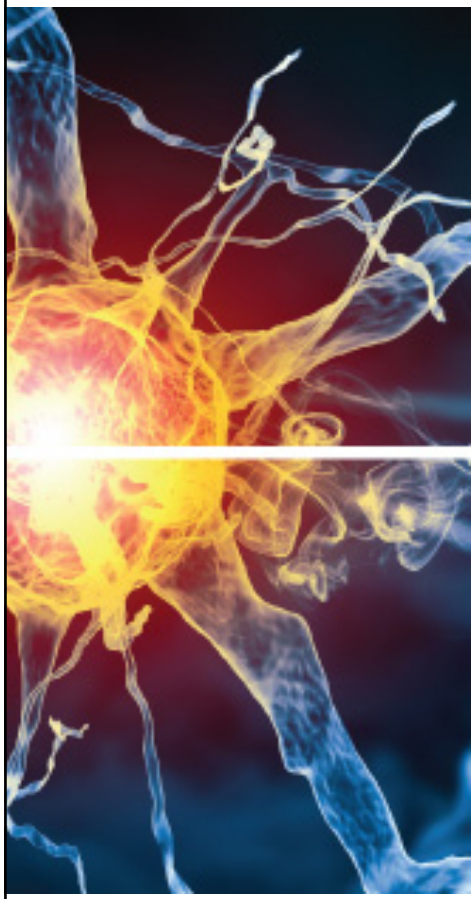
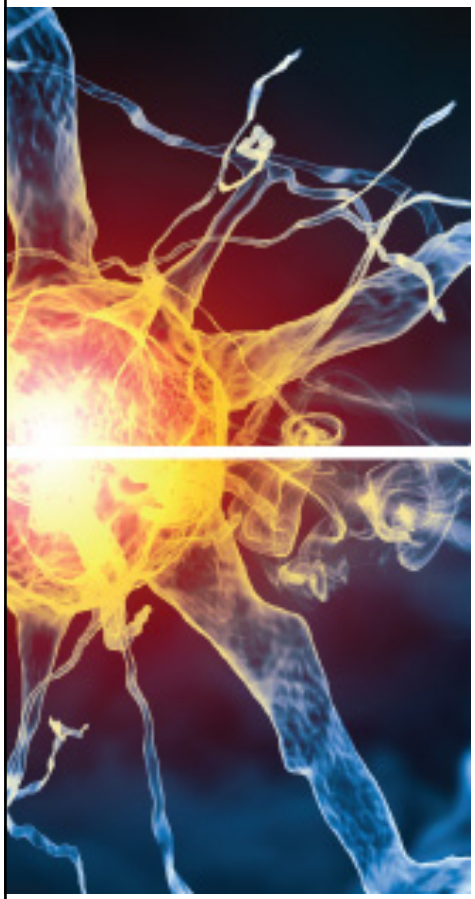


Optimal Treatment of Anxiety Disorders



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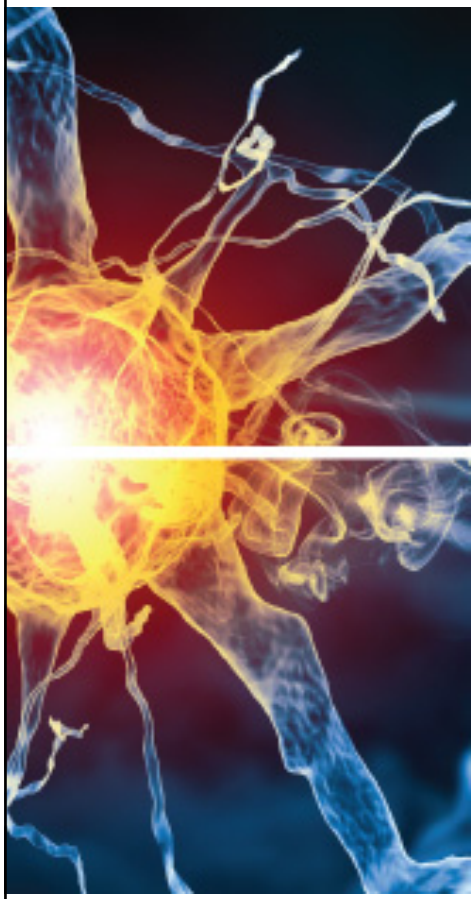
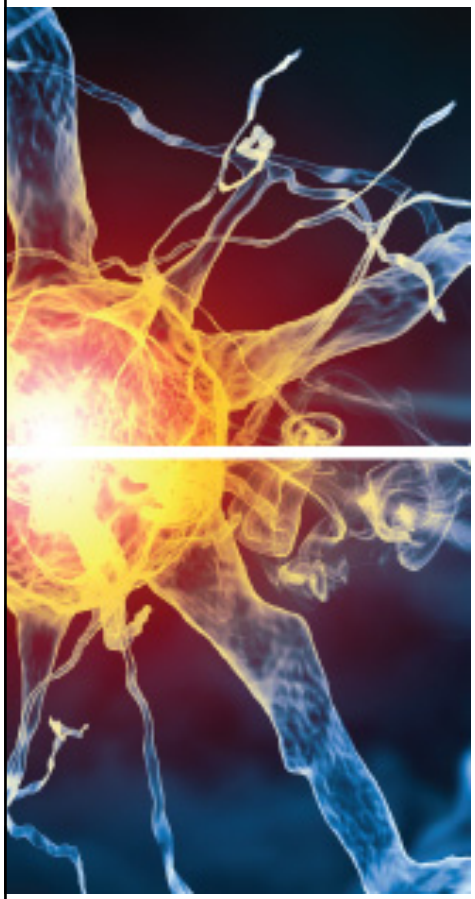
- ***Grants and Research Support***: Forest Laboratories, Inc./Allergan



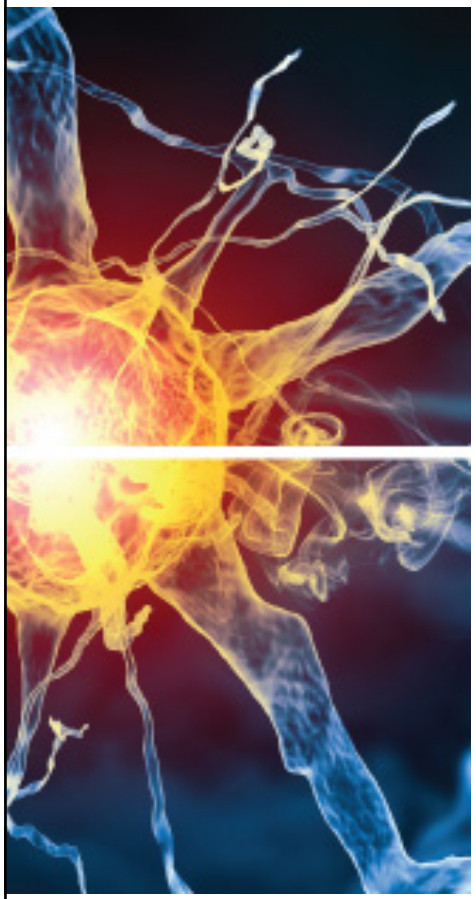
1 Learning Objective

Evaluate features across anxiety disorders.



2 Learning Objective

Implement best practices in the assessment of anxiety disorders.



3 Learning Objective

Select appropriate treatments in anxiety disorders to optimize patient outcomes.

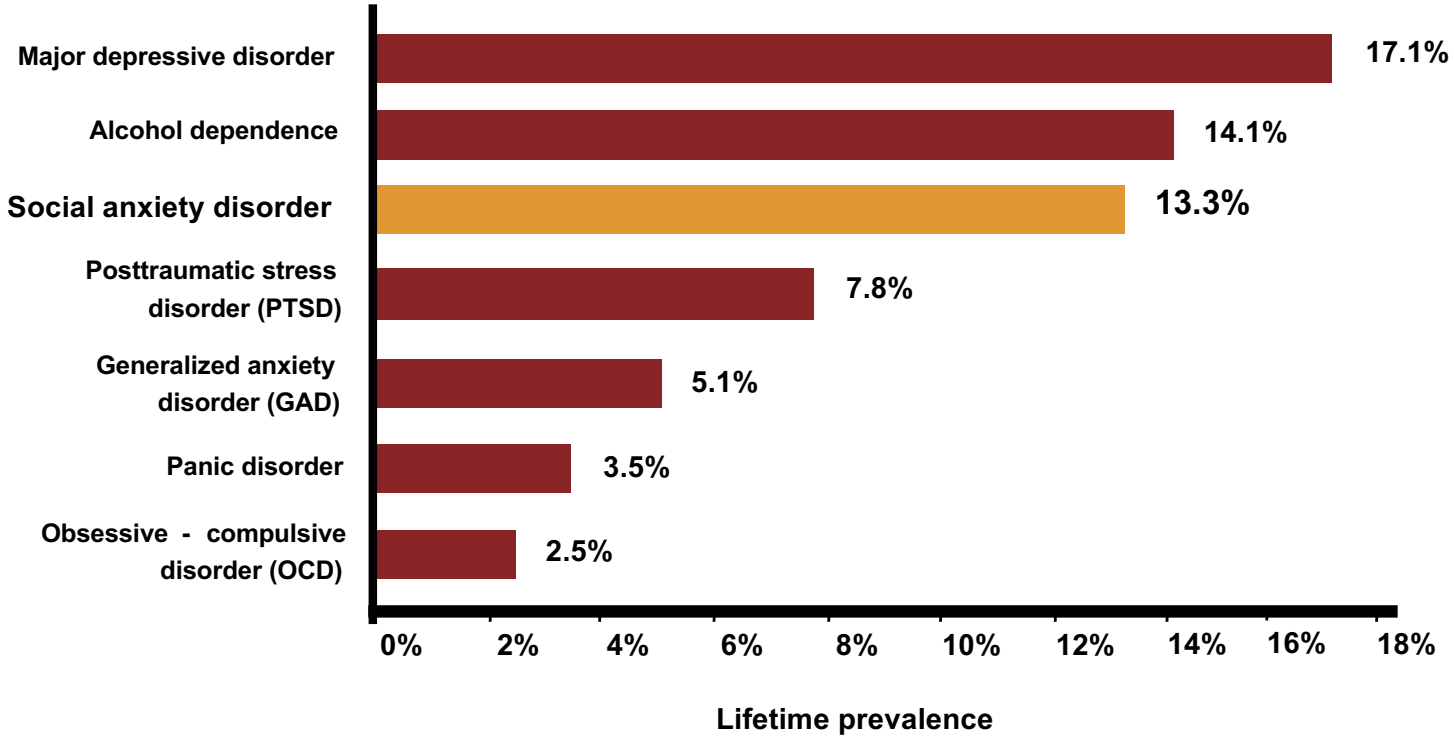
Agenda

- Anxiety Disorder Diagnosis
  - Features common across anxiety disorders
  - Features specific to each disorder
- Approaches to Assessment
- Psychotherapy (Cognitive Behavioral Therapy, CBT)
- Pharmacotherapy
- Optimizing treatments

Anxiety Disorders

- Panic Disorder
- Agoraphobia
- Specific Phobias
- Social Anxiety Disorder (a.k.a. Social Phobia, Social AD)
- Generalized Anxiety Disorder (GAD)
- Separation Anxiety Disorder (SAD)
- Selective Mutism
- Post-Traumatic Stress Disorder (PTSD), Obsessive-Compulsive Disorder (OCD)

Lifetime Prevalence of Psychiatric Disorders

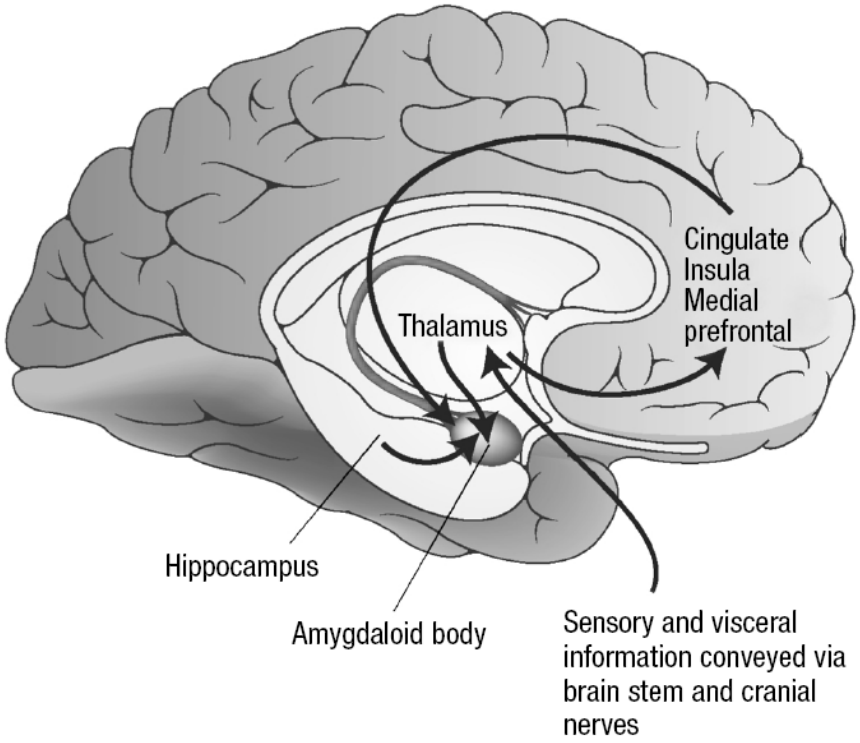


Kessler RC, et al. *Arch Gen Psychiatry*. 1994;51(1):8-19.

Commonalities Across Anxiety Disorders

- Anxiety and Avoidance Behavior prominent
- Early-onset, often chronic
- More prevalent in women (2:1 ratio)
- Significant social and occupational disability
- Risk factor for depression, alcohol abuse, suicide
- Treatments available but underutilized

Fear Neurocircuitry



Kent JM, et al. *Curr Psych Rep*. 2003;;5(4):266-73.

SSRIs 1st Line Pharmacotherapy For:

- Generalized anxiety disorder
- Social anxiety disorder
- Obsessive-compulsive disorder
- Posttraumatic stress disorder
- Panic disorder

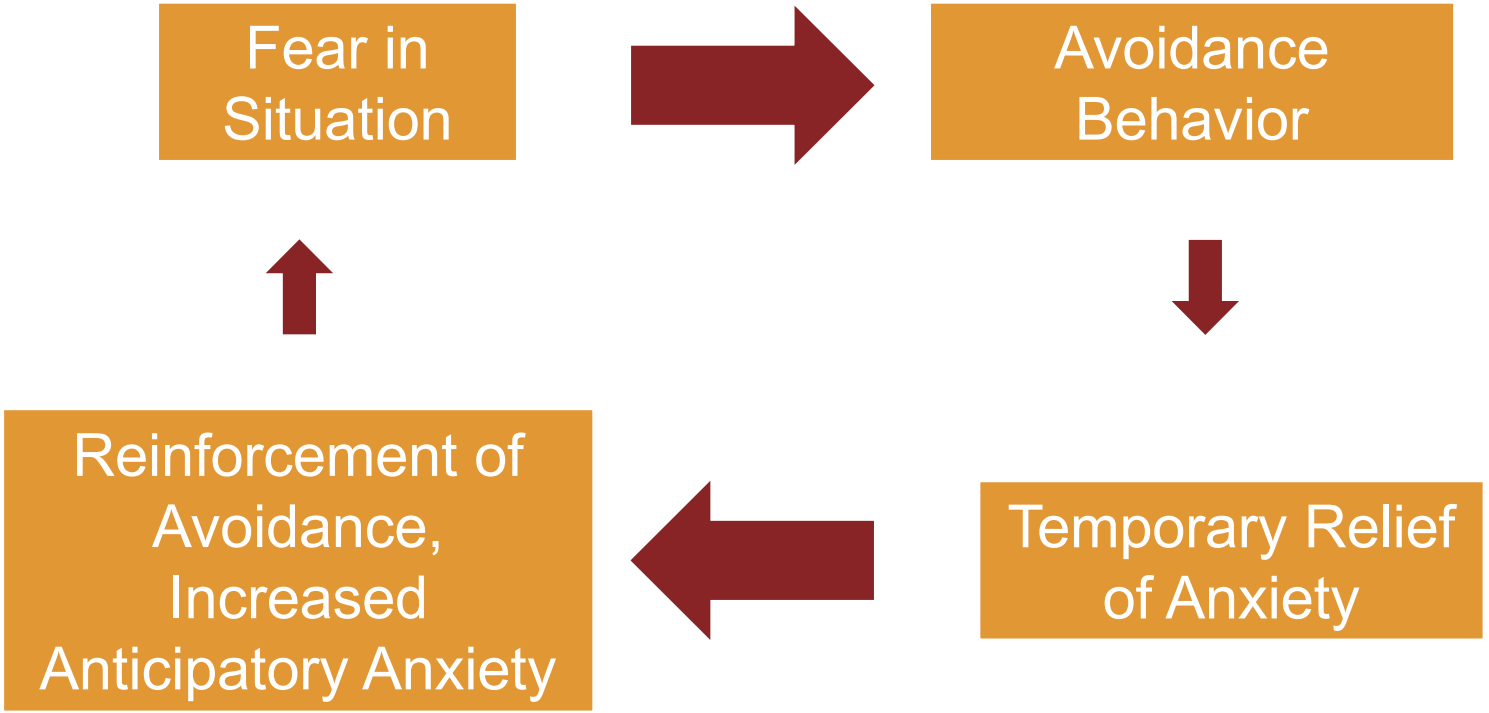
National Insitutes of Health. Available at: https://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml. Accessed on June 6, 2017.

Koenig M, et al. *Pol Arch Med Wewn*. 2009;119(7-8):478-486.

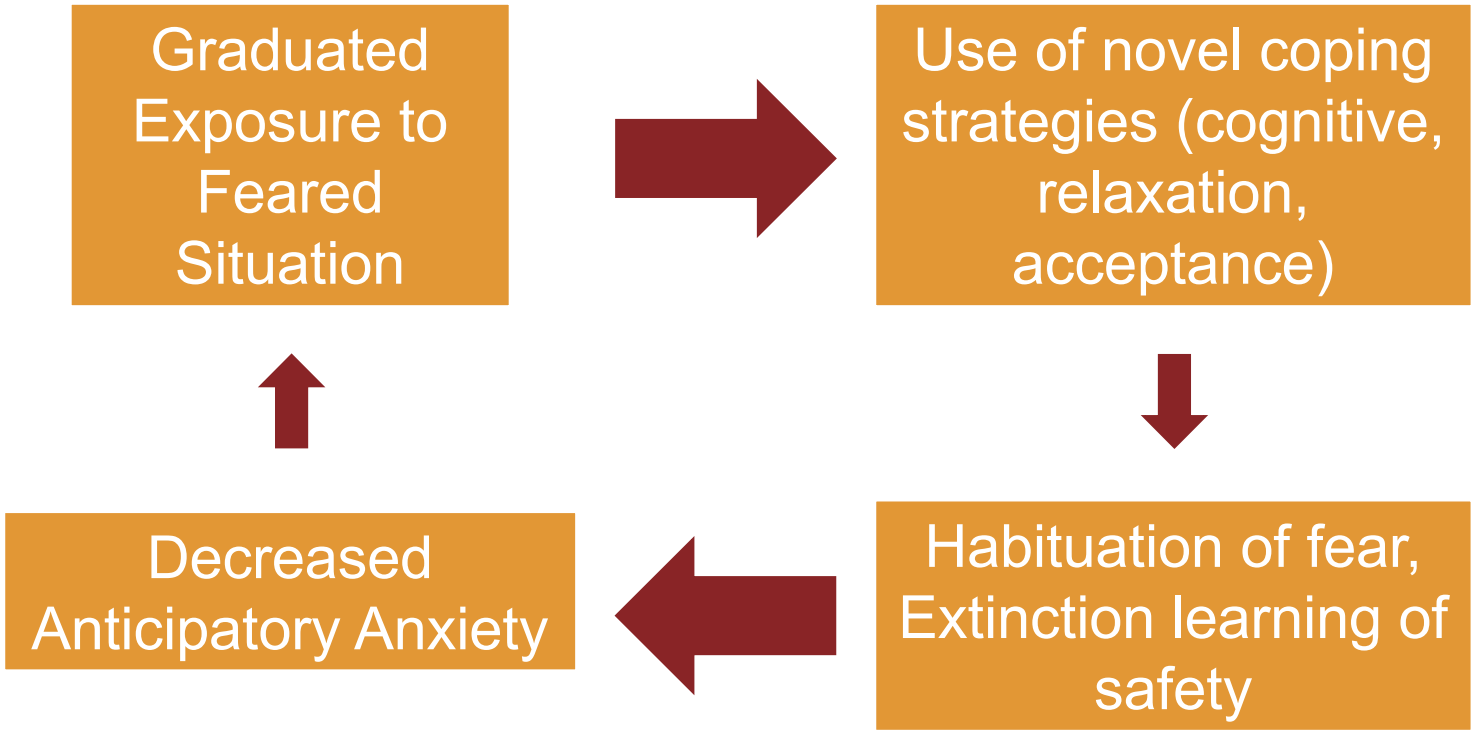
Anxiety Disorders

	Panic Disorder	Social Anxiety Disorder	Generalized Anxiety Disorder
Typical Cognitions	Fear of dying, losing control, heart attack	Fear of embarrassment, negative evaluation	Worries about $, safety, future, relationships
Typical Physical Symptoms	Dyspnea, palpitations, lightheaded	Blushing, sweating, trembling	Tension, insomnia, restlessness
Typical Behaviors	Avoid closed spaces, being alone. Seek medical tests.	Avoid public speaking, social interactions	Avoid reminders of worry, seek reassurance

Maintenance of Fear and Avoidance



CBT Approach to Fear and Avoidance



Cognitive-Behavioral Therapy

- Strongest evidence-base of psychotherapies for anxiety
- Components:
  - Psychoeducation and cognitive restructuring
  - **Exposure** to feared situations
  - Sometimes also relaxation
- Typically 10-20 weekly sessions over a few months
- Some techniques specific to each anxiety disorder
  - PTSD: prolonged exposure to traumatic memories
  - OCD: exposure and response prevention (of compulsions)
  - Social AD: roleplaying exposure to social situations
  - Panic: interoceptive exposure to feared bodily sensations

Medication and/or Psychotherapy

- In several anxiety disorders there is an evidence base comparing pharmacotherapy vs. CBT1
  - In OCD and PTSD, CBT efficacy > medication efficacy[1]
- Combined medication + CBT is sometimes superior, but can also introduce problems[2]
- Select modality based on efficacy data, expert CBT availability, patient preference

1 Borkovec, et al. *J Clin Psychiatry*. 2001;62(Suppl11):37-42.

2 Arch J, et al. J. *Consult Clin Psychol*. 2012;80(5):750-765.

Planning Pharmacotherapy

- Anxiety disorder patients are often also anxious about meds
- Useful to discuss adverse effects, even for hypochondriacal
- Inviting communication may increase adherence
  - Avoidance is default option for many anxiety disorder patients
- Encourage gradual self-exposure to feared situations

Benzodiazepines

- Widely used, but controversial and often misunderstood
- Risks: [1-3]
  - Abuse and dependence
  - Dangerous with excessive alcohol
  - Motor impairment (falls in elderly)
  - Cognitive impairment (potential to interfere w/CBT)
  - Discontinuation difficulties

1 Olfson M, et al. *JAMA Psychiatry*. 2015;72(2):136-142.
2 Gray SL, et al. *BMJ*. 2016;352:i90.
3 Johnson B, et al. *Am Fam Physician*. 2013;88(4):224-225.

Evidence-Based Indications for Benzodiazepines

- GAD, SAD, Panic1
- Other situational anxiety – as needed use[1]
- Little evidence for efficacy in OCD, PTSD
- Often problematic in substance abusers, personality disorders, primary major depressive disorder (MDD)[2]

1 Stevens JC, et al. *Clin Psychiatry*. 2005;66(Suppl 2): 21–27.

2 Charlson F, et al. *Pharmacoepidemiol Drug Saf*. 2009;18(2):93–103.

Benzodiazepine Dosing in Panic, Social Anxiety Disorders

- **As-needed** for situational anxiety or augmentation[1]
- **Standing** dose is usually more effective[2]
  - If feared situations/panic attacks are frequent
  - Prevents anxiety rather than chasing it
  - Tolerance usually develops to early sedation
  - Dose typically increased to 1-4 mg/day of clonazepam[1]
  - Usually a sustained response at stable dose is possible
  - Watch for between-dose rebound anxiety

1 Benzodiazepine. [Package Insert]. Drugs@FDA Website. 2011.

2 Cassano GB, et al. *Dialogues Clin Neurosci*. 2002;4(3):271-285.

Should Benzodiazepines Ever be a Long-Term Treatment?

- In panic and social anxiety disorder there is evidence for sustained efficacy, with doses stable over time[1]
- Cognitive impairment is usually mild; risk must be weighed against risk of impairment from anxiety[1,2]
- But risks increase with advancing age[3]

1 Cassano GB, et al. *Dialogues in Clinical Neuroscience*. 2002;4(3):271-285.

2 Stewart SA, et al. *J Clin Psychology*. 2005;66 Suppl 2:9-13.

3 Barker MJ, et al. *CNS Drugs*. 2004;18(1):37-48.

Generalized Anxiety Disorder (GAD)

- Excessive worry across multiple domains
- Somatic anxiety symptoms: restless, fatigue, tension, insomnia
- Psychic anxiety symptoms: difficulty concentrating, irritability
- Highly comorbid, especially w/ MDD
- Most common anxiety disorder in the elderly

SSRI/SNRI Treatment of GAD

- 1st line pharmacotherapy
  - safety advantages vs. benzodiazepines, tricyclics
- FDA-approved for GAD[1]: paroxetine, escitalopram, venlafaxine ER, duloxetine
- No consistent superiority of one SSRI/SNRI over another[2]

1 [Package Insert]. Drugs@FDA Website.

2 Farach F. Et al. *J Anxiety Disord*. 2012;26(8):833-843.

Response and Remission (ITT) across 3 Escitalopram Trials (N = 840)

	Escitalopram	Placebo	p
Responders			
>50% decrease HAM-A	47.5%	28.6%	<.001
CGI change = 1 or 2	52%	37%	<.001
Remitters			
HAM-A $\leq$ 7 at endpoint	26.4%	14.1%	<.001

Goodman W, et al. *Journal of Affective Disorders*. 2005;87(2):161-167.

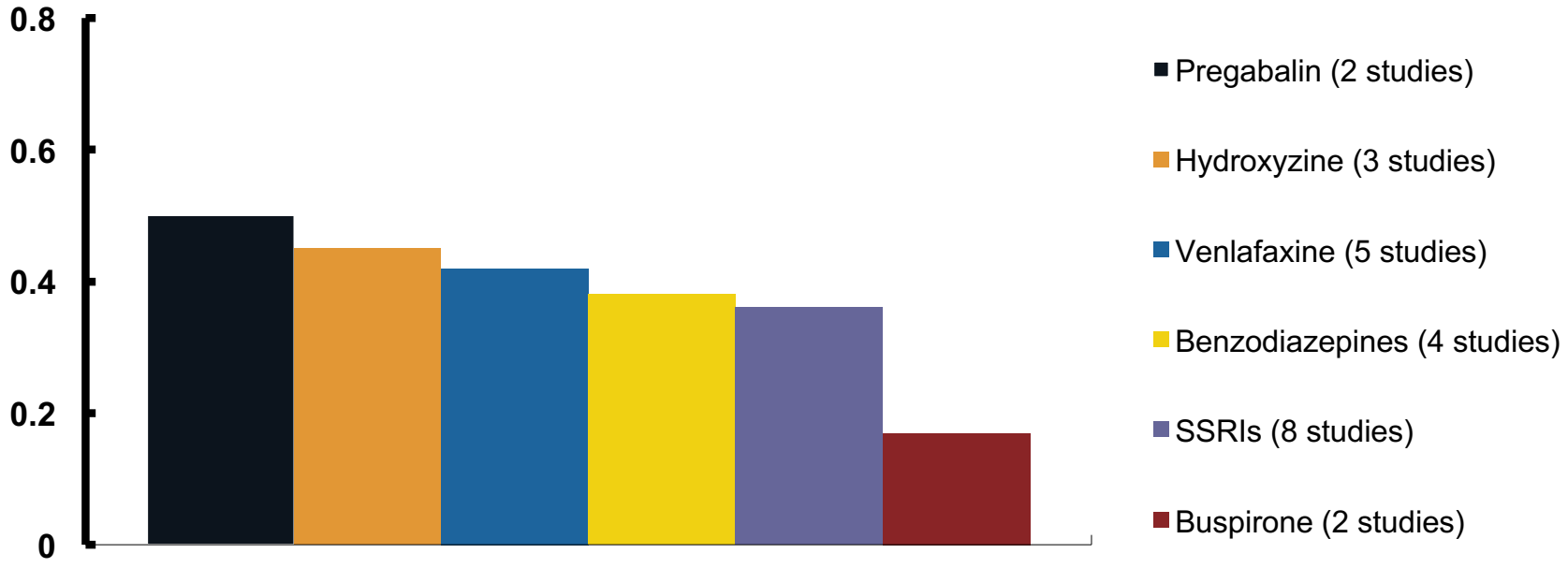
Other Medications Studied for GAD in Controlled Trials

- Benzodiazepines
- Buspirone – 15-60 mg/day (FDA-approved)1
- Off label*:
- Imipramine*, pregabalin*, hydroxyzine*, quetiapine ER monotherapy*, risperidone*, olanzapine*, ziprasidone*

1 [Package Insert]. Drugs@FDA Website.2000.

*not FDA-approved for Generalized Anxiety Disorder.

Effect Sizes of Medications for GAD



Based on Drug-Placebo Difference in HAM-A change

Hidalgo RB, et al. *J Psychopharmacol.* 2007;21(8)864-72.

Social Anxiety Disorder (SAD)

- Marked & persistent fear of embarrassment in social or performance situations
- Recognition that fear is excessive/unreasonable
- Avoids or endures with distress
- Subtypes
  - Generalized (DSM-IV): Anxiety in most social situations
  - Performance: Limited to performance situations

Randomized Clinical Trials in Social Anxiety Disorder

- SSRIs/SNRIs (>20 RCTs)[1,2]
  - Paroxetine,* sertraline,* venlafaxine,* fluvoxamine,* escitalopram; fluoxetine?
- Benzodiazepines: clonazepam, alprazolam[2,3]
- Gabapentin, pregabalin[2,3]
- MAOIs: phenelzine; moclobemide (RIMA, mixed results)[2,3]
- Mirtazapine (mixed results)[2,3]
- Beta-blockers: atenolol, propranolol[2,3]

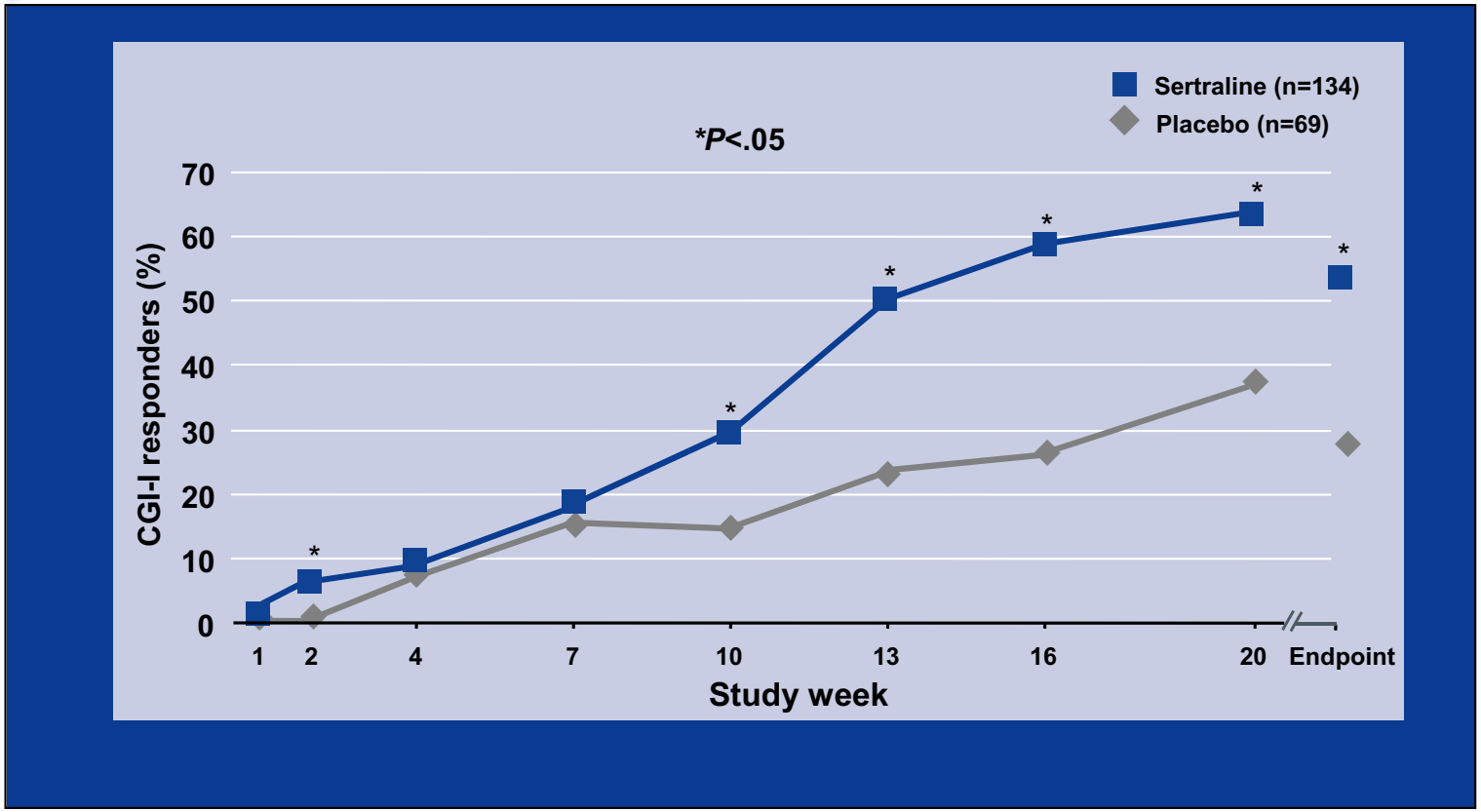
*FDA-approved for the indication of SAD

MAO = Monoamine Oxidase Inhibitor; SSRIs = Selective Serotonin Reuptake Inhibitors; Serotonin-norepinephrine reuptake inhibitors; RCT = Randomized Controlled Trial; RIMA = Reversible Monoamine Oxidase Inhibitor

1 van der Linden, G et al. *Int Clin Psychopharmacol*. 2000;Suppl 2:S15-23.; 2 Schneier F. *N Engl J Med*. 2006;355:1029-1036.

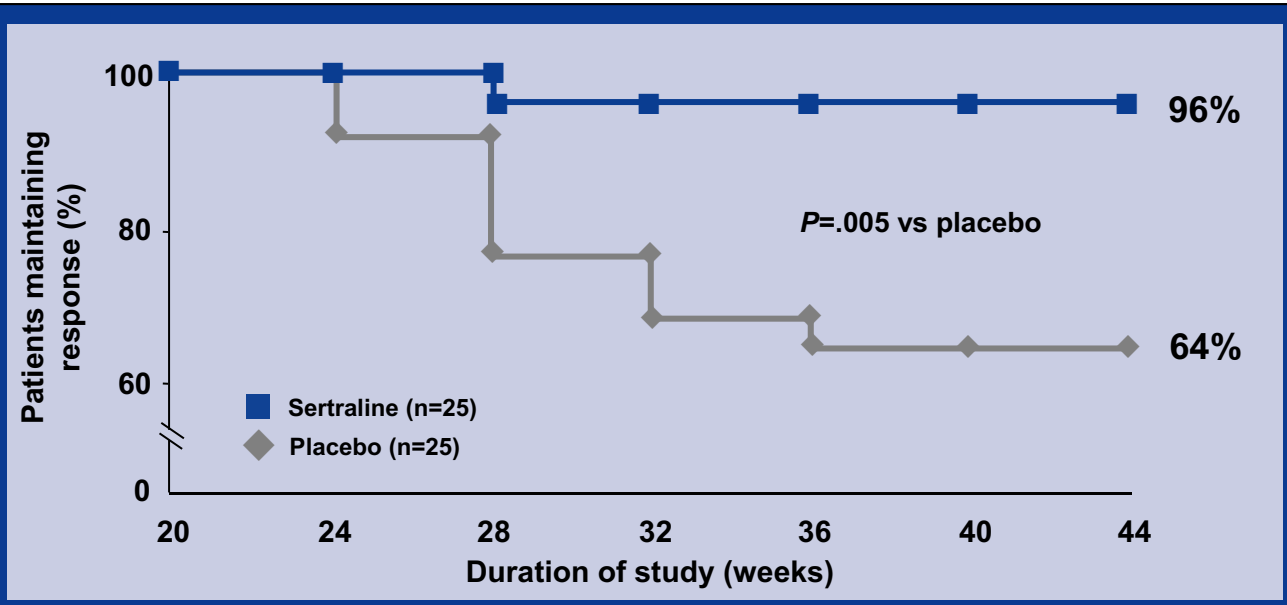
3 Canton J, et al. *Neuropsychiatr Dis Treat*. 2012;8: 203–215.

Sertraline–Significantly Greater Response Rate vs. Placebo



Van Amerigen M, et al. *Am J Psychiatry*. 2001;158(2):275-81.

Sertraline–96% Maintained Response in a Longer Term Continuation Trial



In a rerandomized, 24-week continuation trial of responders to an initial 20-week trial (total treatment time=44 weeks).

In patients receiving ZOLOFT for extended periods, its usefulness should be evaluated periodically.

Walker JR. *J Clin Psychopharmacol*. 2000;20(6):636-44.

Panic Disorder: Targets

- Panic Attacks
- Anticipatory Anxiety
- Phobic Avoidance

Panic Disorder Controlled Trials

- SSRIs[1], venlafaxine[2]
- Benzodiazepines (e.g. clonazepam 1-3mg/d)[3]
- SSRI + Benzodiazepine[4]
- Tricyclic antidepressants (e.g. imipramine)[5]
- Monoamine oxidase inhibitors (phenelzine)[6]
- Generally Ineffective: buspirone, trazodone, gabapentin, beta blockers, bupropion[7]

1Pollack MH. Et al. *Arch Gen Psychiatry*. 1998;55(11):1010-1016.; 2Katzman MA, et al. *Neuropsychiatr Dis Treat.* 2007;3(1):59-67.; 3[Package Insert]. Drugs@FDA Website.; 4Pollack M, et al. *Journal of Psychopharmacology.* 2016;17(3):276-282.; 5Rickels K, et al. *Arch Gen Psychiatry*. 1993;50(11):884-895.; 6Buiges J, et al. *J Clin Psychiatry*. 1987;48(2):55-59.; 7Cassano GB, et al. *Dialogues in Clinical Neuroscience*. 2002;4(3):271-285.

Panic Disorder - Pharmacotherapy Tips

- Antidepressants – start low to minimize early side effects (patients appreciate the idea of starting with a tiny dose)[1]
- Concurrent benzodiazepine can be helpful for initial temporary treatment of patient in crisis[2,3]
- p.r.n. benzodiazepine often cherished
- Make yourself available

p.r.n. = as needed

1Marchesi C. *Neuropsychiatri Dis and Treat*. 2008;4(1):93-106.; 2van Balkom AJ, Centre for Reviews and Dissemination (UK); 1995. Available from: https://ww.ncbi.nlm.nih.gov/books/NBK67034. Accessed June 8, 2017.; 3Pull CB, Damsa C. *Neuropsychiatr Dis and Treat*. 2008;4(4):779-795.

OCD: Targets

- Obsessions: repetitive thoughts that are intrusive, inappropriate, and distressing
  - harm, contamination, sex/religion, symmetry/exactness, somatic, hoarding
- Compulsions: repetitive behaviors or mental acts performed to reduce distress
  - checking, washing, reviewing/repeating, neutralizing, ordering/arranging, saving/collecting
- Avoidance

OCD Pharmacotherapy

- SSRIs are the only established monotherapy
  - 17 SSRI studies, 3100 participants
- Higher end of dose range may be necessary
- Clomipramine may be superior to SSRIs
- Low dose antipsychotics are the only established medication augmentation strategy
- Single RCTs and open trials support augmentation with a variety of other meds

Soomro GM, et al. *Cochrane Database Syst Rev*. 2008;23;(1),16-20.

Augmentation with Antipsychotics for OCD

- Haloperidol*, risperidone*, olanzapine*, quetiapine*, aripiprazole*

*Not FDA-approved for OCD

Augmenting SSRIs: Other Strategies

- **Some promising findings***
  (awaiting confirmation in RCTs)
  - Adding clomipramine to SSRIs
  - Stimulants
  - Anticonvulsants (e.g., topiramate, lamotrigine)
  - Glutamate modulators (e.g., riluzole, memantine, ketamine, NAC)
  - Other (e.g., ondansetron, pregabalin)
- **Negative or inconclusive findings**
  - buspirone, lithium, clonazepam, pindolol, T3, desipramine, inositol, trazodone…

* Strategies listed are not currently approved by the FDA for OCD

PTSD: Targets

- Re-experiencing/intrusion
- Avoidance/numbing
- Hyperarousal
- Insomnia/Nightmares

PTSD Pharmacotherapy: SSRIs

- Meds generally not as effective as CBT for PTSD
- SSRI are best established pharmacotherapy
  - 18 RCTs
- SSRIs are considered a first-line treatment option in some, but not all, published guidelines for PTSD
- Sertraline and paroxetine are FDA-approved
  - There are RCTs of fluoxetine, fluvoxamine, citalopram but not currently FDA approved for PTSD

RCT = randomized control trial

Hoskins, M. et al. *Br J Psychiatry*. 2015:206:(2),93-100.

PTSD Pharmacotherapy: Other Medication Pptions, but Not FDA-Approved

- Mirtazapine[1], nefazodone[2] possibly effective in one RCT
- MAOIs > TCAs, but modest evidence for efficacy[3]
- Olanzapine, risperidone, quetiapine: efficacy in small RCTs[4]

1 Schneier, FR, et al. *Depression and Anxiety*. 2015;32:570-579.

2 Davis L. et al. *Journal of Clinical Psychopharmacology.* 2004;24, 291-297.

3 Ansis GM et al. *Drugs*. 2004;64(4):383-404.

4 Adetunji B, et al. *Psychiatry*. 2005;2(4):43-47.

PTSD Pharmacotherapy - SSRI Augmentation

- α2 adrenergic antagonist prazosin, up to 15mg qhs
  - 4 controlled trials for nightmares and insomnia
- Olanzapine
  - 1 RCT
- Risperidone
  - only 1 of 3 RCTs were positive

Sullivan G, et al. *Curr Opin Investig Drugs*. 2009;10(1):35–45.

Issues To Consider When Combining CBT + Meds

- Potential for additive or synergistic effects
  - If meds reduce severity of symptoms, patient may be more willing to try exposure
- Potential for medication to interfere with CBT
  - Dependence on meds may undermine motivation for CBT
- All pharmacotherapy of anxiety disorders should encourage exposure
  - Medications can facilitate self-exposure

Novel Paradigm: Meds to Enhance Fear Extinction

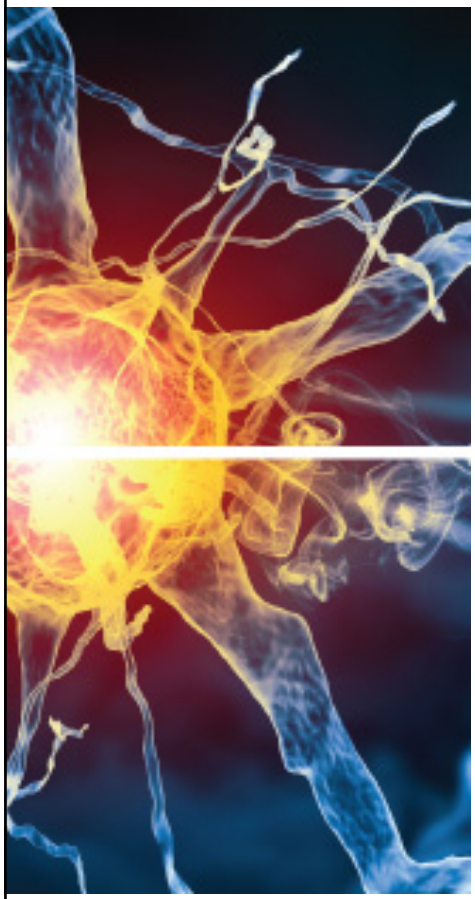
- D-cycloserine* enhances fear extinction in animal models
- Clinical trials of D-cycloserine given immediately before or after exposure exercises in CBT
  - Goal: to enhance learning of safety
  - Some positive results across anxiety disorders
  - But overall effects small (Effect size d = .25)
- Optimal dosage and timing unclear

*Not currently approved by the FDA for anxiety disorders

Otto MW, et al. *Biol Psychiatry*. 2016;80(4):274-83.

SMART Goals

- Explore qualities of anxiety specific to the patient
- Consider comorbidity and context
- Consider CBT as a first option
- After SSRIS, select other classes of meds based on evidence for the specific anxiety disorder and patient's target symptoms



Questions & Answers