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Editor-in-Chief

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IN THIS ISSUE

Focus of the Month:
Positive Psychology

Learning Objectives

After reading these articles, you should be able to:

1. Demonstrate the effectiveness of various first-line pharmacologic options for specific anxiety disorders.
2. Develop skills in empathy, emotional regulation, self-reflection, and acceptance of diverse perspectives.
3. Identify and compare FDA-approved pharmacologic options and off-label treatments for the management of anxiety disorders.
4. Summarize some of the current research findings on psychiatric treatment.

Special Report: Refractory Anxiety Disorders

Part 1: First-Line Treatments

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The authors have no financial relationships with companies related to this material.

There's a reason treatment-resistant anxiety is common in practice. Our first-line medications are not very effective for anxiety disorders. Selective serotonin reuptake inhibitors (SSRIs) have only a small to moderate effect size in panic disorder (0.3–0.5). Cognitive behavioral therapy (CBT) performs a little better, but access to quality psychotherapy is a limitation.

Anxiety disorders are not interchangeable. Certain agents work in some disorders but not in others. In this issue, we'll look at pharmacologic options for generalized anxiety disorder

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Highlights From This Issue

Refractory anxiety disorders. Treatment-resistant anxiety disorders may require you to go off the beaten path. MAOIs, pindolol, pregabalin, lavender extract (Silexan), and quetiapine are candidates, and the choice is best guided by the type of anxiety disorder. More in our two-part special report (on the cover and on page 5).

Q&A on page 1. Most cognitive domains decline with age, but one does not: wisdom.

Research update on page 7. Intermittent theta-burst stimulation, a rapid and potent treatment for depression, reveals an unexpected outcome.

Q&A With the Expert

Wisdom in Psychiatry
Dilip V. Jeste, MD

Director, Global Research Network on Social Determinants of Health and Exposomics; President-Elect, World Federation for Psychotherapy; Editor-in-Chief, International Psychogeriatrics; *Past President, American Psychiatric Association; and coauthor of* Wiser *(Sounds True; 2020).*

Dr. Jeste has no financial relationships with companies related to this material.

TCPR: How did you become interested in wisdom?

Dr. Jeste: In the 1990s I was researching schizophrenia and aging at UC San Diego, and I noticed something that did not make sense. As people with schizophrenia got older, their symptoms started getting better (Jeste DV et al, *Acta Psychiatr Scand* 2003;107(5):336–343). How could we explain that? Their physical health declined faster than the general population, but their mental health improved. I thought "Maybe the notions we have about aging are wrong."

TCPR: What did you learn from there?

Dr. Jeste: I went on to direct an institute for research on aging at UC San Diego. We started a study of 1,500 randomly selected San Diegans from age 20 to 100. We looked at their physical health and mental health and we saw the same thing as we did with schizophrenia. Physical health declined with age, but mental well-being actually improved. People

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Refractory Anxiety Disorders: Part 1

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(GAD), panic disorder, and social anxiety disorder (SAD), starting with the first-line options.

First steps

The anxiety disorders may diverge when it comes to second-line options, but they walk the same path of CBT and an SSRI or serotonin and norepinephrine reuptake inhibitor (SNRI) as first-line treatments. Dosing is similar among the three anxiety disorders and tends toward the higher side for these medications. The various SSRIs and SNRIs have comparable benefits, so how do we choose among them? If FDA approval is the goal, only paroxetine (20–60 mg/day) and venlafaxine (75–225 mg/day) check all the boxes. These are approved in all three disorders, but they carry a higher risk of withdrawal problems than the other serotonergic antidepressants. Paroxetine also has a higher risk of sexual and anticholinergic side effects and teratogenicity than other SSRIs, and venlafaxine carries a unique risk of hypertension.

Escitalopram (10–20 mg/day) and sertraline (50–200 mg/day) offer reasonable alternatives. Although not approved in all three disorders, they are supported by large controlled trials in all three (escitalopram is approved in GAD and sertraline in panic disorder and SAD). Escitalopram stands out for its lack of drug interactions and sertraline for its superior safety profile in heart disease. Fluoxetine (20–60 mg/day) is only approved in panic disorder, and citalopram (20–60 mg/day) and fluvoxamine (50–300 mg/day) have a few controlled trials but no FDA approvals in the three anxiety disorders.

Children and adolescents warrant a different initial approach, at least in GAD. Duloxetine is the only antidepressant with FDA approval in pediatric anxiety disorders, specifically in GAD for ages 7 and up (60–120 mg/day for all ages). However, this SNRI does not have approval or controlled trials in other anxiety disorders, regardless of age.

What doesn't work

In this issue, we'll recommend off-label antidepressants when controlled trials support their use, but the ones that failed that test are just as important to know. Most notable is vortioxetine, which failed in several large, industry-sponsored trials of GAD. Small trials also suggest a lack of efficacy for bupropion, mirtazapine, nefazodone, and trazodone, particularly in SAD and panic disorder. Vilazodone has a small positive trial in SAD, but is otherwise untested in anxiety disorders (Pae CU et al, *J Psychiatr Res* 2015;64:88–98; Charney DS et al, *J Clin Psychiatry* 1986;47(12):580–586).

Anxiety is a nonspecific symptom, and when we endorse or dismiss a medication in this issue, we are speaking only of its effects in specific anxiety disorders rather than any global anxiolytic properties. Many of the medications that failed in anxiety disorders—particularly bupropion, mirtazapine, and vortioxetine—have good evidence to reduce anxiety when it occurs as part of major depression. *(For part 2 of this special report, see page 5.)*

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Expert Interview

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who were wheelchair-bound in their 80s were happier than healthy people in their 20s (Thomas ML et al, *J Clin Psychiatry* 2016;77(8):e1019–e1025).

TCPR: What were your thoughts on that?

Dr. Jeste: At that point I recalled something I had learned growing up in India. There, we are taught that older people must be respected, that older people are wiser. In Western society, there is a lot of ageism. Older people are seen as a burden on society—a "silver tsunami." But I was brought up thinking old age was good, and so I set out to test that scientifically, and that brought me to wisdom.

TCPR: What is wisdom?

Dr. Jeste: Wisdom is a personality trait that has several components. I will sketch them out:

1. Empathy and compassion. This is reflected in what we do for others.
2. Emotional regulation and positivity. This doesn't mean you have no emotions, but you have control, you don't go from one extreme to another, and you tend to be positive much of the time.

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Expert Interview

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3. Self-reflection. This is the ability to look inward and say "Maybe I did something wrong, so I can do better next time" instead of blaming others.
4. Accepting diversity of perspectives. This is the capacity to say "I have my strong opinions and somebody else may have strong but different opinions. I don't agree with that person, but that's all right."

There are also other components like being decisive—not making a quick decision, but making a rational decision. Spirituality may be a component too, but the field is split on whether that should be included.

TCPR: Are you saying that all four of these components increase with age?

Dr. Jeste: In general, yes. But there are some old people who are really unwise, and some young people who are very wise. On psychological tests, older people tend to be better at controlling their emotions, especially negative emotions. They have better self-reflection and insight. They are more compassionate, empathic, and helpful toward others, more accepting of diverse perspectives (Jeste DV et al, *Perspect Biol Med* 2019;62(2):216–236).

TCPR: You are challenging the "Archie Bunker" stereotype of a prejudiced, complaining older person.

Dr. Jeste: Yes, for the average person, positivity increases with age. When you are young and you go to a party and four good things happen along with one bad thing, you only remember the bad thing. In older age, that is reversed. Older people remember the good things for a longer time and forget the bad things. There is biology behind this. An older person's amygdala responds less to negative stimuli compared to a younger person, as seen in functional brain imaging studies (Mather M et al, *Psychol Sci* 2004;15(4):259–263). When people look at a smiling baby, everyone's amygdala lights up—young and old. But when people look at, say, a gruesome car accident, a younger person's brain lights up more.

"In Western society, there is a lot of ageism. Older people are seen as a burden on society—a 'silver tsunami.' But I was brought up thinking old age was good, and so I set out to test that scientifically, and that brought me to wisdom."

Dilip V. Jeste, MD

TCPR: Are there other biological changes associated with wisdom?

Dr. Jeste: Yes. This is a simplification, but by and large, wisdom is housed in the prefrontal cortex, especially the dorsolateral, ventromedial, anterior cingulate and insula, and the limbic striatum, including the amygdala. There are changes that occur in our chemistry that are bad in some ways but good in other ways. For example, the level of dopamine in the brain goes down with age, and that increases the risk of Parkinson's disease. On the other hand, dopamine in the striatum runs the reward system, and lower dopamine can mean less addiction, impulsivity, and dependence on the reward system. Another thing we see with age is the development of new neural networks in subcortical regions such as the dentate gyrus of the hippocampus and the periventricular region.

TCPR: Tell us about that.

Dr. Jeste: This does not happen to everyone, but if a person stays active physically, cognitively, and socially, they may continue to develop new subcortical networks as they age. Now, it is generally the wiser people who tend to stay active like this, so there is a bit of a virtuous cycle going on here.

TCPR: Why are some young people "wise beyond their years"?

Dr. Jeste: Wisdom is partly determined by genes. Like most traits, it is about 50% genetic and 50% environmental, although part of that environment is shaped by our behavior, which is partly influenced by our genes. So if somebody has strong genes for wisdom, then clearly they will be wiser from a younger age. But also, they tend to use even their experiences in young life far better than other kids. You see this from an early age. They share their toys. They don't have as much sibling rivalry or fight as much with other kids.

TCPR: How can we improve wisdom?

Dr. Jeste: The first thing would be self-reflection. Set aside 30 minutes, twice a week, to reflect on things that made you stressed or happy. The key is to make self-reflection a habit. Over time, you will see patterns that you can do something about. Self-reflection is a wisdom trait, and people can reflect on which traits they are strong in and which ones need more work *(Editor's note: See the table "Wisdom Primer" on page 4).*

TCPR: How about empathy and compassion?

Dr. Jeste: Taking up volunteer work is one approach. Another is gratitude. We used to recommend a gratitude diary to increase that, but people got bored keeping a daily diary. So now we recommend the "three good things" approach. Think about three things that made you feel good over the past day, either things that happened to you or things that you did. If you do this every day, it becomes second nature (Montross-Thomas LP et al, *Int Psychogeriatr* 2018;30(12):1759–1766).

TCPR: What do you recommend for emotional regulation?

Dr. Jeste: Like the other traits, this improves through practice. One example that often gives us an opportunity to practice is road rage. We can get angry and curse at the driver, or better, try to reinterpret their behavior. What if they were rushing to an emergency? Another technique is distraction, such as by moving away from the unsettling problem and onto something else, changing the music, counting seven things around you, or recalling a positive memory.

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Expert Interview

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TCPR: How can we become more accepting of diversity?

Dr. Jeste: I recommend meeting people who are different from you on a regular basis, twice a week—these are people who are different in age, sex, skin color, national origin, and even political beliefs. That doesn't mean that you argue with each other and say who is right; rather, the goal is to develop some respect for each other. You can totally disagree with them, but try to understand where their thinking is coming from. It will help you understand the basis of your own beliefs. Now, this will exclude people who are obviously sociopathic—I'm not recommending lunch with murderers and rapists.

TCPR: What role does pleasure play in all this?

Dr. Jeste: There are two types of well-being. One is *hedonic* well-being, which relates to pleasure due to materialistic gains. The other is *eudaimonic* well-being, which is associated with having a purpose and meaning in life. The goal of life is not just to make more money because even if you make more money, you will want more—so the hedonic treadmill never ends and people become even more unhappy eventually. Not only that, but hedonic well-being is associated with increased expression of proinflammatory and proviral genes compared to eudaimonic well-being (Fredrickson BL et al, *Proc Natl Acad Sci USA* 2013;110(33):13684–13689).

Wisdom Primer

Seek Purpose Over Pleasure	Focus on activities that give you a sense of meaning rather than immediate gratification.
Cultivate Empathy	• Perform at least one act of kindness daily. • Volunteer for causes that matter to you.
Counteract Loneliness	• Engage in community events or online forums to connect with others. • Reach out to friends or family regularly for meaningful interactions.
Embrace Diverse Opinions	Have a conversation twice a week with someone who holds different views—try to understand their perspective without debating right or wrong.
Strive for Emotional Regulation	When upset, switch tasks to distract yourself and regain calm. Step back, observe what is happening in a neutral, factual way, and focus on your priorities. Accept what you cannot change and have the courage to change what you can.
Make Thoughtful Decisions	Avoid snap judgments. Take your time to consider all angles before making a decision.
Practice Gratitude	Each day, look for three good things that happened—things for which you were thankful or that made you feel good.
Engage in Self-Reflection	• Schedule 30 minutes twice a week to review situations that made you stressed or happy. • Note your areas of strength and those that need improvement.

TCPR: Can adversity improve wisdom?

Dr. Jeste: It depends upon how you react to the adversity. Anything is fine for the initial reaction—that is almost reflexive and often not how we want to react. What you do next is the question. In general, the Serenity Prayer is a good guide here: "Accept the things that you cannot change, have the courage to change the things you can, and have the wisdom to know the difference."

TCPR: What stands in the way of wisdom in today's society?

Dr. Jeste: One thing that comes to mind is loneliness. Long ago, loneliness was seen as a positive thing because it meant you were closer to God. It came from the word "oneliness." Now there's an epidemic. Between 2015 and 2017 the average lifespan in the US fell for the first time since the 1950s, and it has fallen more since then because of COVID. It fell earlier because of conditions that are related to loneliness: suicides and opioid-related deaths. These are "deaths of despair."

TCPR: Has that affected the elderly more or the younger population?

Dr. Jeste: Both are affected—but there is some surprising information here. In the past 20–30 years, younger adults' mental health has gone down while that of older people has gone up. We saw this during COVID. We expected the pandemic to be harder for older adults, who are more vulnerable to illness and have trouble with technology, but younger people were several times more likely to develop anxiety and depression during COVID than older people (Vahia IV et al, *JAMA* 2020;324(22):2253–2254).

TCPR: There's a related epidemic of burnout.

Dr. Jeste: Yes. Suicide rates are on the rise for clinicians and medical students. There are more stresses for younger clinicians than there were when I started out. The healthcare system is broken, competition is higher, and providers have less power to do what is right for the patient.

TCPR: How can younger physicians reduce burnout?

Dr. Jeste: Empathy and compassion, including self-compassion. Clinicians are so busy helping others that they don't take the time to learn how to be compassionate toward themselves. Often they are self-critical and unforgiving of themselves. Be kind to yourself, just as you want to be kind to your friends. There are common emotions we all have as clinicians—guilt when something goes wrong, embarrassment when we make an error—and we need to teach medical students how to regulate these emotions.

TCPR: Thank you for your time, Dr. Jeste.

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Refractory Anxiety Disorders

Part 2: When First Lines Fail

Generalized anxiety disorder

When SSRIs and SNRIs do not work in GAD, we have two FDA-approved options worth trying: buspirone and the often-overlooked hydroxyzine. Buspirone (15–20 mg BID or TID) is well tolerated, with low rates of sedation and no sexual side effects, but its efficacy is low with an effect size of around 0.2. Hydroxyzine is an antihistamine with decent effect sizes that are close to benzodiazepines for GAD (0.4–0.5). Its main drawbacks are sedation and—especially in the elderly—anticholinergic side effects such as dry mouth, constipation, and confusion. On the other hand, hydroxyzine may still be preferable to benzodiazepines, which are associated with confusion, falls, and addiction.

For refractory cases, lavender extract (Silexan), pregabalin, and quetiapine are reasonable options. All of these were studied as monotherapy but can be safely added to antidepressants as well.

Silexan is a proprietary lavender extract with demonstrated efficacy in GAD. Taken orally, it is approved in Europe for this disorder. In the US it is sold over the counter as CalmAid. Although not studied in treatment-resistant anxiety, Silexan boasts a larger effect size than SSRIs, SNRIs, and benzodiazepines, coming in at 0.5–0.9 across placebo-controlled trials (80–160 mg/day). In GAD, it surpassed paroxetine in a large head-to-head trial and equaled low-dose lorazepam in a network analysis (Yap S et al, *Sci Rep* 2019;9(1):18042). Silexan is well tolerated with typical side effects of mild GI symptoms such as lavender-flavored burping, which improve by taking it at night. It does not cause sedation yet helps with anxiety-related sleep problems. Dependence, withdrawal, and drug interactions have all been examined and do not appear to be issues (see *TCPR,* July 2020).

Pregabalin (Lyrica) is approved for GAD in many countries and is available as a generic in the US. In anxiety disorders, it can be used as a sole treatment or an adjunct in doses from 150–600 mg/day total, given in two divided doses. It has a moderate effect size of 0.37 and a reasonable safety profile (Generoso MB et al, *Int Clin Psychopharmacol* 2017;32:49–55). Benefits are seen as early as the first week, which is faster than the SSRIs and SNRIs by a few weeks. Side effects tend to be mild and include dose-dependent sedation, dry mouth, and weight gain.

Pregabalin might be your agent of choice for patients who have comorbid fibromyalgia or diabetic neuropathy, which are FDA-approved indications. Pregabalin has two "gabapentinoid" cousins, but one failed in three large, industry-sponsored trials of GAD (tiagabine) and the other—although popular—is supported only by a single case report (gabapentin).

Quetiapine is approved for GAD in Europe but did not earn approval in the US despite multiple randomized controlled trials (RCTs) showing substantial efficacy. The FDA believed this antipsychotic carried too many risks to justify approval in a seemingly mild condition like GAD, but for patients with disabling anxiety, the benefits may outweigh those risks.

Quetiapine's effect size in GAD is in the large range, compared to a small effect with SSRIs. Quetiapine might be particularly useful for GAD among patients who also have mood disorders where it is FDA approved, such as bipolar and unipolar depression.

Another off-label avenue to address anxiety is sleep. Adding eszopiclone (Lunesta) to escitalopram significantly improved anxiety, sleep, and daytime functioning among patients with GAD, suggesting it also works as an augmentation agent overall (Pollack MH et al, *Arch Gen Psychiatry* 2008;65(5):551–562). Eszopiclone is metabolized into a benzo-like compound that is active during the day, which may be why other hypnotics like zolpidem did not treat anxiety in studies with similar design.

CARLAT TAKE

Consider Silexan, pregabalin, and quetiapine when first-line treatments don't bring recovery in GAD.

Panic disorder

As many as 50% of patients with panic disorder do not achieve full or stable

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Refractory Anxiety Disorders: Key Clinical Points

First-line treatment for generalized anxiety disorder (GAD), panic disorder, and social anxiety disorder (SAD):

- Use cognitive behavioral therapy, a selective serotonin reuptake inhibitor (SSRI), or a serotonin and norepinephrine reuptake inhibitor (SNRI)
- Paroxetine and venlafaxine are FDA approved but have a higher risk of withdrawal problems
- Escitalopram and sertraline are reasonable alternatives
- Duloxetine can be used for pediatric GAD

The following medications generally do not work well for specific anxiety disorders:

- Vortioxetine, bupropion, mirtazapine, nefazodone, and trazodone

How to choose medications for treatment-resistant anxiety disorders:

- GAD:
  - Buspirone and hydroxyzine are FDA-approved options
  - Lavender extract (Silexan), pregabalin, and quetiapine can be used for refractory cases
  - Eszopiclone improves both sleep and anxiety in GAD
- Panic disorder:
  - Up to 50% of patients do not achieve remission with SSRIs or SNRIs
  - Consider switching to tricyclic or augmenting with a benzodiazepine or pindolol
  - Valproate can be helpful for panic disorder with comorbid bipolar disorder
- SAD:
  - There are performance-only and generalized social anxiety types
  - Phenelzine has a large effect in the generalized type
  - Clomipramine, gabapentinoids (gabapentin and pregabalin), and possibly vilazodone are also effective for SAD

Refractory Anxiety Disorders: Part 2
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remission with first-line treatments like the SSRIs and SNRIs. Among these antidepressants, fluoxetine, sertraline, paroxetine, and venlafaxine are FDA approved in panic disorder, but there is evidence that citalopram, escitalopram, fluvoxamine, and duloxetine are effective as well.

For patients who don't respond well to first-line treatments, options include switching to a tricyclic or augmenting with a benzodiazepine or pindolol.

Among the tricyclic antidepressants, imipramine, clomipramine, and desipramine all have RCTs showing efficacy, but they are not much more effective than agents that are more easily tolerated, such as the SSRIs and SNRIs. The nonselective monoamine oxidase inhibitors (MAOIs) phenelzine and tranylcypromine have significant efficacy for panic disorder, but only when it is comorbid with SAD. Dietary restrictions and side effects such as orthostasis, sedation, sexual dysfunction, constipation, and dry mouth limit their use as tolerability is relatively low.

Benzodiazepines have more empiric support in panic disorder than any other anxiety disorder, but their side effect profile—including risk of addiction—puts them lower in treatment algorithms. Alprazolam and clonazepam are the two benzodiazepines that have FDA approval for panic disorder. These agents may be necessary when patients don't respond to other options or as a temporary addition for symptom relief while waiting for SSRIs or SNRIs to take full effect, although this use has not been studied. In a recent meta-analysis, benzodiazepines were 27% more likely to lead to remission than SSRIs but had higher rates of adverse effects (Chawla N et al, *BMJ* 2022;376:e066084).

Daily use of benzodiazepines may be appropriate if the medication improves functioning. The approved dose ranges for panic disorder are quite large (up to 10 mg/day for alprazolam and 4 mg/day for clonazepam), but sticking to lower doses reduces tolerability problems. Average doses in panic disorder trials were clonazepam 1–2 mg/day and alprazolam 2–5 mg/day.

The beta blocker pindolol may be the only medication with evidence in well-defined, treatment-resistant panic disorder, but this has only been shown in a small RCT (Hirschmann S et al, *J Clin Psychopharmacol* 2000;20(5):556–559). In that study, pindolol was added to fluoxetine among patients who had failed two antidepressant trials and an eight-week trial of fluoxetine alone. Pindolol 2.5 mg TID added to fluoxetine 20 mg/day was significantly better than the addition of placebo in improving panic disorder symptoms.

Valproate may have some utility in panic disorder, though the evidence comes only from small open-label trials using doses of 500–2250 mg/day total. Like benzos, valproate has GABAergic properties and may be an option for patients with comorbid panic and bipolar disorders (Keck PE et al, *Biol Psychiatry* 1993;33(7):542:546). Other anticonvulsants (tiagabine, gabapentin) have been explored without success in panic disorder, and topiramate has induced panic attacks in case reports. Antipsychotics do not have a role here either. Despite its success in GAD, quetiapine failed in a double-blind randomized placebo-controlled trial of panic disorder.

CARLAT TAKE

Consider pindolol augmentation for treatment-resistant cases of panic disorder and short-term benzodiazepines for immediate relief.

Anxiety Disorders: Quick Pharmacotherapy Guide

First-Line Options for GAD, Panic Disorder, and SAD	• Escitalopram, sertraline, paroxetine, venlafaxine • Adult and pediatric GAD: duloxetine
GAD	• Second line: buspirone, hydroxyzine • Third line: lavender extract (Silexan), pregabalin, quetiapine • GAD with insomnia: eszopiclone
Panic Disorder	• Second line: tricyclics (clomipramine, desipramine, imipramine) • Augmentation: with a benzodiazepine or pindolol • Panic disorder with comorbid bipolar disorder: valproate
SAD (Generalized)	• Second line: phenelzine, clomipramine, gabapentin, pregabalin, possibly vilazodone

Social anxiety disorder

There are two types of SAD: performance-only social anxiety and generalized social anxiety. Performance-only social anxiety seems to respond to pre-performance beta blockers like propranolol, although there is a surprising lack of RCT evidence for this popular strategy. Beta blockers do not work in generalized social anxiety, which is characterized by anxiety related to a variety of situations and more pervasive impairment.

SSRIs and SNRIs work for some patients with SAD, but they leave many patients shy of full remission. In those situations, phenelzine offers hope. This medication had a large effect size across five RCTs of SAD totaling 454 patients, compared to the small effect seen with MAOIs. In some of these trials, phenelzine compared favorably to group CBT and successfully augmented psychotherapy. The starting dose for phenelzine is 15 mg, and doses up to 90 mg may be needed. Preliminary evidence supports tranylcypromine, another nonselective MAOI, in SAD.

Outside of SSRIs and MAOIs, most antidepressants have failed in this population (eg, imipramine, mirtazapine, buspirone). Exceptions are clomipramine (25–150 mg/day) and vilazodone (40 mg/day), which have small positive controlled trials in SAD (Simpson HB et al, *J Clin Psychopharmacol* 1998;18(2):132–135; Careri JM et al, *Prim Care Companion CNS Disord* 2015;17(6):10.4088/PCC.15m01831).

The gabapentinoids also have a role in SAD, and in this case the evidence supports both gabapentin and pregabalin. The doses need to get quite high to show effect, such as 2000 mg/day for gabapentin (Pande AC et al, *J Clin Psychopharmacol* 1999;19:341–348) and 600 mg/day total for pregabalin (Feltner DE et al, *Int Clin Psychopharmacol* 2011;26;213–220), given in divided doses three times per day. Quetiapine has a positive placebo-controlled trial, but the sample size (15) was too small to endorse it in SAD.

Benzodiazepines have successfully augmented SSRIs, and they can be useful on an as-needed basis prior to

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CME Post-Test

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1. Which SSRI/SNRI is FDA approved for generalized anxiety disorder, panic disorder, and social anxiety disorder (SAD) (LO #1)?
   - [ ] a. Escitalopram (10–20 mg/day)
   - [ ] b. Sertraline (50–200 mg/day)
   - [ ] c. Paroxetine (20–60 mg/day)
   - [ ] d. Duloxetine (60–120 mg/day)

2. Which strategy does Dr. Jeste no longer recommend to cultivate wisdom (LO #2)?
   - [ ] a. Keep a daily gratitude diary
   - [ ] b. Practice self-reflection
   - [ ] c. Focus on positive experiences
   - [ ] d. Spend 30 minutes twice a week thinking about stressful or happy events

3. Which medication showed a large effect size across randomized controlled trials totaling 454 patients and is recommended as a potential option for SSRI- and SNRI-refractory SAD (LO #3)?
   - [ ] a. Clomipramine
   - [ ] b. Vilazodone
   - [ ] c. Phenelzine
   - [ ] d. Gabapentin

4. What was a key finding in the quadruple-blind randomized trial that compared active versus sham treatments of intermittent theta-burst transcranial magnetic stimulation for major depression (LO #4)?
   - [ ] a. Sham treatment resulted in a greater improvement in suicidality
   - [ ] b. Both active and sham treatments showed similar antidepressant effects
   - [ ] c. Active treatment had a greater antidepressant effect
   - [ ] d. Significant antisuicidal effects were seen with both active and sham treatments

5. According to Dr. Jeste, how can patients improve their emotional regulation when they encounter road rage (LO #2)?
   - [ ] a. Get angry and yell at the driver
   - [ ] b. Ignore the situation
   - [ ] c. Dwell on what happened
   - [ ] d. Try to understand the driver's behavior

Research Update IN PSYCHIATRY

NEUROMODULATION

Intermittent Theta-Burst Stimulation for Depression and Suicidality

Kate Travis, MD. Dr. Travis has no financial relationships with companies related to this material.

REVIEW OF: Wilkening J et al, *Acta Psychiatr Scand* 2022;146(6):540–556

STUDY TYPE: Randomized, quadruple-blind, sham-controlled crossover trial

Intermittent theta-burst stimulation (iTBS) is a form of transcranial magnetic stimulation that uses higher magnetic frequencies to deliver the treatment in shorter sessions (3–10 minutes instead of 20–40 minutes). It was approved by the FDA in 2018 for treatment-resistant depression. This study examined the effects of iTBS on suicidality among patients with depression.

Eighty-one adults with moderate to severe major depression were enrolled in this six-week, quadruple-blind (patients, care providers, investigators, and raters were all blinded), sham-controlled crossover trial. Participants received five consecutive days of active or sham treatment, then switched to the other arm after a one-week break. Although the sham version had no magnetic pulses, the two treatments were indistinguishable. There were two primary outcomes: (1) change in baseline depression between the active and sham treatments as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) and (2) change in suicidality between the active and sham treatments as measured by a composite "suicide score" (0–1) that the authors derived from the MADRS, the Hamilton Depression Scale, and the Beck Depression Inventory-II.

Participants' depression and suicidality improved over the trial, with the greatest improvement occurring after the first five days of treatment in the active *and* sham groups, indicating an initial placebo effect. When the active and sham treatments were compared, the results showed that active treatment had a greater antidepressant effect (MADRS score improvement 5.02 with active, 2.11 for sham), but the antisuicide effects were similar. Dropouts were similar after active and sham treatments, and no serious adverse events occurred.

CARLAT TAKE

In this study, iTBS treated depression but did not have antisuicide effects.

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Refractory Anxiety Disorders: Part 2

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anxiety-provoking situations (Seedat S and Stein MB, *J Clin Psychiatry* 2004;65(2):244–248). Many patients with SAD tend to use alcohol to self-medicate, so be cautious when considering a benzodiazepine prescription to ensure the patient does not combine these two GABAergic sedatives. They are best avoided when patients are undertaking exposure therapies like CBT, as benzodiazepines can block fear-extinction learning. We would avoid adding a benzo in those situations, but tapering off an existing benzo may be too challenging.

We don't have a lot of good evidence on what to do after an initial trial with an SSRI or SNRI for a patient with persistent symptoms—should we augment or switch? One study examined this in SAD among patients who did not respond sufficiently to sertraline. Patients were randomized to placebo, augmentation with flexible-dose clonazepam (up to 3 mg), or a switch to venlafaxine. Adding clonazepam led to significant reduction in SAD symptoms, but there was no significant difference in the number of patients achieving remission across the three groups (Pollack MH et al, *Am J Psychiatry* 2014;17(1):14–53).

CARLAT TAKE

In SAD, phenelzine may work when first-line options have failed.

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