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Focus of the Month:
Anxiety Disorders

Learning objectives for this issue:
1. Prescribe benzodiazepines appropriately for your patients with anxiety disorders. **2.** Identify the medications used to treat post-traumatic stress disorder (PTSD). **3.** Describe cognitive behavioral therapy for panic disorder. **4.** Explain exposure and response prevention therapy for obsessive compulsive disorder (OCD). **5.** Understand some of the current findings in the literature regarding psychiatric treatment.

Benzodiazepines: A Guide to Safe Prescribing

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Dr. Shah and Dr. Borresen have disclosed that they have no relevant relationships or financial interests in any commercial company pertaining to this educational activity

Most of us who prescribe benzodiazepines (BZs) have a love-hate relationship with them. On the one hand, they work quickly and effectively for anxiety and agitation, but on the other hand, we worry about sedative side effects and the fact that they can be difficult to taper because of withdrawal symptoms. We also fret about BZ dependency, tolerance, and abuse. In this article, we help guide you through these dilemmas.

First, some history. If you think BZs are problematic, consider barbiturates, the sedative of choice through the 1950s. Medications such as pentobarbital (Nembutal), secobarbital (Seconal), and phenobarbital were widely used as hypnotics and anxiolytics for a variety of psychiatric disorders, including schizophrenia (López-Muñoz F et al, *Neuropsychiatr Dis Treat* 2005;1(4):329–343). While they often improved some symptoms, they were notoriously sedating, had a high abuse potential, and could easily be overdosed (Marilyn Monroe famously overdosed on barbiturates).

Benzodiazepines came on the scene as a replacement for barbiturates in the early 1960s. The first benzodiazepine, chlorodiazepoxide (Librium) was serendipitously discovered by a Roche chemist, Leo Sternbach in 1957. Diazepam (Valium) was introduced in 1963 and rocketed to stardom in the 1960s and 1970s for what was often called "anxiety neurosis," a diagnostic category in the DSM-II. In 1981, after the publication

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Update on Medications for PTSD

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Dr. Berlin has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

While psychotherapy remains the gold standard for treatment of post traumatic stress disorder (see for example, Foa EB et al, *Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies.* New York: Guilford Press; 2008), medications are often used to alleviate the symptoms of the illness. Since we last visited the topic of pharmacologic treatment for PTSD (*TCPR,* June 2007), there's been some interesting research on this subject, including the use of antibiotics, steroids, and even the drug of abuse, ecstasy.

First, though, a quick review of more mainstream treatment. Keep in mind that the current general aim of psychopharmacology in PTSD is to minimize its symptoms, rather than to "cure" it. Getting some comfort from meds can often enable a patient to more easily face the tough work of exposure or other psychotherapies. Symptoms that are most easily addressed by medications include those of hyperarousal, along with nightmares.

SSRIs. Sertraline (Zoloft) and paroxetine (Paxil) are still the only drugs that are FDA approved for the treatment of PTSD, and SSRIs in general are recommended as first-line treatment by the APA practice guidelines (from

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of the DSM-III, alprazolam (Xanax) was aggressively marketed for the new diagnosis of "panic disorder," followed eventually by clonazepam (Klonopin).

How Do They Work?

BZs work by affecting the receptor sites for GABA (gamma aminobutyric acid), which is our major inhibitory neurotransmitter. GABA normally attaches to postsynaptic GABA-A receptors, causing them to open chloride ion channels, slowing down neurotransmission. BZs attach to a specific benzodiazepine modulatory site next to GABA-A, and enhance the opening of the ion channel, essentially turbo-charging the efficacy of native GABA. This leads to decreased neuronal firing throughout the brain, which presumably then leads to its anti-anxiety effects, as well as its hypnotic, anticonvulsant, and muscle relaxant effects.

How do BZs differ from the "non-benzodiazepines" such as zolpidem (Ambien)?

It is thought that the alpha-1 subunit of the GABA-A receptor mediates sedation, while the alpha-2 subunit mediates anxiety. BZs work on both, while non-BZs work mostly on the alpha-1 (sedation) subunit. Alcohol mediates GABA receptor sites as well, but in ways that are more complex. (For a review, see Kumar S et al, *Psychopharmacology (Berl)* 2009;205(4):529–564.)

Which Psychiatric Disorders Do Benzodiazepines Work for?

BZs work for anxiety in all its manifestations, whether in the form of official DSM disorders, such as panic disorder, GAD, or social anxiety disorder, or in the more clinically common form of "mixed" disorders, such as "mixed depression/anxiety."

It's nice to know which BZs are officially approved for what (if for medicolegal protection alone). The table on page 3 lists each drug's official indication along with other practical tidbits, such as dosing, onset of action, mg equivalents, and clinical duration of action.

Pharmacokinetics of Benzodiazepines

The first step in drug metabolism is absorption from the gastrointestinal tract. Most BZs are swallowed and absorbed from the small intestine fairly quickly—within 20 to 30 minutes. Taking medications sublingually speeds up absorption and also sends the drugs directly to the brain, bypassing the first pass effect in the liver. While lorazepam (Ativan) is the only benzodiazepine with an official sublingual version, alprazolam is often used this way as well, and theoretically any of these medications could be dissolved under the tongue, though some will dissolve too slowly or taste too bad to make it worthwhile.

Sustained release alprazolam (marketed as Xanax XR) is encased in a fancy hyroxy-propyl-methylcellulose matrix. This allows sustained release alprazolam to be released slowly and more consistently over several hours, with benefits lasting more than 10 hours. There are randomized controlled trials (RCTs) to show this method of delivery works just as well as immediate release alprazolam for panic disorder (Pecknold J et al, *J Clin Psychopharmacol* 1994;14(5):314–321; Sheehan D and Raj B. Benzodiazepines. In: Schatzberg A and Nemeroff CB eds. *The American Psychiatric Publishing Textbook of Psychopharmacology;* 2009:486). Tell your patients that eating food or taking an antacid before swallowing a benzodiazepine can slow the rate of absorption, therefore slowing the onset of action.

A common measure of the speed of metabolism is the "half-life," defined as the time required for the body to metabolize half of the dose. But for many BZs, half life turns out to be a poor measure of how long the patient feels the effects of the medication. Consider immediate release alprazolam: the half-life of the medication is 10 to 15 hours, but in clinical practice it only feels like it works for about three or four hours. The reason is that a benzodiazepine's actual duration of action is determined by its lipophilicity, or "lipid solubility." Lipophilicity determines the rate a medication leaves the bloodstream and moves into fatty tissue, and it also determines how quickly a BZ crosses the blood brain barrier (Sheehan and Raj, ibid).

For example, diazepam (Valium) has a long half-life (26 to 50 hours), but because of its higher lipophilicity, it crosses the blood brain barrier more quickly than lorazepam (half life of 10 hours) and actually has a *shorter* duration of action clinically. Thus, diazepam's onset of action is rapid, but its duration of action is short. The long half-life of diazepam can, however, become burdensome because it gradually accumulates in the fatty tissue and then can slowly cause more side effects when dosed long term for chronic anxiety (Sheehan and Raj, ibid).

BZs are rendered inactive by metabolism in the liver. Lorazepam, oxazepam (Serax) and temazepam (Restoril) (a useful acronym is "LOT") are metabolized by the liver through glucuronidation. This has two important implications for clinicians: first, there are no active metabolites; and second, these drugs are rarely susceptible to drug-drug interactions. This means that the LOT drugs are especially appropriate for patients who are

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elderly, have cirrhosis, or have complex medical/pharmacological issues.

Drug-drug interactions. Several potential drug-drug interactions are relevant when choosing a benzodiazepine other than the "LOT" drugs. Potent inhibitors of the P450-3A4 enzyme like fluoxetine (Prozac), fluvoxamine (Luvox), and certain oral contraceptives can increase the plasma level of alprazolam and several other BZs, requiring dose reduction in some cases.

Switching Benzodiazepines

When switching from one BZ to another, refer to the dosage equivalence information in the table below. A rule of thumb is to use lorazepam as the standard. Thus, 1 mg of lorazepam = 5 mg of diazepam = 0.25 mg of clonazepam = 0.5 mg alprazolam (these equivalencies are estimates and may vary from patient to patient).

Standing Doses Versus PRN

One question that often comes up in clinical practice is whether to dose these medications "standing," ie, with a fixed schedule, or as a "PRN," as needed. We are all tempted to use medications as a PRN for good reason: this allows patients to take the medication when they most need it and prevents too much medication from accumulating in the fatty tissues, hopefully preventing chronic side effects. On the other hand, a standing dose of a long acting medication, like clonazepam, is sometimes the best option, especially when you are starting treatment with a very anxious patient. This will predictably relieve symptoms and prevent clock-watching for the next dose.

Another important but often overlooked downside to using PRN dosing is that this may adversely affect cognitive behavioral therapy (CBT). The specific goal of CBT is to allow the patient to become more comfortable with sensations and emotions related to panic attacks and confront their automatic thoughts about how dangerous these feelings are. Reaching for a BZ, while giving a patient relief quickly, can interfere with the patient habituating to these "dangerous" feelings and sensations. It can also relieve anxiety to such an extent that the patient may lose motivation to continue the CBT (Cloos JM & Ferreira V, *Curr Opinion Psychiatry;*22(1):90–95). In general, we recommend prescribing BZs as standing doses rather than PRN (or not prescribing them at all) with

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Commonly Prescribed Benzodiazepines: A Comparison Chart

Generic (Brand) Approval Date	FDA Approval for Psychiatric Indications*	Tablet or Capsule Strengths**	Average Dosage Range for Anxiety	Equivalent Dose (to lorazepam 1 mg)	Onset of Action after Oral Dose	Clinical Duration of Action (Hours)†
Alprazolam (Xanax) 1981	•Anxiety •Panic disorder	0.25 mg, 0.5 mg, 1mg, 2 mg	1–4 mg/day	0.5 mg	30 min	3–4
Chlordiazepoxide (Librium) 1960	•Anxiety •Alcohol withdrawal	5 mg, 10 mg, 25 mg	15–100 mg/day	25 mg	2 hours	4–6
Clonazepam (Klonopin) 1975	•Panic disorder	0.5 mg, 1 mg, 2 mg	0.5–2 mg/day	0.25mg–0.5mg (sources differ on dose equivalence of clonazepam)	1 hour	6–8
Diazepam (Valium) 1963	•Anxiety •Alcohol withdrawal	2 mg, 5 mg, 10 mg	5–40 mg/day	5 mg–10 mg (sources differ on dose equivalence of diazepam)	30 minutes	4–6
Lorazepam (Ativan) 1977	•Anxiety	0.5 mg, 1 mg, 2 mg	1–4 mg/day	1 mg	30–60 minutes	4–6
Temazepam (Restoril) 1981	•Insomnia	7.5 mg, 15 mg, 30 mg	15–30 mg/day	15 mg	30–60 minutes	4–6

*Many benzodiazepines were approved before DSM-III, and were therefore indicated for a miscellaneous array of anxiety disorders that are labeled differently in modern parlance. Most of these "anxiety" indications would correspond either to generalized anxiety disorder or for the short-term relief of anxiety symptoms.

**Many are available in other forms, such as injectible or orally disintegrating—see online table for these details.

†This is the answer to a patient's question, "how long will it last?" assuming prn dosing. When dosed chronically, duration of action will usually be longer due to accumulation.

For a more detailed table, including more medications, go to www.thecarlatreport.com.

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patients who are undergoing CBT psychotherapy for panic.

Side Effects

In most cases, BZs have a benign side effect profile. Patients often resist taking BZs during the day (when they most need them) because they fear sedation, but you can reassure them that this side effect is usually mild and goes away within a few days. All BZs cause physiological dependence if a patient takes a high enough dose for several weeks. "Dependence" in this context simply means that abrupt cessation may lead to withdrawal symptoms such as insomnia, anxiety, or tremor. Serious withdrawal symptoms, such as delirium tremens or seizures, are very rare among patients who have taken therapeutic doses of BZs without adding alcohol or illicit drugs. The side effect situation is more worrisome among the elderly, who are at higher risk of falls (Woolcott JC et al, *Arch Intern Med* 2009;169(21):1952–1960) and delirium (Clegg A and Young JB, *Age Ageing* 2011;40(1):23–29) when using BZs.

In both the elderly and the young, BZs can cause cognitive impairment that can be overlooked (Barker MJ et al, *CNS Drugs* 2004;18(1):37–48). Most of us have had patients who stop their BZs after years of use and have an "awakening" experience of clear-mindedness. Consider tapering BZs in your patients from time to time to rule out the presence of occult side effects.

Tapering and Discontinuation of Benzodiazepines

How do you taper most successfully? BZ tapers are most successful in patients with lower baseline levels of anxiety, who have been on lower daily doses for fewer months. Regardless of the patient, the best way to taper is very, very slowly—it often takes five to six weeks but may take months. For example, one published slow-taper program for alprazolam recommends reducing the daily dose by 0.25 mg every two days for doses above 2 mg, and then reducing by 0.125 mg every two days once the patient is down to 2 mg or less. This taper schedule lasts about five weeks for patients taking a daily dose of 2 mg, and seven weeks for patients taking 4 mg per day (Otto MW & Pollack MH. *Stopping Anxiety Medication.* 2nd Edition. Oxford, UK: Oxford University Press; 2009).

You can use this kind of schedule—about 5% reduction every two days—as a guideline for other BZs. Most patients appreciate it if you write out the schedule in detail.

Consider CBT during tapering for patients who have difficulty tolerating tapering and are motivated. (Special thanks to Kate Salvatore, MD for her input on this article.)

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Update on Medications for PTSD

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2004—now frightfully out of date). While most studies to date have shown a rather modest effect for SSRIs in PTSD (as low as 60% for response and 40% for remission), they all seem to have similar efficacy for its treatment and are well-tolerated in this population. Dose SSRIs as you would for depression.

Other antidepressants. SNRIs, MAOIs, tricyclics, nefazodone (Serzone), trazodone (Oleptro), and mirtazapine (Remeron) have all been shown to have some efficacy with PTSD. Since disrupted sleep is a frequent complaint of patients with PTSD and this often does not completely improve with psychotherapy or SSRIs, mirtazapine or a sedating tricyclic such as doxepin (Sinequan) can be helpful, alone or in combination with an SSRI (van Liempt S et al, *Internat Clin Psychopharmacol* 2006;21(4):193–202).

What about a non-sedating antidepressant to address the dysphoric mood that is often seen in these patients? It may not be of much use. In a placebo-controlled trial, bupropion (Wellbutrin) had no significant effect even as an adjunct for PTSD (Becker ME et al, *J Clin Psychopharm* 2007;27(2):193–197).

Atypicals. Again, the more sedating of these can be effective in addressing hyperarousal. Risperidone (Risperdal), quetiapine (Seroquel), and olanzapine (Zyprexa) have all had positive results in some studies—not surprising given their sedating properties. Risperidone has probably been the most studied. (For a review of studies on risperidone and PTSD, see Berger W et al, *Prog Neuropsychopharmacol Biol Psychiatry* 2009;33(2):169–180. They conclude that it is "an effective add-on therapy when patients did not fully benefit from previous treatment with SSRIs.")

Obviously, given the metabolic and other side effect concerns of atypicals, these are not a first-line treatment in providing what is essentially sedation, since that can come from other medications with gentler side effect profiles.

Mood stabilizers. Because hyperarousal can include mood lability, you might think of using a mood stabilizer for these patients. Although results are mixed, in general, mood stabilizers have surprisingly often been shown to be *in*effective in PTSD, especially as monotherapy. Among others, a double-blind randomized trial of divalproex (Depakote) as monotherapy in combat veterans showed no difference from placebo (Davis L et al, *J Clin Psychopharm* 2008;28(1):84–88).

Benzodiazepines. These are a sticky topic. Since PTSD is by definition an anxiety disorder, and since the hyperarousal of PTSD can often be its most disabling feature, a benzodiazepine would seem to be a natural choice. However, benzodiazepines are sometimes found to be not only *not* very helpful in PTSD, but potentially harmful. Why? There are multiple reasons. First, there is significant comorbidity of substance use disorders in people with PTSD—up to 40% and even perhaps as high as 75% for combat veterans with PTSD (Jacobsen LK et al, *Am J Psychiatry* 2001;158(8):1184–1190). Prescribing benzodiazepines to either actively or recently substance abusing patients is something we'd prefer to avoid if possible.

A second disadvantage of benzos is that they might contribute to the emotional numbing of PTSD and prevent

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integration of the traumatic event. While there is not much actual clinical evidence of this, in animal models benzodiazepines given after a stressor are found to inhibit normal HPA-axis response to stress, and even increase vulnerability to future stressors (Matar MA et al, *European Neuropsychopharm* 2009;19(4):283–295).

And finally, benzodiazepines just may not be very effective for the disorder. Although there is surprisingly little direct research on this topic, one small prospective study found no improvement on multiple PTSD scales compared to the placebo group after one or six months of treatment (Gelpin E et al, *J Clin Psychiatry* 1996;57(9):390–394).

However, with these caveats, we often still find benzos useful for a selected group of patients, particularly for treating sleep disruption. Buspirone (BuSpar) theoretically might address the hyperarousal without worsening numbing, but there has been little evidence one way or another for this medication in PTSD.

Other Potentially Effective Medications

Much of the pharmacologic treatment of PTSD involves addressing particular symptoms. For hypervigilance and activation symptoms, try a beta blocker like propranolol (Inderal), an alpha-2-agonist like clonidine (Catapres), or the alpha-1 antagonist prazosin (Minipress)—these can be quite helpful and do not carry the stigma that patients new to psychiatric treatment can associate with classic psychiatric meds. A good starting dose of propranolol is 10 mg taken three or four times daily. While you do not need to monitor heart rate or blood pressure in the typical patient, check for interaction with other cardiac meds.

Prazosin, discussed in our 2007 PTSD issue as helpful with both sleep and daytime PTSD symptoms (*TCPR,* June 2007), is dosed initially at 1 mg at bedtime and increased gradually, watching for orthostasis. Prazosin works by decreasing CNS adrenergic activity, which makes sense since this is heightened in PTSD.

For nightmares, another common and debilitating complaint in PTSD, a thorough meta-analysis of drug treatment for sleep disruption in PTSD found an astounding number of medications that have been effective in studies ranging from case reports to clinical trials, including buspirone, gabapentin (Neurontin), topiramate (Topamax), imipramine (Tofranil), phenelzine (Nardil), mirtazapine, prazosin, clonidine, and multiple atypical antipsychotics (van Liempt S et al, *op.cit*). In my experience, topiramate (25 mg to 100 mg at bedtime), clonidine (0.1 mg to 0.2 mg at bedtime; warn patients of orthostasis when getting up in the morning initially), and quetiapine (at a dose as low as 25 mg at bedtime) are particularly helpful for nightmares.

Drugs in the Pipeline

D-cycloserine (Seromycin). This drug is an antibiotic developed for the treatment of tuberculosis. However, it also acts as a partial agonist at the NMDA glutamate receptor, and glutamate is found throughout the nervous system, being our major excitatory neurotransmitter. In randomized double blind trials, D-cycloserine has been shown to enhance the effectiveness of exposure therapy for both social phobia and acrophobia (the fear of heights). (For social phobia, see Hofmann SG et al, *Arch Gen Psychiatry* 2006;63(3); 298–304.) While there have not yet been any human studies published on D-cycloserine in PTSD, it has shown efficacy in animal models of conditioned fear (Cukor J et al, *Ann N. Acad Sci* 2010;1208:82–89). Perhaps in the future we will see patients taking this medication while undergoing exposure therapy for PTSD to enhance its effects.

Steroids. After the World Trade Center bombing, there was a lot of interest in immediate pharmacologic interventions that could be done in the emergency room after a traumatic exposure, with the idea that these could lessen development of acute stress and then PTSD further down the road. With the aim of decreasing initial activation, propranolol was one of the more common interventions, with mixed results. Now researchers are suggesting that giving glucocorticoids in the emergency room may decrease later development of symptoms. At the 2011 American Psychosomatic Society annual meeting, Douglas Delahanty et al presented results of a randomized, double blind, placebo controlled study in which patients with a recent trauma were started on hydrocortisone 20 mg twice a day at hospital admission, and had fewer PTSD symptoms one and three months later (Delahanty D et al, Abstact 1755. Presented at: 69th Annual Meeting of the American Psychosomatic Society; 2011; San Antonio, TX). The theory behind this is that HPA axis activation is involved in the development of PTSD.

Interestingly, steroids have also been implemented to enhance extinction learning during exposure therapy, similar to D-cycloserine, with positive results. Veterans with PTSD underwent a single session of exposure therapy after being given either glucocorticoid or placebo, and a week later the subjects who had the glucocorticoid had a reduction in symptoms. This was transient, however, and the effect was gone by the one-month assessment (Suris A et al, *Ann Clin Psychiatry* 2010;22(4):274–279).

MDMA. What? *Ecstasy* for PTSD? Well, don't expect to see it anytime soon. However, MDMA, a Schedule I drug, has been employed in a small (n=20) randomized, double blind, placebo controlled trial for PTSD, with the idea that when given before exposure therapy, its use induces relaxation and a sense of well-being and helps the patient tolerate and incorporate a greater degree of exposure. Significant improvement in PTSD symptoms was found up to two months later in the treatment group (Mithoefer MC et al, *J Psychopharmacol* 2011;25(4):439–452).

TCPR'S VERDICT: Medications for PTSD? The research base remains pretty thin, but there are plenty of options to try. Psychotherapy is still the bedrock of treatment for most PTSD patients. For a review of treatments, see Bisson J, *Clin Evid (Online)* 2010;Feb 3.

Q&A With the Expert

This Month's Expert

Cognitive Behavioral Therapy for Panic Disorder

Jesse Wright, MD

Professor of psychiatry
University of Louisville School of Medicine

Dr. Wright has disclosed that he receives book royalties from American Psychiatric Publishing, Simon and Schuster, and Guilford Press, and payment from Empower Interactive and Mindstreet for CBT computer programs. Dr. Carlat has reviewed this article and found no evidence of bias in this educational activity.

TCPR: In your 2010 book, *High Yield Cognitive Behavior Therapy for Brief Sessions* (American Psychiatric Publishing, Inc, 2010), you discuss how psychiatrists and other prescribing professionals have slipped away from using psychotherapy, and you offer some tactics for fitting it back into a psychopharmacology practice. Is there a certain type of patient that you think CBT works best for?

Dr. Wright: I think every session to some extent has psychotherapeutic qualities if one is interested in paying attention to the therapeutic relationship, having people manage stressors in their lives, and solving problems. In CBT, there is a fair amount of teamwork—this is called "collaborative empiricism." I often liken the therapist in CBT to a really good coach or a teacher. You are trying to help people gain skills and build knowledge about how to examine their thinking and behavioral patterns, and then use CBT techniques to turn those around. So someone who can participate as a member of the team, and is motivated to do that, is a reasonably good candidate for CBT. Some illnesses respond better to CBT, such as mood and anxiety disorders, than others. But CBT can be useful for a broad range of problems.

TCPR: Let's discuss CBT techniques for people with anxiety disorders—in particular, panic disorder.

Dr. Wright: Some of the techniques that have proven effective for panic disorder include breathing retraining, cognitive restructuring, and relaxation training.

TCPR: Tell us about breathing retraining.

Dr. Wright: This method is usually easy to teach and often is effective for people who hyperventilate as part of a panic attack (Clark DM et al, *J Behav Ther Exp Psychiatry* 1985;16(1):23–30). The goal is to help your patients bring breathing patterns from irregular back to a normal pattern, and to use positive imagery to further calm their cognitions.

TCPR: Walk us through how you would actually do this.

Dr. Wright: First, I ask patients to watch me breathe normally, and I say, "Do I look nervous or anxious right now?"And they say, "No, you look pretty calm." Then I ask them to explain what my breathing looks like. When people are calm and not in a panic attack their breathing is fairly slow and it is hardly noticeable. So I ask them what they think a panic attack looks like. And they will usually say, "Well it is obviously not calm like that. I struggle with my breathing." Then I will role-play what a panic attack looks like, and the anxiety responses that one might see in a person's face and body. So I will perform a hyper pattern of breathing, and the patient will usually say, "Yeah that's it. That is exactly what it is like for me." And I will say, "Well if I kept going with this, I could probably feel like I am in a panic attack myself because I get sort of dizzy and I might have funny feelings in my hands or my feet and I will feel like I am out of control." Sometimes, if a patient is willing, I will ask him or her to over breathe in a panicky way. If they don't want to, that's fine; we just go on to the next step.

TCPR: So you first get them to notice the difference between normal breathing and panicked breathing. Then what?

Dr. Wright: I will give them a simple technique that can really help if they find themselves getting into this pattern of breathing that goes along with panic attacks. Here's how it works: If a patient can just simply recognize that he is having this panicked type of breathing, all he has to do is look at a watch with a second hand and use that to try to reduce the pattern of breathing down to the normal of about 15 breaths or so per minute, which is roughly one breath every four seconds.

TCPR: And where does the positive imagery come in?

Dr. Wright: I will suggest that once a patient has started slowing his breathing down and getting into a calm state, then he can let his mind go to a place that is very calming and peaceful; a place where there is really no worry or anxiety. So for me that might be walking along the beach with my feet sort of in and out of the waves on a warm day. But it's different for everyone, so the patient needs to decide. This mix of breathing training coupled with positive calming imagery can help lots of people begin to get some control of panic attacks.

TCPR: Great tips. Next, what is cognitive restructuring?

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Expert Interview, Jesse Wright, MD *Continued from page 6*

Dr. Wright: This technique works by helping people spot, and then change, the catastrophic thoughts they are having during panic attacks. Some classic automatic thoughts would be, "I'm going to have a stroke. I'm going to have a heart attack. I'm going to lose control." Those kinds of thoughts, when added to the physical sensations of a panic attack, create a vicious cycle and worsen the panic.

TCPR: And how do you teach people to restructure these thoughts?

Dr. Wright: First, I ask the patient to write those fears down on a "thought record," and then take a look at how realistic they are. Next, we come up with some alternate thoughts that the patient can write down on a piece of paper or an index card and keep with him or her to look at when a panic attack is starting. Examples of these thoughts might be, "This is just a panic attack. I can control it by breathing regularly at about one cycle every four seconds." "I have seen my doctor and there is no evidence of heart disease. I'm misinterpreting a fast heart beat. I can calm my thoughts, and I'll be okay."

TCPR: While these sound like extremely helpful techniques, is it really possible to accomplish all this within the time constraints of short psychiatric office visits?

Dr. Wright: I have found that if I can get someone going on a "thought change record" or some of the other methods that we discussed earlier, he or she can work with this self-help exercise for homework between visits, and this skill-building method often is quite beneficial. Some patients with uncomplicated disorders can be treated just with brief CBT sessions combined with pharmacotherapy. But, of course, there are others who may need more extensive psychotherapy. One option to consider is "front loading" of CBT. This means that in the early phase of treatment, a patient might have more frequent and/or intensive sessions to learn the techniques. They might see a psychiatrist or another psychotherapist for six to 10 sessions, and then the rest of the treatment is done by a psychiatrist with brief sessions only. This method may be particularly useful for patients with illnesses such as chronic depression or bipolar disorder that may require long-term management by a psychiatrist.

TCPR: So once a patient knows how to do CBT, it is possible to do maintenance therapy during short visits.

Dr. Wright: Yes. The brief session format can work quite well for patients who require ongoing treatment. Another method that can help clinicians and patients make good use of brief sessions is computer-assisted cognitive therapy. It's a great way for people to build basic knowledge and skills so that the therapist doesn't have to spend a whole session teaching how to do a thought record or what an automatic thought is. I also strongly suggest having a stack of handouts or suggesting workbooks to give patients for home study.

TCPR: Now, please tell us about relaxation training.

Dr. Wright: A psychiatrist can teach relaxation training in the office or recommend a digital recording or a website where the patient can learn how to use this calming exercise. Relaxation techniques are easy, effective, and can be implemented in the space of five to 10 minutes in a session. Relaxation training typically involves teaching patients how to systematically control the muscle tension in major muscle groups throughout the body. Often it is coupled with positive imagery. This method was introduced by Jacobsen in the 1930s and has been used extensively as part of CBT methods for anxiety disorders for many years.

TCPR: How do you think medication fits with CBT in treating panic?

Dr Wright: Therapy and serotonin-active antidepressants can work well together, although benzodiazepines can interfere with the effectiveness of CBT, particularly alprazolam (Xanax) (Marks IM et al, *Brit J Psychiatry* 1993;162(6):776–787). There is some thought that longer acting benzodiazepines may not have that problem. So if I am using combined pharmacotherapy and CBT for panic disorder, I would typically choose an SSRI and would try to avoid a benzodiazepine if possible. If a benzodiazepine seems to be necessary, lorazepam (Ativan) or clonazepam (Klonopin) might be a better choice than alprazolam.

TCPR: Thank you, Dr. Wright.

The editors at *The Carlat Psychiatry Report* love to hear from our readers. Do you have story ideas, feedback on articles, or other information you would like to share? You can email managing editor Amy Harding at aharding@thecarlatreport.com, or find us on Facebook. Search for "The Carlat Report." We look forward to hearing from you!

Q&A With the Expert

This Month's Expert

Exposure and Response Prevention Therapy for OCD

Bruce Hyman, PhD

Director
OCD Research Center of Florida

Dr. Hyman has disclosed that he receives books royalties from Lerner Publishing and New Harbinger Publications. Dr. Carlat has reviewed this article and found no evidence of bias in this educational activity.

TCPR: Dr. Hyman, most of your day-to-day work is with OCD patients. What therapeutic techniques are best for these patients?

Dr. Hyman: Exposure and response prevention (ERP) is an extremely effective therapy. Of course, the individual response varies from patient to patient, but we know that this is an effective treatment regimen. Patients are not used to therapists saying: "This will work." Usually we say: "Well there is a chance it will work. We will give this a shot," and so on. But you can say with conviction that if a patient commits to this therapy, it really has a good chance of reducing suffering.

TCPR: What is ERP?

Dr. Hyman: Basically, it is exposing a patient to the thing or things that cause anxiety or avoidance, and then helping him or her learn appropriate alternative responses to those situations. The art of this is in how you get patients to do things that are uncomfortable. But if you can enroll the patient in the possibility of significant relief with full participation in the therapy process, we see some really good outcomes.

TCPR: It must be a real challenge, though, getting people to sign on to expose themselves to something they are obsessed with avoiding.

Dr. Hyman: There is an inbred kind of resistance to the whole notion of exposure therapy among a fairly sizeable proportion of OCD patients. A lot of them have seen television shows and documentaries on ERP, and the first thing they say to themselves is, "No way am I doing that!" The other problem is the availability of these treatments. You can't just pick a therapist out of your provider panel from your insurance company and think he or she will be familiar with this.

TCPR: So how do you "sell" this treatment to a patient?

Dr. Hyman: Well, I start with the overall theories of how the symptoms are maintained from a cognitive behavioral perspective. For example, I will explain to the patient the process by which obsessions and compulsions are initiated and maintained. Typically it starts with a situation that causes anxiety or concern, which can happen completely by accident, like standing in line at the checkout counter at the grocery store, and noticing an oozing cut on the arm of the cashier. Then the thought occurs, "What if that person bleeds all over my groceries?! I'll surely get AIDS and die!" But you don't want to appear rude so you tough it out, buy your groceries, then leave. But over the course of days and weeks, the patient starts developing avoidance strategies to situations involving blood and bodily fluids for the purpose of preventing some potential danger or harm to themselves or to someone they care about. So it starts with a thought, and that fearful thought is fueled by the behaviors or compulsions that are performed to neutralize the anxiety of that thought.

TCPR: And this is where people get into avoidant behavior.

Dr. Hyman: Yes, so I talk about what avoidance is and that by avoiding a situation or a thought, they actually increase the prevalence and intensity of that thought. I compare it to the familiar Chinese finger trap—the harder you pull to get out of the trap, the tighter it gets. I often tell patients that the OCD is mislabeled. It really should be compulsive-obsessive disorder because as much as the obsessions leads to the compulsions, the compulsions lead to the obsessions. What I try to get across to the patient is that as much as we try, we do not have control over our thoughts; what we do have control over is our response to those thoughts. So we are going to gear efforts in treatment to changing our relationship to those thoughts and not the thoughts themselves. Acting directly to change thoughts is not nearly as helpful as learning to change our responses to those thoughts.

TCPR: And how do you do that?

Dr. Hyman: We do it by purposefully activating our fears in a number of different situations that we typically avoid. In the course of the evaluation process I will ask for a list of situations that trigger anxiety and those avoidance responses. I explain to the patient that if we can activate your fear in these myriad situations, and at the same time try to control, manage, or change your response to those situations repeatedly over time, our experience is that the obsessions will decrease, the anxiety will go down, and the urge to do the compulsions actually diminishes as well.

TCPR: Let's say we as psychiatrists want to start doing this with some of our patients. Can you give us a typical patient scenario?

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Research Updates IN PSYCHIATRY

Section Editor, Glen Spielmans, PhD

Glen Spielmans, PhD, has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

ANXIETY DISORDERS

Novel Program Effective for Anxiety Disorders in Primary Care

Jamie Horder, MD

Dr. Horder has disclosed that he has no relevant relationships or financial interests in any commercial company pertaining to this educational activity

Anxiety disorders are commonly seen in primary care, whether they present on their own, or comorbid with other illnesses. There's good evidence for both cognitive-behavioral therapy (CBT) and pharmacotherapy in anxiety disorders, but many patients don't receive such treatment.

A team led by Michelle Craske of UCLA recently evaluated an evidence-based treatment program for anxiety in primary care patients. More than 1,000 patients from primary care practices throughout the U.S. were enrolled, all of whom suffered from one or more of the following: generalized anxiety, panic, social phobia, and PTSD. Patients were randomly assigned to either the active intervention, "CALM" (Coordinated Anxiety Learning and Management), or treatment as usual.

Patients who were randomized to CALM treatment had the option of choosing CBT, medication treatment, or a combination of both. (The majority chose the combination, followed by CBT only, while less than 10% opted for meds only.) The CBT entailed six to eight sessions of computer-aided therapy provided by "anxiety clinical specialists," who were primarily either social workers or registered nurses with no prior expertise in CBT. They were given a three day intensive CBT training specifically for this research study. The medication treatment was based on an algorithm directing PCPs to start with either SSRIs or SNRIs, and to push the dose as high as the patient could tolerate before switching meds.

The control group received "usual care," which was whatever treatment their primary care physicians were able to provide, including referral to a mental health specialist.

Did CALM make these patients calmer? Mostly. For all patients except those with primary PTSD, the CALM group reported better outcomes than the controls on standard rating scales such as the Panic Disorder Severity Scale–Self-Report. The effects were moderate with numbers-needed-to-treat (NNT) of five to seven. Most of the benefits were maintained 18 months later. Unfortunately, the authors did not report outcomes separately for CBT vs combination vs meds only, presumably because there weren't enough subjects to make such comparisons statistically meaningful (Craske MG et al, *Arch Gen Psychiatry* 2011;68(4):378–388).

TCPR's Take: We already knew that CBT and drugs work in anxiety. This study shows that these treatments can be implemented effectively in primary care settings. More novel is the suggestion that only three days of training is needed for nurses and social workers to provide effective computer-aided CBT. The computer program used can be viewed on YouTube at www.youtube.com/user/CHAMMPTraining

DEPRESSION

Serotonin Transporter Genotype: Involved In Depression After All?

Steve Balt, MD

Dr. Balt has disclosed that he has no relevant relationships or financial interests in any commercial company pertaining to this educational activity

Demonstrating the value of genetic testing in psychiatry is a tricky proposition. The latest case in point is the debate over whether determining variations in the gene coding for the serotonin transporter pump (5-HTTLPR) is useful for predicting future risk for depression.

A widely cited 2003 study showed that the homozygous SS genotype of the 5-HTTLPR gene predisposes people to developing depression if they are subject to stressful life events (Caspi A et al, *Science* 2003;301(5631):386–389). As a result of the excitement generated by this finding, dozens of studies tried to replicate the result, but two large meta-analyses of these studies, both published in 2009 quashed the enthusiasm, both concluding that there was no "gene × environment" interaction with the S allele (Munafò MR et al, *Biol Psychiatry* 2009;65(3):211–219; Risch N et al, *JAMA* 2009;301(23):2462–2471).

Now, these wet blankets are being called into question. A brand new study analyzed all 54 studies they could find (total n=40,749), while the previous meta-analyses only included five and 14 studies, respectively. The new study (Karg K et al, *Arch Gen Psychiatry* 2011;68(5):444–454) included childhood maltreatment and other specific medical stressors (such as hip fracture, interferon-alfa treatment, and heart disease) rather than limiting the studies to those that measure recall of general "stressful life events."

This larger study found that the presence of the S allele seems to make patients more sensitive to childhood maltreatment and to specific medical conditions (with p=0.00007 and p=0.0004, respectively). There was less evidence for an association with stressful life events, although this was significant, too (p=0.03). Although odds ratios were not reported, and the 54 studies varied widely in how they measured stressors or depression scores, the findings were generally consistent across all published papers. The authors even calculated that an additional 729 negative unpublished

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Expert Interview, Bruce Hyman, MD

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Dr. Hyman: Let's say someone has anxiety about touching a napkin in a public place. I create a set of exposure exercises where she actually comes into direct contact with what she considers a contaminated napkin. You can do this physically in your session or encourage her to go to the food court at the mall and take the first napkin on the top of the pile, which a lot of people with OCD won't do. So a psychiatrist can encourage the patient to take a chance to do some of things that she avoids, because that avoidance is keeping the OCD problem active and frequent and intense.

TCPR: Is it possible for a psychiatrist to successfully do this kind of therapy if he or she sees a patient no more than every month or so?

Dr. Hyman: The dose of treatment has to be in proportion to the severity of the symptoms. So more severe patients need more frequent exposure sessions, and more monitoring of their exposures between sessions. But you can check in with them over the phone or via email to make sure they're keeping up with their exposures when you don't get to see them in person. Patients who are really severe need more guidance and oversight and accountability to do things that they are really afraid of. If you tell these people to go to the mall and touch a toilet seat, they're just not going to do it. But for more mild to moderate cases, they will more likely do some self-directed exposure.

TCPR: Tell us about treating intrusive thoughts in OCD.

Dr. Hyman: There is a technique called imaginal exposure that we do specifically with patients who have intrusive thoughts. Imaginal exposure narratives are three to five minute long first-person accounts of a situation where a person's anxiety is activated and his or her worst fear actually comes true. I have the patients actually write these out and then we go over them together.

TCPR: For example?

Dr Hyman: Let's say a female patient has the thought: "What if I lose control and stab my child?" I would have her write an imaginal exposure narrative describing the scene where she has a knife; she's in the kitchen; she loses control; she plunges it into the child's heart. This is a gruesome kind of scene, but the idea here is to activate the patient's fear by making her think these thoughts. And in doing this imaginative exposure narrative over and over, she will see that she is not going to act on these thoughts, that she is still in control of herself despite what her thoughts say or what she believes her thoughts tell her to do.

TCPR: Are many of your patients also being treated with an SSRI when you see them?

Dr. Hyman: I would go so far as to say 90% to 100% of my patients have been through the gamut of SSRIs. In many cases they are non-responders or partial responders. I always get a complete medication history, because especially in the more severe and disabling cases, you would like to see at least a modicum of symptom relief from medication as it will make the cognitive behavioral therapy go more smoothly.

TCPR: Thank you, Dr. Hyman.

Suggested Reading for OCD Patients, Families, and Therapists

The OCD Workbook, 3rd edition. By Bruce Hyman and Cherry Pedrick. New Harbinger Publications (2010).

Loving Someone with OCD: Help for You and Your Family. By Karen J. Landsman, Kathleen M. Rupertus, and Cherry Pedrick. New Harbinger Publications (2005).

What to do when your Child has Obsessive-Compulsive Disorder: Strategies and Solutions. By Aureen Pinto Wagner. Lighthouse Press, Inc (2002).

Research Updates

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studies would be necessary to negate their results, demonstrating no obvious publication bias.

The authors conclude that the 5-HTTLPR genotype does, after all, moderate the relationship between stress and depression. Readers may also recall a similar reversal involving 5-HTTLPR genotype and SSRI response, in which a larger study showed no relationship between antidepressant response and genotype, after isolated smaller studies had shown a correlation (*TCPR,* November 2010).

TCPR's Take: The S allele of the 5-HTTLPR gene may interact with specific early life stressors in the development of depression. But given the complexity of genetic studies and the history of reversal of findings after efforts to replicate, we don't recommend that you refer your patients for genetic analysis quite yet.

ANTIDEPRESSANTS

Combined Antidepressants No More Effective than Monotherapy

The well known Star*D trial yielded disappointingly low remission and response rates in depressed patients who were put on citalopram (Celexa) for eight weeks. Recently, some clinicians have advocated starting depressed patients with a combination of antidepressants, in the hopes that targeting multiple neurotransmitters will boost efficacy. While this makes sense theoretically, the practice has thus far been tested only in a couple of small short-term trials, with positive results. A recent NIMH-funded study represents the first large study of combination treatment vs monotherapy as an initial treatment for depressed patients.

A total of 665 patients with chronic or recurrent depression were randomly assigned to one of three treatments: escitalopram (Lexapro) 10 mg to 20 mg + placebo; Lexapro + bupropion SR (Wellbutrin) 300 mg to 400 mg; or venlafaxine XR (Effexor) 150 mg to 300 mg + mirtazapine (Remeron) 15 mg to 45 mg (this last combination has

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CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer at least six questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by July 31, 2012. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password or if you cannot take the test online, please email info@thecarlatreport.com or call 978-499-0583.

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Below are the questions for this month's CME post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning objectives are listed on page 1.

1. When tapering benzodiazepines, what is a good rule of thumb to follow (Learning Objective #1)?
   [ ] a. abrupt discontinuation [ ] b. reduce by about 50% every day
   [ ] c. reduce by about 5% every day [ ] d. reduce by about 5% every two days

2. For the equivalent of a 1 mg tablet of lorazepam (Ativan), your patient could take which of the following (LO #1)?
   [ ] a. two 0.25 mg tablets of alprazolam (Xanax) [ ] b. two 25 mg capsules of chlordiazepoxide (Librium)
   [ ] c. two 10 mg tablet of diazepam (Valium) [ ] d. one 7.5 mg capsule of temazepam (Restoril)

3. Which of the following drugs are FDA approved for the treatment of PTSD (LO #2)?
   [ ] a. doxepin (Sinequan)
   [ ] b. sertraline (Zoloft) and paroxetine (Paxil)
   [ ] c. olanzapine (Zyprexa) and risperidone (Risperdal)
   [ ] d. there are currently no medications approved by the FDA for PTSD

4. In "cognitive restructuring," what types of thoughts might a person with a panic disorder write down on a "thought change record," according to Dr. Jesse Wright (LO #3)?
   [ ] a. The details of the panic attack, "I can't breathe, my heart is racing"
   [ ] b. An image of a scene he or she might find comforting, "I am on a beautiful beach"
   [ ] c. A simple prayer or chant to recite, "Ohm"
   [ ] d. An alternate thought to the panic, "This is just a panic attack; I will be okay."

5. What is "imaginal exposure" according to Dr. Bruce Hyman (LO #4)?
   [ ] a. This is a person's irrational fear of certain situations that can lead to avoidant behavior
   [ ] b. A therapeutic technique whereby a patient writes a narrative where his or her worst fears come true
   [ ] c. A tool people with OCD can use that involves positive imagery to distract from obsessive thoughts
   [ ] d. A therapeutic technique whereby a patient physically places him- or herself in an uncomfortable situation

6. What were the numbers needed to treat for the CALM intervention in the Craske et al study of treatments for anxiety disorders in primary care (LO #5)?
   [ ] a. 2 to 3 [ ] b. 4 to 5 [ ] c. 5 to 7 [ ] d. 10 to 12

7. The Karg et al meta-analysis found that the presence of the S allele of the 5-HTTLPR gene makes patients more sensitive to childhood maltreatment and specific medical stressors (LO #5)?
   [ ] a.True [ ] b. False

8. In the Rush et al study of combination treatment for depression, which treatment group had the most significant response at 12 weeks (LO #5)?
   [ ] a. Lexapro + placebo [ ] b. Effexor + Remeron
   [ ] c. Lexapro + Wellbutrin [ ] d. There was no difference in response among groups at 12 weeks

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achieved anecdotal renown as "California Rocket Fuel").

Dosing was increased if patients did not meet remission criteria as the study progressed. Patients were aware of the first medication (Lexapro or Effexor) but were blind to the second medication in their pair, though study physicians were aware of the second medication. Empirically supported psychotherapies for depression or other antidepressants were forbidden during the study. Outcomes were assessed at both 12 weeks and seven months.

There was no difference in response (52% for all groups at 12 weeks, 57% to 59% at seven months) or remission rates (38% to 39% at 12 weeks, 42% to 47% at seven months) among treatments. Further, all groups had roughly equal change on depression rating scales and measures of quality of life, anxiety, and work/social adjustment. Dropout rates also did not differ between treatments. Effexor-Remeron and Lexapro-Wellbutrin had higher side effect frequency and intensity compared to Lexapro-placebo at both 12 weeks and seven months, with the highest intensity, frequency and burden of side effects occurring in the Effexor-Remeron group (Rush AJ et al, *Am J Psychiatry* online ahead of print).

TCPR's Take: A couple of much smaller studies showed promising results for combination therapy but the current large trial severely dampens any enthusiasm for starting patients on combined treatment. We recommend following the standard practice of starting with a single antidepressant and tinkering with combinations only if there is no significant response.

Next Month in *The Carlat Psychiatry Report:* The treatment of alcoholism, with articles on current medications and an update on diagnostic issues.

This Month's Focus:
Anxiety Disorders

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