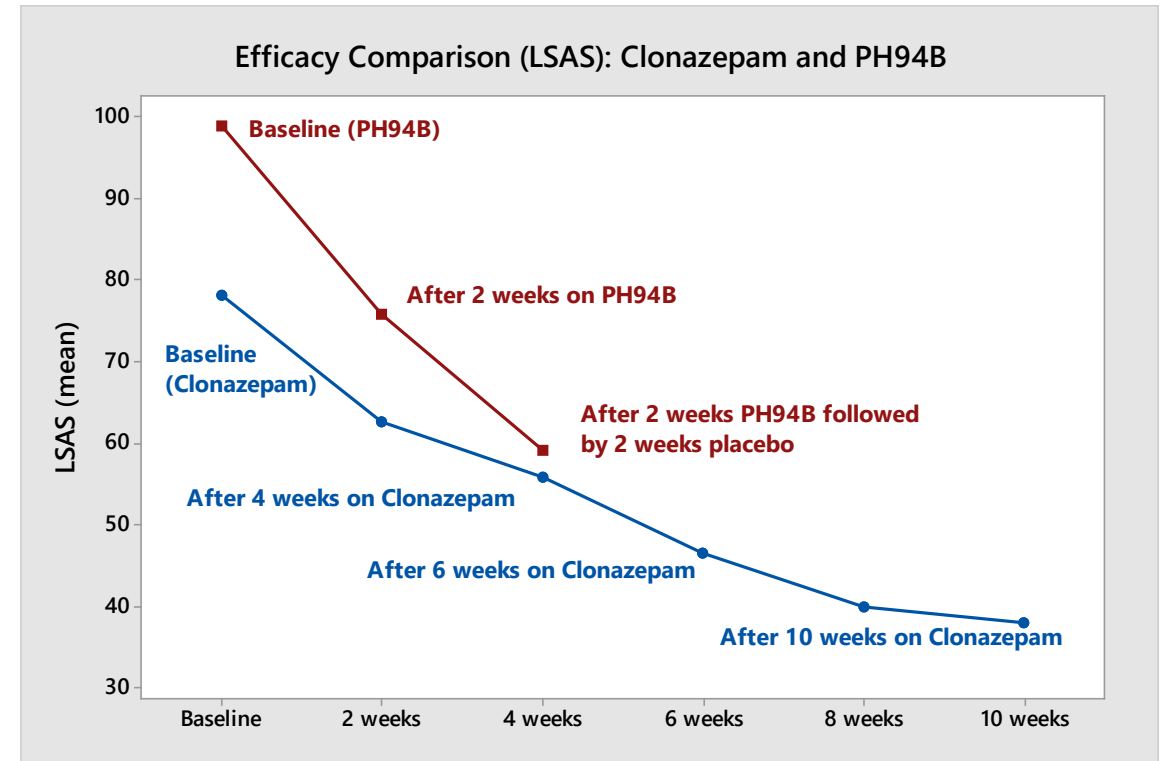


Sertraline Findings vs PH94B Findings for SAD (not head to head)



Clonazepam vs PH94B for SAD (not head to head)

♦ (



Difficult to Treat Case of SAD

Single male in his early 40's

Wants to get married

Reports difficulty connecting with women he dates

Is fairly isolated socially

Lives with mother, works in family business

In social interactions always searching for the perfect thing to say next; focuses on himself and not the person he is with

Intellectually ok

Was more socially comfortable in grade school

Difficult to Treat Case of SAD (2)

Not much benefit from sertraline

Not much benefit from duloxetine
supplemented with risperidone

Some benefit from prn clonazepam

Some benefit from glass of wine before a date

Not much benefit from cognitive therapy

Has not had rigorous CBT

Treatment of Difficult OCD Cases

- ♦ Push SSRI to high dose if needed.
- ♦ Use genetic testing to see how patient metabolizes meds
- ♦ Add low dose neuroleptic; best evidence for Risperdal or Abilify
- ♦ Switch SSRI to clomipramine and monitor blood levels
- ♦ Combine clomipramine with fluoxetine to achieve higher levels of clomipramine and lower levels of desmethylclomipramine
- ♦ Combine medication treatment with exposure and response prevention