THE CARLAT REPORT PSYCHIATRY

A CME Publication

Subscribe today! Call 866-348-9279

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Steve Balt, MD
Editor-in-Chief

Volume 11, Number 9
September 2013
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Anxiety Disorders

Learning objectives for this issue: **1.** Describe the use of antipsychotics and anticonvulsants for anxiety disorders. **2.** List medications approved by the FDA to treat anxiety disorders. **3.** Detail how anxiety is addressed in *DSM-5*. **4.** Understand some of the current findings in the literature regarding psychiatric treatment.

Antipsychotics and Anticonvulsants for Anxiety Disorders

Steve Balt, MD, MS
Editor-in-chief

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

We know how frequently our patients complain of anxiety. Anxiety disorders are common, chronic conditions. They also increase the risk for mood and substance disorders, and complaints of anxiety are found in a wide range of other psychiatric and medical conditions, as well.

Pharmacologically, the two pillars of anxiety treatment for several decades have been the benzodiazepines and antidepressants (MAOIs, TCAs, SSRIs, and SNRIs), but new medications—particularly the atypical antipsychotics and anticonvulsants—have emerged in recent years to expand our repertoire.

Atypical antipsychotics (AAPs) are prescribed widely—sometimes with data to support their use, sometimes not. As

Continued on page 2

In Summary

- No atypical antipsychotics are FDA approved for anxiety indications; in studies, quetiapine (Seroquel) XR has the best evidence for effectiveness in GAD
- Two first-generation antipsychotics are approved for anxiety: trifluoperazine (Stelazine) and perphenazine and amitriptyline (formerly marketed as Triavil)
- Except for benzos and barbituates, pregabalin (Lyrica) is the best anticonvulsant for GAD
- Lack of FDA approval or evidence for most AAPs and anticonvulsants may be more a result of heterogeneity among anxiety disorders than issues with effectiveness of medications

Q&A With the Expert

Anxiety Disorders in DSM-5 and Beyond

Daniel Pine, MD

Chief, Section on Development and Affective Neuroscience
National Institute of Mental Health
Chair, DSM-5 Work Group on Child and Adolescent Psychiatric Disorders

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

TCPR: Dr. Pine, can you describe the background on the two new categories for anxiety disorders in *DSM-5:* Obsessive-Compulsive Disorders and Trauma- and Stressor-Related Disorders?

Dr. Pine: First, I will say that the overall changes from the standpoint of the day-to-day practice of a clinician are pretty mild and minor. The biggest change to anxiety disorders in *DSM-5* is taking a collection of syndromes that were all grouped together in *DSM-IV* and splitting them into these three groups. One group, the obsessive-

Continued on page 4

Antipsychotics and Anticonvulsants for Anxiety Disorders
Continued from page 1

of September 2013, no AAP has been approved for use in anxiety, although it's not uncommon to see one used when a patient is refractory to other treatments.

The mechanism of action of AAPs in anxiety is unclear. Some, like aripiprazole (Abilify) have serotonin-1A partial agonist properties, similar to buspirone (BuSpar), while others, like quetiapine (Seroquel), have strong antihistamine properties, similar to hydroxyzine (Vistaril, Atarax). No common mechanism has been determined.

As an important historical footnote, two first-generation antipsychotics have been approved for anxiety: trifluoperazine (Stelazine) for short-term treatment of generalized anxiety, and the combination of perphenazine and amitriptyline (formerly marketed as Triavil) for "depression and anxiety" (Pies R, *Psychiatry* (Edgemont) 2009;6(6):29–37). But these drugs rarely appear on psychiatrists' radar screens these days.

EDITORIAL INFORMATION

President and CEO: **Steve Zisson**

Executive Editor: **Amy Harding, MA**

Associate Editor: **Marcia L. Zuckerman, MD,** director of Psychiatric Services at Walden Behavioral Care.

Editor-in-Chief: **Steve Balt, MD,** psychiatrist in private practice in the San Francisco Bay area.

Editorial Board:

Ronald C. Albucher, MD, director of counseling and psychological services, clinical associate professor of psychiatry, Stanford University, Palo Alto, CA

Richard Gardiner, MD, psychiatrist in private practice in Potter Valley, CA

Ivan Goldberg, MD, creator, Depression Central website, psychopharmacologist in private practice, New York City, NY

Alan D. Lyman, MD, child and adolescent psychiatrist in private practice, New York City, NY

James Megna, MD, PhD, director of inpatient psychiatry, associate professor of psychiatry and medicine at SUNY Upstate Medical University, Syracuse, NY

Robert L. Mick, MD, contract physician in addiction medicine and military psychiatry in Bloomfield, NY.

Michael Posternak, MD, psychiatrist in private practice, Boston, MA

Glen Spielmans, PhD, associate professor of psychology, Metropolitan State University, St. Paul, MN

All editorial content is peer reviewed by the editorial board. Dr. Albucher, Dr. Gardiner, Dr. Goldberg, Dr. Lyman, Dr. Megna, Dr. Mick, Dr. Posternak, Dr. Spielmans and Dr. Zuckerman have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity. Dr. Balt discloses that his spouse is employed as a sales representative for Otsuka America, Inc. This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

Generalized Anxiety Disorder

So how is the evidence? For generalized anxiety disorder (GAD), the best data are for quetiapine (Seroquel), particularly the XR form. In three industry-funded, placebo-controlled trials enrolling more than 2,600 subjects, subjects responded better to quetiapine XR (50 or 150 mg/day, but not 300 mg/day) than to placebo, as measured by a ≥50% decrease in the Hamilton Anxiety Scale (HAM-A) over eight weeks. One study also found quetiapine XR to be superior to escitalopram (Lexapro) 10 mg/day while another showed equivalence to paroxetine (Paxil) 20 mg/day. Remission was significantly more common with the 150 mg dose than with placebo (Gao K et al, *Expert Rev Neurother* 2009;9(8):1147–1158).

Despite these impressive numbers, quetiapine XR has not earned FDA approval for GAD, most likely because of the potential for widespread and prolonged use of this agent—which has well-known metabolic side effects and requires close monitoring—when safer alternatives are available. It's also possible that its short-acting (and cheaper) cousin quetiapine may do just as well as the XR form, but the two have not been studied head-to-head.

Randomized controlled trials of other AAPs in GAD have been unconvincing. Risperidone (Risperdal) was no more effective than placebo in a large (N=417) trial of patients with GAD refractory to anxiolytics (Pandina GJ et al, *Psychopharmacol Bull* 2007;40(3):41–57) even though a smaller study (N=40) was positive (Browman-Mintzer O et al, *J Clin Psychiatry* 2005;66:1321–1325). Olanzapine (Zyprexa) was effective in a very small study (N=46) as an adjunctive agent with fluoxetine (Prozac), but subjects experienced significant weight gain (Pollack MH et al, *Biol Psychiatry* 2006;59(3):211–225). Several smaller, open-label trials have shown some benefit for other AAPs (reviewed in Gao K, op.cit) but, other than the ones discussed here, larger placebo-controlled studies have been equivocal.

Other Anxiety Disorders

What about other anxiety disorders? For OCD, a pooled analysis of three studies of risperidone (0.5 to 2.25 mg/day) found risperidone to be slightly better than placebo, but the authors of the analysis suggested that these studies may have been affected by publication bias, given the variation in effect sizes (Maher AR et al, *JAMA* 2011;306(12):1359–1369).

PTSD is a complex disorder in which AAPs are frequently used, and small studies of olanzapine (15 mg/day, N=19) (Stein MB et al, *Am J Psychiatry* 2002;159:1777–1779) and risperidone (Bartzokis G et al, *Biol Psychiatry* 2005;57(5):474–479) as adjunctive treatment for combat-related PTSD have shown some promise, but other published trials, including a more recent larger PTSD trial (Krystal JH et al, *JAMA* 2011;306(5):493–502), have been negative.

Because most trials have been small, and negative trials have been as numerous as positive ones—not to mention the lack of head-to-head trials of these agents—it's difficult to make a solid recommendation for any particular AAP in the treatment of anxiety. The existing meta-analyses of these agents for specific anxiety disorders argue for "further study" (Fineberg NA, *FOCUS* 2007;5(3):354–360) and larger trials. Of course, what we're *treating* may also vary in significant ways, a point we'll return to later.

Anticonvulsants

Newer on the anti-anxiety scene are the anticonvulsants. All anticonvulsants work via some combination of sodium- or calcium-channel blockade, GABA potentiation, or glutamate inhibition, but individual agents vary in their precise mechanisms. Because anxious symptoms are thought to result from activation of fear circuits, primarily involving the amygdala, hippocampus, and periaqueductal gray, and because anticonvulsants are designed to specifically prevent excessive neuronal activation, their use in anxiety seems rational. Do the data support this?

Unfortunately, despite more than

Continued on page 3

Antipsychotics and Anticonvulsants for Anxiety Disorders
Continued from page 2

a dozen anticonvulsants approved for human use, only one anticonvulsant (other than the benzodiazepines and barbiturates, which won't be discussed here) shows a benefit for anxiety in several randomized clinical trials, and that's pregabalin (Lyrica), for GAD.

Pregabalin is a GABA analogue but its primary effect appears to be blockade of the alpha-2-delta subunit of the N-type calcium channel, preventing neuronal excitation and neurotransmitter release. (This is also one mechanism of action of gabapentin [Neurontin], a close relative.)

Generalized Anxiety Disorder

Several controlled trials, all funded by the drug's manufacturer, have shown that pregabalin, at doses ranging from 300 to 600 mg/day, can reduce symptoms of generalized anxiety as measured by the HAM-A. Three of these studies also found pregabalin's effect to be similar to that of lorazepam (Ativan), alprazolam (Xanax), and venlafaxine (Effexor), respectively. A later meta-analysis of placebo-controlled anxiety trials (with no pharmaceutical industry funding) found pregabalin to have a higher effect size (0.5) in reduction of HAM-A scores than the benzodiazepines (0.38) and SSRIs (0.36) for GAD (Hidalgo RB et al, *J Psychopharm* 2007;21(8):864–872).

Despite its apparent efficacy, pregabalin is also associated with an elevated, dose-dependent risk of dizziness, somnolence, and weight gain (Strawn JR and Geracioti TD, *Neuropsych Dis Treat* 2007;3(2):237–243). It is likely that these adverse effects explain why pregabalin was rejected by the FDA as a treatment for generalized anxiety disorder back in 2004, and again in 2009, even though it was approved in Europe in 2006 for this indication.

Other Anxiety Disorders

Other than pregabalin, placebo-controlled clinical trials reveal few other bright spots for anticonvulsants in anxiety disorders. For the treatment of panic disorder, gabapentin, at doses as high as 3600 mg/day, has been shown in an open-label study to be more effective than placebo. Several open-label studies in PTSD show some benefit of topiramate (median 50 mg/day) and lamotrigine (500 mg/day but N=10 only), while social phobia may benefit from pregabalin (600 mg/day) and gabapentin (900–3600 mg/day). Anecdotal reports of improvement in OCD can be found for just about every anticonvulsant, but the only one with several such reports is topiramate (Topamax) (mean dose 253 mg/day), particularly in augmentation with SSRIs (for a review, see Mula M et al, *J Clin Psychopharm* 2007;27(3):263–272). As always, open-label studies need to be interpreted with caution, as those that are negative are unlikely to be published.

Why the Mixed Results?

A casual read of the data, not to mention abundant case reports and anecdotal evidence, suggests that many anticonvulsants and atypical antipsychotics *could* work for anxiety disorders, but in controlled trials, most show little or no effect compared to placebo. Why the discrepancy? A very likely answer is because of the heterogeneity of anxiety disorders themselves. Not only are the "typical" presentations of OCD, PTSD, and social phobia likely to be very dissimilar to each other (see the Expert Q&A with Dr Pine in this issue), but even within a given diagnosis, anxiety can manifest very differently.

Moreover, comorbidity is very high in anxiety disorders. "Fear" disorders like phobia, panic, and OCD are commonly seen together, as are the "distress" or "misery" disorders like GAD and PTSD. All of the above are highly comorbid with mood disorders and substance abuse or dependence (Bienvenu OJ et al, *Curr Top Behav Neurosci* 2010;2:3–19), not to mention medical illnesses.

The way we describe and measure anxiety itself creates tremendous variability. There are distinct differences, for instance, between criteria for GAD in the DSM (used in most American research), and in the ICD-10 (used primarily in Europe). ICD-10, for instance, requires autonomic arousal while the DSM does not; and the DSM criteria for GAD require "significant distress or impairment," unlike ICD-10. Similarly, the most commonly used symptom rating scale, the HAM-A, contains some items that pertain to somatic anxiety, and others addressing psychic anxiety. Medications may target somatic and psychic symptoms differently (Lydiard RB et al, *Int J Neuropsychopharmacol* 2010;13(2):229–241).

And then there's the consideration of what we call anxiety in the first place. We've shed the vague psychoanalytic label of "neurosis," and since *DSM-III* we've described these conditions as "anxiety disorders," but the boundaries have continued to shift. *DSM-5,* for instance, includes two new categories of "Obsessive-Compulsive Disorders" (which includes OCD, body dysmorphic disorder, and others) and "Trauma- and Stressor-Related Disorders" (which includes PTSD and adjustment disorders), reflecting differences in neurobiology and treatment relative to other anxiety disorders. Some even argue that anxiety, in many cases, is simply the brain using its own fear circuitry in an adaptive way, in which case, nothing is "dysfunctional" at all (Horowitz AV and Wakefield JG, *All We Have To Fear.* New York: Oxford University Press; 2012; see also Kendler KS, *Am J Psychiatry* 2013;170(1):124–125).

So when it comes to medication management, asking whether a given medication is useful for anxiety is like asking whether a turkey sandwich is a good lunchtime meal: for some people, it hits the spot, but for others (like vegetarians) it should be avoided. A better understanding of the neurobiology of different anxiety disorders, the response of individual symptoms to particular medications, and the role of other drugs—and psychotherapies—in their management, will help us to optimize, and individualize, outcomes for our anxious patients.

TCPR'S VERDICT: Atypical antipsychotics and anticonvulsants may have a role in the treatment of anxiety disorders. The lack of FDA approval or strong evidence supporting any individual treatment—with a few exceptions—may speak more to the problems of diagnosis and clinical trial methodology than to the failures of medications themselves.

Expert Interview
Continued from page 1

compulsive and related disorders, has OCD as its signature condition; a second, the trauma- and stressor-related disorders, contains PTSD and adjustment disorders; and a third comprises all the other anxiety disorders. When you look at the external validators—or the things besides the symptoms, such as the patterns of comorbidity, longitudinal associations, familial aggregation, or biology—the three groups of disorders kind of fall out in terms of how closely related they are to each other.

TCPR: What are some of the relationships among anxiety disorders that help to shape these new categories?

Dr. Pine: One of the most striking associations is the relationship between tic disorders and obsessive-compulsive disorders, which is uniquely strong, and there is some hint that they also follow the same familial pattern. Similarly, from a longitudinal perspective, particularly when OCD has an onset in childhood, I think the disorder is more stable. It is less likely to have a spontaneous remission. There is also some suggestion that the treatment approach is different in that there tends to be a pretty low placebo response rate and response rate to some of the antidepressants, such as imipramine (Tofranil). There are some hints from neuroscience to suggest that obsessive-compulsive disorder, much like the tic disorders, involves a certain type of dysfunction in the prefrontal cortical striatal-thalamo-cortical loops that is different from the kind of dysfunction that one sees in phobias, generalized anxiety disorder, or panic disorder, where there is thought to be a more prominent amygdala component.

As of now, there really is no test using brain imaging, genetics, or any other measure that can tell us that this patient with anxiety that presents in this way will respond to this treatment vs that treatment.

Daniel Pine, MD

TCPR: What new data have come up since *DSM-IV* in terms of treatment?

Dr. Pine: One important message to come out since *DSM-IV* is that in different clinical scenarios there is different evidence for the relative advantages and disadvantages of various combinations of serotonergic antidepressants and cognitive behavioral therapy (CBT). For instance, in pediatric anxiety disorders there are probably the clearest findings that combination treatment worked better than either therapy alone (Walkup JT et al, *NEJM* 2008;359(26):2753–2766). For the other anxiety disorders, there hasn't been a greater advantage for combination therapy, and if anything, I think that particularly for obsessive-compulsive disorder, both in children and adults, cognitive behavioral therapy has emerged as a really solid treatment (see for example, Simpson HB et al, *JAMA Psychiatry* 2013;Sept 11, online first). Overall, there is a real success story in terms of both the range of treatments that are available for people with anxiety disorders and their durability or ability to get people with anxiety well.

TCPR: What is new on the treatment horizon for anxiety disorders?

Dr. Pine: There has been a great interest in using what we have learned about neuroscience to come up with new treatments. And there really are two main exciting avenues. One is through extending what we know about the underlying neurocircuitry of extinction. Extinction is a process that is usually studied in rodents where a rodent learns to overcome a fear that has been acquired through learning. There is a great interest in using our knowledge of the underlying neural architecture, and the associated molecular targets of that architecture, to come up with better ways to enhance cognitive behavioral therapy. D-cycloserine is the agent where there has been the most interest, and there are some suggestions that it enhances cognitive behavioral therapy, though maybe not as much as we had hoped when the first set of studies came out. But more important, this is a different approach in that it generates hypotheses about novel treatments that are based on what we have learned in neuroscience. The other really good example refers to aspects of cognitive perturbations where we have mapped the underlying neurocircuitry and then we have used that knowledge to come up with novel ways to train cognition.The major interest has been on attention, and the observation has been that people with anxiety disorders have a very rapidly deployed bias in their attention that is thought to at least partially reflect perturbations in the amygdala. And the idea here is that this bias is deployed incredibly rapidly, so rapidly that patients aren't even aware of it. So there has been interest in computer-generated training to shift patients' biases. And again there is a hint that this might be a way to develop new efficacious treatments. Again, it is early, and like in d-cycloserine I don't think we are ready to broadly apply these clinically, but it does kind of point to a path where basic neuroscience gives us ideas about novel treatments that can then be tested.

TCPR: Let's talk basics: We all have a lot of people come into our offices with complaints of "anxiety," but what exactly is clinical anxiety?

Dr. Pine: Anxiety is the way the body responds to danger, and there are many aspects of this response. There are changes in physiology that prepare the body to respond to danger; there are hormones, neurochemicals, and autonomic responses that normalize the body to cope with danger; there are behavioral responses, such as avoidance; and there are subjective responses, such as the feeling of being afraid. While anxiety involves increases in all of these things, they don't always go together. So in some situations people might have a very robust autonomic or physiologic response, but they might not feel particularly afraid. In other situations, they might have a robust behavioral response, but they might not have such changes in physiology. Having an anxiety response is something that is adaptive, functional, and allows people to live safe and productive lives. In fact, people who don't have anxiety responses can be thought of as suffering from a problem. But the question is: How exactly do we draw a line between where normal anxiety ends and abnormal anxiety starts? It is easiest to recognize anxiety as a problem when it is interfering with an individual's ability to do something that they really have to do, such as the daily activities

Continued on page 6

FDA-Approved Medications for Anxiety		
Medication Name	**Brand/Trade Name**	**FDA Indications (anxiety indications in bold)**
Antipsychotics		
Perphenazine and amitriptyline	Triavil (discontinued)	**Moderate to severe anxiety and/or agitation and depressed mood, depression with severe anxiety and/or agitation, depression and anxiety in association with chronic physical disease,** schizophrenia (approved in adults only)
Trifluoperazine	Stelazine	**Generalized anxiety disorder (GAD),** schizophrenia (ages 6+)
Benzodiazepines		
Alprazolam	Xanax, Xanax XR	**GAD, panic disorder** (approved in adults only)
Chlordiazepoxide	Librium	**GAD (ages 6+),** perioperative anxiety, alcohol withdrawal
Chlordiazepoxide and amitriptyline	Limbitrol	Depression with anxiety, moderate to severe (approved in adults only)
Clonazepam	Klonopin	Seizure disorder, **panic disorder with or without agoraphobia** (approved in adults only)
Clorazepate	Tranxene	**GAD,** partial seizures (ages 9+), alcohol withdrawal
Diazepam	Valium	**GAD,** alcohol withdrawal, adjunct for skeletal muscle spasm and convulsive disorders (ages 6 months+)
Flurazepam	Dalmane	Insomnia (approved in adults only)
Lorazepam	Ativan	Status epilepticus (age 6 months+), preanesthetic, **GAD**
Oxazepam	Serax (discontinued)	**GAD,** alcohol withdrawal (approved in adults only)
Temazepam	Restoril	Insomnia (approved in adults only)
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)		
Desvenlafaxine	Pristiq	Major depressive disorder (MDD) (approved in adults only)
Duloxetine	Cymbalta	MDD, **GAD,** diabetic peripheral neuropathic pain (DPNP), fibromyalgia, chronic musculoskeletal pain (approved in adults only)
Venlafaxine	Effexor, Effexor XR	MDD, **GAD, social anxiety disorder, panic disorder with or without agoraphobia** (approved in adults only)
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Citalopram	Celexa	MDD (approved in adults only)
Escitalopram	Lexapro	MDD (ages 12+), **GAD** (approved in adults only)
Fluoxetine	Prozac, Prozac Weekly, Sarafem	MDD (ages 8+), **OCD (ages 7+), panic disorder,** bulimia, premenstrual dysphoric disorder (PMDD)
Fluvoxamine	Luvox, Luvox CR	**OCD (ages 8+), social anxiety disorder**
Paroxetine	Paxil, Paxil CR, Pexeva	MDD, **OCD, panic disorder with or without agoraphobia, social anxiety disorder, GAD,** PTSD (approved in adults only), PMDD
Sertraline	Zoloft	MDD, **OCD (ages 6+),** panic disorder with or without agoraphobia, PTSD, premenstrual dysphoric disorder (PMDD), social anxiety disorder
Vilazodone	Viibryd	MDD (approved in adults only)
Tricyclic Antidepressants		
Clomipramine	Anafranil	**OCD (ages 10+)**
Doxepin	Sinequan (discontinued)	**Anxiety (ages 12+)**
Amitriptyline, desipramine, imipramine, nortriptyline, protriptyline		MDD (none approved for anxiety indications)
Other		
Buspirone	BuSpar	**GAD (ages 6+)**

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.

PSYCHOSIS

Is Dose Reduction the Ideal Strategy after First Episode of Psychosis?

What's the optimal treatment for a first episode of psychosis? Few would argue against antipsychotic treatment, but what happens when the patient achieves remission? Is it best to continue medication indefinitely, or can the antipsychotic be reduced or discontinued altogether?

One hundred and twenty eight patients who had a first episode of psychosis (FEP) in 2001–2002 were successfully treated with antipsychotics. Of these, half were randomized to continue medications (MT), and the other half to reduce their doses (DR) after six months of remission, tapering off of medications if possible. Most (N=103) were identified seven years later for a follow-up evaluation. Of these, half (N=52) had been randomized to the symptom-guided dose reduction (DR) strategy.

At the seven-year mark, investigators evaluated the patients for both symptomatic and functional recovery. Symptoms were measured by the Positive and Negative Syndrome Scale (PANSS); function was measured by the Groningen Social Disability Scale (GSDS). Rates of symptomatic remission were essentially identical between the two groups (MT, 66.7%; DR, 69.2%) while functional remission was significantly higher in those randomly assigned to the dose-reduction group (MT, 19.6%; DR, 46.2%). "Recovery," defined as both symptomatic and functional remission, was also higher in the DR group (MT, 17.6%; DR 40.2%).

Some patients in the MT group had discontinued antipsychotics or reduced their doses to amounts comparable to those in the DR group. When the investigators looked at all the patients who had either discontinued or reduced their doses to subtherapeutic levels (N=34), symptomatic remission was found in 85.3% (vs. 59.4% of those who had not, N=69) and functional remission in 55.9% (vs. 21.7%). These patients were also more likely to have recovered (52.9% vs. 17.4%).

When investigators looked at relapse rates over the seven-year trial, they found, perhaps not surprisingly, higher relapse rates in the DR group over the first three years. But they observed roughly equivalent rates thereafter. They argue that the key difference between the two groups after seven years is neither in relapse rate nor in level of symptoms, but in the degree of functional recovery, and that this measure requires further investigation, as it represents a better measure of patients' overall status (Wunderlink L et al, *JAMA Psychiatry* 2013, online ahead of print).

TCPR's TAKE: Few would argue that first-episode psychosis requires treatment, but this study suggests that maintenance of antipsychotics after remission may not be necessary. After the decrease or discontinuation of medications, symptoms do not become worse. In fact, function may actually improve over a seven-year period. The reasons are unclear, but they argue for a greater focus on functional improvement and psychosocial interventions than on maintenance antipsychotic medication.

Expert Interview

Continued from page 4

in their social life with their family or at work. When anxiety is so high that it prevents an individual from performing those duties, that is when we can think about anxiety as a problem that needs to be treated.

TCPR: You talked about the three aspects of anxiety being the autonomic, behavioral, and subjective. If we are able to differentiate those symptoms as they present in our patients, does that dictate treatment as well?

Dr. Pine: I think that is where people want to get, but we're not there yet. There is interest in biomarkers or tests that we can use to guide treatment. However, as of now there really is no test using brain imaging, genetics, or any other measure that can tell us that this patient with anxiety that presents in this way will respond to this treatment vs that treatment.

TCPR: Do you recommend any clinical scales or questionnaires for diagnosis or evaluating treatment?

Dr. Pine: There are many research scales, such as the Hamilton rating scale, that as a clinician I use. I like to use both clinician-based measures and self-report measures. However, I think that there is no substitute for a careful, thorough clinical assessment performed by the clinician. So I think rating scales are helpful to guide the clinician's thinking, but ultimately decisions about diagnosis and the appropriate way to treat have to be based on a clinical assessment that comes from sitting down with patients and hearing their stories and having the chance to question them about the kinds of things that they might fill out on a rating scale.

TCPR: In your paper in the journal *Depression and Anxiety* (Craske MG et al, *Depression Anxiety* 2009;26:1066–1085)

Recommended Resources on Anxiety Disorders

Anxiety and Depression Association of America (ADAA): www.adaa.org
The American Journal of Psychiatry: ajp.psychiatryonline.org
JAMA Psychiatry: archpsyc.jamanetwork.com/journal.aspx
Depression and Anxiety (journal): http://bit.ly/crvnoZ

Annual Meetings
Anxiety and Depression Association of America (ADAA)
The Society of Biological Psychiatry
The American Psychological Association
The American Psychiatric Association
The Association for Behavioral and Cognitive Therapies (ABCT)

Continued on page 7

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 four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by September 30, 2014. 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.

The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of two (2) *AMA PRA Category 1 Credit*™ or 2 CE for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

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. In clinical trials, which of the following atypicals shows the best results for anxiety (Learning Objective #1)?

   [ ] a) quetiapine (Seroquel) XR [ ] b) olanzapine (Zyprexa)
   [ ] c) risperidone (Risperdal) [ ] d) escitalopram (Lexapro)

2. In clinical trials, which of the following anticonvulsants has shown the best results for anxiety (LO #1)?

   [ ] a) gabapentin (Neurontin) [ ] b) pregabalin (Lyrica)
   [ ] c) topiramate (Topomax) [ ] d) lamotrigine (Lamictal)

3. Which of the following medications is FDA-approved to treat generalized anxiety disorder (LO #2)?

   [ ] a) aripiprazole (Abilify) [ ] b) paroxetine (Paxil)
   [ ] c) pregabalin (Lyrica) [ ] d) risperidone (Risperdal)

4. *DSM-5* distinguishes between anxious misery disorders and fear disorders (LO #3).

   [ ] a) True [ ] b) False

5. In the Wunderlink et al study of dose reduction, what percentage of patients in the dose reduction group achieved functional remission (as compared to 19.6% in the "continuing medication" group) at the seven-year mark (LO #4)?

   [ ] a) 8.2% [ ] b) 17.6% [ ] c) 46.2% [ ] d) 66.7%

PLEASE NOTE: WE CAN AWARD CME CREDIT ONLY TO PAID SUBSCRIBERS

Expert Interview

Continued from page 6

you draw an interesting distinction between the anxious misery disorders and the fear disorders. Can you summarize those differences?

Dr. Pine: Generalized anxiety disorder shows a particularly strong association with major depressive disorder, which is something that was recognized at *DSM-IV.* And there was a lot of thought about how this uniquely strong connection might be reflected in the nosology: might these two syndromes be part of this broader group of conditions that we can think of as "anxious misery disorders," which are different from things like panic disorder or the phobias. In the end, the data were not strong enough to justify making a change in *DSM-5* that would have grouped generalized anxiety and major depressive disorder in the same group of such "anxious misery" disorders.

TCPR: Is there any particular way to tackle the problem of comorbid depression and anxiety versus how we might treat a straightforward major depressive disorder?

Dr. Pine: Depression with concurrent anxiety is a common and particularly severe and worrisome condition. Unfortunately, there are no treatments that have definitively been established to work particularly well for major depression with anxiety disorders as opposed to without.

TCPR: What are some ways that practicing psychiatrists can learn CBT techniques for anxiety?

Dr. Pine: It is possible to learn, and it is a wonderful skill to have. To get started, you can find resources online. (See Dr. Pine's "recommended resources" box for more information.) ADAA (Anxiety and Depression Association of America) and ABCT (Association for Behavioral and Cognitive Therapies) both hold wonderful conferences where people can also start to learn all about CBT. The bigger question is the economics of it all. I think that the way reimbursement is going, it is not clear that psychiatrists are going to be reimbursed, at the rates that they desire, to deliver CBT. Unfortunately, CBT is the kind of thing where, if you are going to be good at it, you need to do it a lot. These economics issue could make it hard for psychiatrists to do a lot of CBT and get paid at the rates that they might be used to being paid.

TCPR: Thank you, Dr. Pine.

News of Note

MEDICATIONS

Fetzima Approved for Depression

In July 2013, the FDA approved the SNRI Fetzima (levomilnacipran) for major depressive disorder (MDD) in adults (Forest Laboratories, Inc). The efficacy of Fetzima at doses 40 mg to 120 mg once daily was established in three, eight-week, randomized, double-blind, placebo-controlled studies in adults diagnosed MDD.

Levomilnacipran is an active enantiomer of milnacipran, the active ingredient in the SNRI Savella, which is approved for the treatment of fibromyalgia. However, Fetzima is not approved for fibromyalgia and Savella is not approved for depression.

Common side effects include nausea, constipation, hyperhidrosis, heart rate increase, erectile dysfunction, tachycardia, vomiting, and palpitations.

❖ ❖ ❖

❑ Yes! I would like to try *The Carlat Psychiatry Report* for one year. I may cancel my subscription at any time for a full refund if not completely satisfied.

Regular subscriptions – $109
Institutions – $149
International – Add $20 to above rates

❑ Please send me the *TCPR Binder* – $14.99

Enclosed is my check for
Please charge my
- ❑ Visa
- ❑ MasterCard
- ❑ Amex

Card # Exp. Date

Signature

Name

Address

City State Zip

Phone E-mail

Please make checks payable to Carlat Publishing, LLC
Send to *The Carlat Psychiatry Report*,
P.O. Box 626, Newburyport, MA 01950
Or call toll-free 866-348-9279 or fax to 978-499-2278
Or subscribe online at www.TheCarlatReport.com

Next month in *The Carlat Psychiatry Report*: Dementia and Alzheimer's Disease

This Month's Focus:
Anxiety Disorders

The Carlat Child Psychiatry Report

CCPR offers all of the same great features as *TCPR*, with a focus on child psychiatry.

One year: $129
Two years: $229

To subscribe, visit www.thecarlatchildreport.com

THE CARLAT REPORT: PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950

PRSRT STD
US Postage
PAID
Nashville, TN
Permit 989