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IN THIS ISSUE

Focus of the Month:
Bipolar Disorder and Psychotherapy

Learning objectives for this issue:
1. Describe the FDA-approved medications for treatment of bipolar depression. **2.** Describe evidence-based strategies for the diagnosis and treatment of bipolar disorder.**3.** Determine how transference-focused psychotherapy is used to treat borderline personality disorder. **4.** Summarize some of the current findings in the literature regarding psychiatric treatment.

Pharmacologic Treatment of Bipolar Depression

Robin Berlin, MD
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Dr. Berlin has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

In bipolar disorder, depression is often the neglected stepchild.

Mania gets more attention, perhaps because it presents so dramatically. Imagine two bipolar patients in an emergency room: one withdrawn and depressed, sitting quietly, and another ranting and pacing the room. Which one would be seen first?

This discrepancy is also seen in the FDA-approved medications for acute

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In Summary

- Three medications have been approved by the FDA to treat bipolar depression
- Lurasidone (Latuda) is the newest medication, approved in 2013
- Reasonable off-label options include lithium and lamotrigine

Q&A With the Expert

Diagnosis and Treatment of Bipolar Disorder

Claudia Baldassano, MD

Assistant Professor of Clinical Psychiatry
University of Pennsylvania, School of Medicine
Director, Bipolar Outpatient Program

Dr. Baldassano has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: Dr. Baldassano, it's great for generalist psychiatrists to talk to an expert in bipolar disorder because, let's face it, it can be a tough and confusing diagnosis, and deciding on treatment isn't always easy either. How much of your time is spent treating patients with bipolar disorder?

Dr. Baldassano: Quite a bit of it. At UPenn, I'm the director of the bipolar outpatient clinic and co-director of our mood disorder consultation service. I see patients with bipolar disorder and educate residents through hands-on teaching. We follow over 500 patients with bipolar disorder, often seeing patients who are relatively refractory to treatment.

TCPR: I'm guessing that many of the patients you see come into the clinic with a diagnosis of bipolar disorder already?

Dr. Baldassano: Often that's true, but even when patients come in with the diagnosis, an important part of my job is to review their history and not make the assumption that they have the disorder. Just because they've carried the diagnosis in the past doesn't mean they actually have it.

TCPR: So how does one go about doing a world-class evaluation for bipolar disorder?

Dr. Baldassano: You have to be as systematic as possible. Before we talk to patients, we have them fill out some forms that are useful. These include a diagnostic screening form, the Mood Disorder Questionnaire (MDQ), three symptom scales—the

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treatment in bipolar disorder, 10 of which are approved for mania, and three for depressive episodes (see "FDA-Approved Medications for Bipolar Disorder" on p. 3).

Nevertheless, most people with bipolar disorder spend more time in a depressive episode than they do in a manic or hypomanic state—on average about three times more for bipolar I (Judd LL et al, 2002;59(6):530–537) and nearly 40 times more for bipolar II; (Judd LL et al, *Arch Gen Psychiatry* 2003;60(3):261–269).

Additionally, depression causes at least as much—if not more—morbidity and impact on quality of life as does mania (Vojtca C et al, *Compr Psychiatry* 2001;42(3):190–195). A 20-year prospective study by researcher Lewis L. Judd and his colleagues found that even subsyndromal depressive episodes cause substantial disability, while on the other side of the spectrum hypomania causes very little (Judd LL et al, *Arch Gen Psychiatry* 2005;62(12):1322–1330).

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A Closer Look at Bipolar Depression

DSM-5 uses the same criteria for defining a bipolar depressive episode as it does for a unipolar depressive episode. Patients must have at least five of the following nine symptoms over two weeks: depressed mood, anhedonia, weight or appetite change, change in sleep, psychomotor agitation or retardation, fatigue, worthlessness or guilt, indecisiveness or trouble concentrating, and/or suicidal ideation.

Clinically, does bipolar depression differ from unipolar depression? That is a controversial topic, but the short answer is "a little." There is general agreement that depressive episodes likely occur earlier and more frequently, and involve more psychomotor slowing in bipolar disorder than they do in unipolar recurrent depression (Mitchell PB et al, *Br J Psychiatry* 2011;199(4):303–309; Cuellar AK et al, *Clin Psychol Rev* 2005;25(3):307–339). However, other distinguishing features of bipolar depression that have been proposed—eg, worse concentration, more incidence of psychosis, more insomnia, or more hypersomnia—have not been consistently replicated. Interestingly, both types of depression appear essentially the same on functional brain imaging (Cuellar AK et al, *op.cit*).

In general, instead of simply exploring current symptoms when seeing a depressed patient for the first time, it's useful to get a very careful personal *and* family history of potential mania, as most experts propose that a positive family history is suggestive of bipolarity. (For ideas about how to elicit a personal history of mania, see our interview with Ross J. Baldessarini, MD [*TCPR*, January 2011], the article by Descartes Li, MD [*TCPR*, July/August 2012], and this month's interview with Claudia Baldassano, MD, starting on p. 1.) When asking about family members, the Family History Screen, which collects information on 15 psychiatric disorders and suicidal behavior in patients and their first-degree relatives, can be a helpful tool (Weissman MM et al, *Arch Gen Psychiatry* 2000;57(7):675–682).

Once we suspect that the depressive episode is a component of bipolar disorder, what are the treatment options? While there are several psychotherapeutic approaches that can be helpful here, in this article we'll focus on medications.

FDA-Approved Medications

Pharmacologically, the FDA has split its indications for bipolar disorder into three categories: acute manic episodes, acute depressive episodes, and maintenance treatment. The medications approved at this time for acute bipolar depressive episodes are quetiapine (Seroquel), the combination of fluoxetine and olanzapine (Symbyax), and, as of 2013, lurasidone (Latuda).

Quetiapine. The immediate-release formulation of quetiapine was approved by the FDA for bipolar depression in 2006, and approval of the XR formulation followed two years later. The approval was based on several eight-week trials of 300 mg and 600 mg dosages as compared with placebo groups; patients on both doses of active medication scored significantly lower (less depressed) on the Montgomery-Asberg Depression Rating Scale (MADRS).

Longer-term follow up studies of up to two years have shown continued efficacy in maintenance treatment of bipolar disorder, although it was not used as monotherapy (see Chiesa A et al, *Int Clin Psychopharmacol* 2012;27(2):76–90 for a good review). Most long-term studies compared quetiapine plus a mood stabilizer to placebo plus a mood stabilizer. Quetiapine can cause somnolence, substantial weight gain, and lipid and glucose abnormalities, which should make us think twice before committing a patient to long-term treatment. You'll need to do regular metabolic screening of such patients. (See "Recommended Metabolic Screening for Patients Taking Antipsychotics" on p. 8 for the American Psychiatric Association (APA) guidelines.)

Symbyax—one of the first drugs in a trend of packaging two drugs together in one pill to create a new patented medication—was first approved in 2003 as treatment for bipolar depression. It is a combination of fluoxetine and

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olanzapine. Again, the approval was based on short (eight-week) trials, with comparisons only to placebo, and not to other medications. Despite its FDA approval, Symbyax is rarely used (when was the last time you prescribed it?), for several reasons. A pill that combines two agents limits our flexibility with dosing. Also, olanzapine can cause mega-weight gain and many psychiatrists try to avoid using it when possible.

Lurasidone, an atypical antipsychotic, is the newest medication to get an FDA nod for bipolar depression. It is approved for both monotherapy and as an adjunct to lithium or valproate (Depakote). The approval was based on two six-week trials, in which patients were given doses ranging from 20 mg to 120 mg and were compared to a placebo control group. Lurasidone has little affinity for the H1 receptor (higher affinity is most often the culprit for weight gain in this category) and appears to have fewer weight-gain and metabolic concerns than other atypical antipsychotics, so it is one of the better choices among atypicals. In a long-term (up to 12 months) study of lurasidone as compared to risperidone (Risperdal) for schizophrenic patients, only about 7% of participants taking lurasidone gained more than 7% of their body weight over the study period, while 13% actually lost at least this amount. Waist circumference decreased and there was no significant change in fasting glucose, HbA1C, or lipids (Citrome L et al, *Int Clin Psychopharmacol* 2012; 27(3):165–176).

You should know that lurasidone is not yet approved for either acute mania or maintenance treatment, but it is undergoing clinical trials for these purposes. Feedback from some psychiatrists who have used it off-label for these purposes has been generally good. Common side effects include akathisia, nausea, and sedation.

Other Medication Options

Lithium is an old and effective standby; it works rapidly and is substantially less expensive than the medications listed above, and it's the only agent discussed here found to substantially decrease risk of suicide. It is listed as first-line treatment for acute bipolar depression in the APA practice guidelines (although these have not been updated since 2002). See our January 2011 issue of *TCPR* for a primer on the use of lithium, as well as the interview "Diagnosis and Treatment of Bipolar Disorder" on p. 1.

So why is lithium only approved by the FDA for acute mania and bipolar *maintenance*, not acute depressive episodes? Part of the answer might simply be money. Obtaining FDA approval requires substantial time and effort, almost always invested by the drug's manufacturer. Because lithium has been a generic medication for many years and because it is already used in bipolar disorder, there is little incentive for anyone to seek approval for a specific indication such as bipolar depression.

In a 1993 review of lithium for bipolar depression, eight of nine placebo controlled studies were positive (Zornberg GL & Pope HG Jr, *J Clin Psychopharmacol* 1993;13(6):397–408). Since then, there haven't been many studies of lithium's utility in bipolar depression.

One negative result of lithium was in the EMBOLDEN I trial (Young AH el al, *J Clin Psychiatry* 2010;71(2):150–162), in which lithium pretty much tanked for bipolar depression—not only did it perform worse than quetiapine, it also did not separate from placebo on the MADRS. However, note that the

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FDA-Approved Medications for Bipolar Disorder

Generic name	Brand name(s)	Year approved	Generic available?
Medications for acute bipolar depression			
Olanzapine/fluoxetine	Symbyax	2003	yes (separately)
Quetiapine Quetiapine XR	Seroquel Seroquel XR	2006 2008	yes no
Lurasidone*	Latuda	2013	no
Medications for acute bipolar mania			
Lithium	Lithobid	1970	yes
Chlorpromazine	Thorazine	1973	yes
Divalproex Divalproex ER	Depakote Depakote ER	1994 2005	yes yes
Olanzapine*	Zyprexa	2000	yes
Risperidone*	Risperdal	2003	yes
Quetiapine Quetiapine XR	Seroquel Seroquel XR	2004 2008	yes no
Ziprasidone	Geodon	2004	yes
Aripiprazole*	Abilify	2004	no
Carbamazepine ER	Equetro	2004	no
Asenapine*	Saphris	2009	no
Medications for bipolar maintenance			
Lithium	Lithobid	1974	yes
Lamotrigine	Lamictal	2003	yes
Olanzapine	Zyprexa	2004	yes
Aripiprazole*	Abilify	2005	no
Quetiapine Quetiapine XR†	Seroquel Seroquel XR	2008 2008	yes no
Risperidone LAI*	Risperdal Consta	2009	no
Ziprasidone†	Geodon	2009	yes

*Approved for adjunctive and monotherapy
†Approved as adjunctive therapy only
Key: ER, XR = extended release; LAI = long-acting injectable

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Beck Depression Inventory, the Beck Anxiety Inventory, and the Quick Inventory of Depressive Symptomatology—and finally, and very importantly, we've created a medication history form that allows them to quickly circle all the meds they've been on in the past [Editor's note: This form is available at http://bit.ly/1rTgHyu]. It may sound like a lot, but patients can fill these out in the waiting room and it takes them less than 10 minutes.

TCPR: What sorts of questions do you begin with in order to ascertain patients' diagnoses?

Dr. Baldassano: I start with the usual things, "Why are you here? Are you coming here for ongoing care, or consultation?" and then I always ask, "What diagnosis have previous physicians given you?" and if they say bipolar, my first question is often, "Well why did they diagnose you with bipolar?" Because the answer to that question can really help with the rest of your interview. They might say, "I was in the hospital after a manic episode," and then you would go right to that episode and ask about that, which helps very quickly to identify if the patient has bipolar. But if they're not sure—which is more common than you'd think—they'll often come in and say, "Well I don't know, someone diagnosed me with this, but I don't know why."

One of my favorite go-to questions is, "Do you feel like the Energizer bunny but you have nowhere to go?" If a patient acknowledges that, I'm more likely to suspect bipolar.

Claudia Baldassano, MD

TCPR: Where do you go from there?

Dr. Baldassano: At that point I will start by focusing on previous depressive episodes. I'll go through a structured clinical interview, starting with, "Have you ever had an episode where you felt sad or down for most of the day for nearly two weeks?" Then we'll go through all the *DSM-5* symptoms and ascertain that they've had a depressive episode. Then I want to know how many episodes of depression they've had, and a lot of times patients will say, "I've been depressed my whole life," and I say, "Really? Let's talk more about that. Have you ever had a period of two months or so when you felt better than that?" And you'll often find that although patients perceive these as one long episode, if you persist, you discover that there were actually periods of inter-episode recovery. Another way I'll put it is: "Over the past two years what's the longest period your mood has been well or normal?" My goal here is to avoid the "snap shot" and attempt to put together an entire photo album. I want to understand their longitudinal course. I'm trying to figure out how many depressive episodes they've had, and what percent of time they've suffered from depression. Now it's possible that they've in fact had a two-year depression, but that is unusual. After I ask about depression, I'll go through a similar string of questions for mania, and in this case I try to focus on whether their periods of mania really interfered with their functioning (which would qualify them for bipolar type 1) or whether they were milder hypomanic episodes, which would imply bipolar type 2.

TCPR: Does it really matter what kind of bipolar you diagnose?

Dr. Baldassano: For research it does, but even clinically it can have an impact. For example, if the mood elevations are milder and had little impact, I would be more likely to prescribe lamotrigine (Lamictal) as monotherapy—as it has more evidence for preventing depression than preventing manic episodes, and its side effect profile is good.

TCPR: Does a bipolar 2 diagnosis also make you more comfortable prescribing antidepressants, because you might be less concerned about the consequences of triggering a hypomanic episode?

Dr. Baldassano: Not really. My main qualm about using antidepressants in type 2 is a lack of efficacy rather than a manic switch. That being said, I don't often use antidepressants in either type 1 or type 2.

TCPR: What about patients with other syndromes, like anxiety or substance abuse. How do you disentangle these kinds of symptoms from bipolar disorder?

Dr. Baldassano: Let's start with anxiety, because anxiety is the single most common comorbid condition in bipolar patients. It certainly adds a layer of complexity. I get referrals from anxiety disorder clinics and find that patients who were diagnosed with anxiety actually have bipolar, but it goes the other way too—patients come to me with a bipolar diagnosis and it's actually anxiety.

TCPR: Which comorbid anxiety disorder muddies the diagnosis the most?

Dr. Baldassano: Probably generalized anxiety disorder (GAD). These patients will describe racing thoughts and feeling restless, and many clinicians will not probe deeply enough when they hear about "racing thoughts." They'll jump right to manic symptoms. But patients with GAD may have racing thoughts that sound more like anxious ruminations. To clarify, I'll ask about symptoms such as irritability, sleeplessness, and feeling hyper. One of my favorite go-to questions is, "Do you feel like the Energizer bunny but you have nowhere to go?" If a patient acknowledges that, I'm more likely to suspect bipolar.

TCPR: Any tips on diagnosing bipolar disorder in substance abusers?

Dr. Baldassano: My rule of thumb is to refrain from making the diagnosis until there is a period of sobriety. For example, I recently saw a patient with a history of cocaine abuse. He had been off drugs for several months and when I evaluated him he had clear cut hypomania, was sleeping less, and feeling good; his thoughts were racing, he was more likely to want to spend money. I saw him two weeks later when his mood dropped into a depression, and he said he was more likely to want to use cocaine during depression. In that case I felt pretty certain that the primary disorder was bipolar disorder, and the secondary diagnosis was cocaine abuse—but it can be challenging to make these distinctions.

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TCPR: I'd like to shift to a topic that psychiatrists probably don't think about as much as we should, which is how we discuss our diagnostic impressions with our patients. How do you approach this in your work with bipolar disorder?

Dr. Baldassano: I do think it's important in your diagnostic interview to save enough time for psychoeducation. If we did that, we would be more likely to have compliant patients, because they would understand the need for treatment. I will typically spend 15 to 20 minutes explaining to my new patients what I believe their diagnosis to be. I'll come right out and say, "I think you have bipolar disorder." You look at their reaction. Sometimes they are obviously uncomfortable with the diagnosis, and sometimes they might disagree. I'll say, "This is why I think you have it," and go through my thought process. If I sense it's a difficult diagnosis for them to accept, I'll soften the blow by saying something such as, "There are two major types of depression—unipolar depression and bipolar depression. You suffer from bipolar depression."

TCPR: Are there other things you discuss with patients?'

Dr. Baldassano: I also talk to patients about the prognosis and treatment course, saying something such as: "Bipolar disorder is lifelong, we don't cure it, but we have medications that can help treat it and our goal is to extend your period of wellness as long as we can." I'll often use the analogy of diabetes, and it's an analogy that works well, because bipolar disorder, like diabetes, is lifelong. You probably have to stay on medication, but it's not enough to just take meds—you have to eat right, get exercise, check your blood glucose. In both illnesses, you have to be an active participant in your care by adhering to a routine and structure. For bipolar, I talk about the importance of mood charting, being aware of what triggers your mood episodes, knowing that early identification of episodes tends to help treatment. And I give them handouts and recommend two books in particular, one is *Take Charge of Bipolar Disorder* (Fast JA, Preston J. New York: Warner Wellness; 2006), and the other is a cognitive therapy workbook titled *Managing Bipolar Disorder: A Cognitive Behavior Treatment Program Workbook* (Otto MW, Reilly-Harrington NA, Kogan JN, Henin A, Knauz RO, Sachs GS. New York: Oxford University Press; 2009).

TCPR: I thought we might wrap up by talking about ways that we non-specialists can improve. What are one or two of the biggest improvements you'd like to see in the way referring clinicians practice?

Dr. Baldassano: One of the things I see is that patients often come to me on very complex regimens of too many medications. We tend to be good at adding medications, but not good at taking away meds. We as a field need to get better at evaluating how a patient is responding to a course of medications, and if they are not responding, we need to be willing to discontinue some of them. And related to that, we need to do a better job of ascertaining whether patients are taking their medications at all. In my interviews, I usually ask patients if they are taking their medication, because unless you ask it, they won't tell you. The other major thing I've seen is a reluctance to prescribe lithium, which can be very effective for patients in all phases of bipolar disorder. So often, I'll do a four hour consultation for someone with treatment-resistant bipolar disorder only to find that they've never had a lithium trial, and are not doing well on the more modern and more expensive medications.

Dr. Baldassano's Approach to Prescribing Lithium

TCPR: Well why don't we help our readers learn more about lithium. You've prescribed it to hundreds of patients. Tell us how you prescribe it.

Dr. Baldassano: First, I prepare patients because many of them are scared of lithium and associate it with the severely mentally ill in state hospitals. I tell them it's one of the gold standard treatments for bipolar; that it's been around since 1970 and we have long clinical experience with it. I also say, "It is a natural element. You'll find it on the periodic chart," which helps defuse the fear of taking it to some extent. And then I prepare patients for the monitoring required: "This is a medication that requires a level of responsibility because there are certain precautions. For example, we'll need to get blood levels, because it has a narrow therapeutic index, meaning that if it goes too high it can be dangerous, and if it goes too low it won't be effective." I also tell patients right away that they need to stay hydrated while taking it, and by that I don't mean forcing down eight glasses of water a day. I mean if they are dehydrated for some reason, such as having the flu or running a marathon, they need to be especially aware of the need to drink. Finally, I make sure they tell their other doctors that they are taking it, because there are various drug interactions possible.

TCPR: And once you've laid this groundwork for your patients, what formulation do you use and how do you dose it?

Dr. Baldassano: I start by prescribing 300 mg immediate-release lithium taken at night. Data shows immediate-release at bedtime is better for kidney function, because the kidney likes having one peak level that goes down, rather than a constant level all day which results from controlled-release formulations. I instruct them to stay at 300 mg for five days, then take 600 mg for five days, then 900 mg. After at least five days on 900 mg, I have them go to the lab for a trough blood level, drawn 12 hours after the last dose. However, in geriatric patients I will have them stay at 600 mg and get that level.

TCPR: What baseline labs do you order, and do you make sure to see baseline labs before they take their first dose?

Dr. Baldassano: I order baseline tests to measure thyroid stimulating hormone (TSH), a blood urea nitrogen (BUN) test to see how well the kidney and liver are working, and a creatinine blood test. While textbooks will tell you to get labs before the patient starts taking lithium, in clinical practice this means you end up delaying the first dose, sometimes substantially. Meanwhile, your patient is suffering. So I don't have patients wait, but I do impress upon them the importance of getting labs soon, within a week of starting the lithium.

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Q&A With the Expert

Transference-Focused Psychotherapy for Borderline Personality Disorder

Kenneth N. Levy, PhD

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Associate Director of Research, Personality Disorders Institute at Cornell University

Dr. Levy has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity. Jay Coburn, MA, MS, conducted this interview. He is a case coordinator at the Cape Ann Behavioral Learning Center in Beverly, MA. He has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: Dr. Levy, there are so many different "brands" of therapy for personality disorders. Can you start by giving us a little background on how and when transference-focused psychotherapy (TFP) was developed, and the evidence that it's helpful for patients?

Dr. Levy: Sure. TFP is a modified psychodynamic psychotherapy developed by psychoanalyst Otto Kernberg, MD, specifically for severe personality disorders such as borderline and narcissistic personality disorders. To date, three randomized controlled trials (RCTs) have examined TFP and show that it is an effective treatment for borderline personality disorder (BPD), including one RCT showing it to be as effective as dialectic behavior therapy (DBT). TFP is now considered an evidence-based therapy by Division 12 (Society of Clinical Psychology) of the American Psychological Association, as well as by the National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom, and the Cochrane Collaboration.

TCPR: Now please describe the technique. How is it administered?

Dr. Levy: TFP is a face-to-face individual therapy that takes place twice weekly in 45 to 50 minute sessions. The focus is on reducing symptomatology that is associated with personality disorders (PD), particularly parasuicidality, suicidality, and self-destructive behaviors. Treatment begins with a thorough assessment of the person's difficulties, which leads into a very specific discussion of the treatment frame.

TCPR: Please tell us more about that. What do you mean by "treatment frame?"

Dr. Levy: When a patient starts psychotherapy, the therapist usually begins by setting a treatment frame that lays out how often you meet, when you meet, etc.—basic things. But with patients with severe personality disorder, such as borderline personality disorder or narcissistic personality disorder, it is even more important to come to an explicit agreement with the patient about the roles and responsibilities of the patient and therapist in the treatment. You want to discuss what the treatment looks like, the rationale for working this way, and what to expect. This includes the structure of the treatment, such as the number of sessions, how often we meet, and what happens in and even between sessions, as well as what kinds of behaviors/events we might expect to arise during the course of treatment. And we will talk very explicitly with patients about what has transpired in past therapies, feelings and difficulties that the patients may have had, and how best to safeguard against, and be prepared for, what happens when they come up in the current treatment.

TCPR: Do you discuss with the patient why past therapies did not work?

Dr. Levy: Yes. For instance, if you have a patient who has dropped out of lots of different treatments, which is often the case with patients with BPD, we can predict that he or she may have impulses to drop out again. We examine with the patient what kind of things might have led to their dropping out before, and we're very clear that not only *might* these thoughts and feeling re-occur, but we expect that they would occur in this treatment, too. And then we discuss how we will handle those feelings or impulses in a collaborative way.

TCPR: And what would you say to a patient?

Dr. Levy: I might say, "I realize that right now you are feeling very good about the treatment, and you are feeling hopeful and want to continue in this treatment. But it is possible that as treatment goes on, there may be times you may feel differently about treatment. I am suggesting that may occur here too, and rather than drop out, I suggest you talk very directly to me in session about those feelings, even if you are afraid that I may not like what you have to say." So essentially we try to get the patient to recognize that there are these patterns, and these patterns are somewhat independent of the specific people involved, and that rather than behave the way they may have behaved in the past, they should be open to reflection and discussion.

TCPR: And this therapy also involves psychoeducation?

Dr. Levy: Yes, most explicitly during the setting of the treatment frame. One component of TFP is providing psychoeducation about how we understand a patient's difficulty and how the psychotherapy will unfold as a result of their difficulties. This is a core aspect of setting the treatment frame because frequently patients come in for treatment never having been diagnosed with or told they have a personality disorder. It is very common, for instance, for people with borderline personality disorder to have been diagnosed with bipolar disorder or some other disorder instead. Sometimes therapists believe their patient has BPD but are scared to tell him or her or feel it will be hurtful to tell them. We feel it is important to share our understanding of the patients' difficulty with them, albeit in a tactful and sensitive manner. When a patient is diagnosed with a non-BPD disorder, bipolar for instance, they

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Expert Interview: Dr. Levy

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can become quite invested in the diagnosis. However, often I find patients are ambivalent about having a bipolar disorder diagnosis—there may be a part of them that does not like the diagnosis, but often another part of them actually likes it because it absolves them from some of their behaviors: "It's not me, it's my bipolar disorder." And so we spend a lot of time educating them about how we understand what they have told us.

> **"I have seen people recapture really good lives—lives that are consistent with their interests and their abilities."**
>
> Kenneth N. Levy, PhD

TCPR: Can you give us an example of how you do that?

Dr. Levy: I might say, "It sounds like you were diagnosed with bipolar disorder because of the way people might have understood the shifts in mood that you describe, which is a key symptom of bipolar disorder. But the swings between moods in bipolar disorder tend to be between extreme elation and depression, and tend not to occur moment-to-moment, but actually over periods of days or weeks. The kinds of changes in mood you have described, particularly between anger and feeling very depressed, are more moment-to-moment. These changes are actually more characteristic of personality difficulties, what the Diagnostic and Statistical Manual used by therapists calls a personality disorder, specifically what is called borderline personality disorder." And I explain that there are pros and cons to being diagnosed with BPD rather than bipolar disorder, including the fact that it is important to have an accurate diagnosis in order to best treat their difficulties. In addition, we know how to treat personality disorders and therefore the prognosis can be quite good.

TCPR: How exactly do you structure a TFP session?

Dr. Levy: We have two principles for deciding when, why, and how to intervene in a session. One is that you focus on the material that has the most affect, what we call following the dominant affect. The second is a focus on the hierarchy of treatment priorities that were identified when setting the treatment frame with the patient. Similar to DBT, the highest priority in session is on homicidal and suicidal thoughts and behaviors. Those are followed in priority by parasuicidal thoughts and behaviors, and then treatment-interfering behaviors. In contrast to DBT, we then focus on a range of additional treatment priorities such as: withholding of information or dishonesty, deviations from the treatment frame, acting out (ie, communicating through actions, often destructive, rather than through verbal communication) in session or between sessions, and focusing on trivial matters.

TCPR: You've spoken about working on patients' distortions in perception. Can you elaborate on that?

Dr. Levy: A central aspect of TFP is that we focus on the here and now of the interaction between the patient and therapist. When a patient comes in and tells you about how horrible his parent was, for example, you can't really know if that is the case or not. But you do know what is happening in the room between you and the patient, and you can understand what distortions he may have of you on the basis of your being present with him. For example, I might say to a patient, "Can you tell me more about that?"—a simple clarification that therapists make all the time. And the patient might respond to me by lashing out angrily or saying, "You don't believe me." And then I can say, "From your reaction, it seems to me that you experienced my question as if I was attacking you, rather than asking you to clarify what you were saying so I could better understand you." We can talk about how the patient experienced me in that moment and whether they can see that maybe rather than attacking them that I was actually interested in them and helping them. One of the stereotypes of psychodynamic or psychoanalytic therapy is that it is about understanding early childhood experiences, reconstructing the past, and discovering the root of the patient's problem, but it is actually not at all like that. Certainly transference-focused psychotherapy is not that way. It is much more here-and-now focused psychotherapy based on what is happening in the relationship between the patient and the therapist.

TCPR: When this process works, what kinds of changes do you see?

Dr. Levy: We see improvements in affect regulation. Patients start to be aware of disparities between what they might be saying or doing in one moment versus another—especially in the present relationship between them and the therapist. Then, patients begin to better tolerate these kinds of disparities and become more integrated in their view of themselves and others. This is one difference, for instance, between DBT and TFP. In DBT, these difficulties with affect regulation are seen as biological byproducts. In TFP, the affect dysregulation is seen as a byproduct of having unintegrated representations of oneself and others. If you get into a fight with somebody that you care about and you don't have an integrated representation of yourself and them and the relationship, that fight takes on paramount importance and the patient may feel like the relationship is crumbling. But if you have an integrative representation, you understand that this is a disagreement in the context of a solid relationship, and can tolerate these moments of disagreement a lot better. This change leads to an ability to think more flexibly and benevolently, have better affect regulation, better behavioral control, and relationships infused with less aggression and with greater tolerance for intimacy. Ultimately this change leads to less self-destructive behaviors.

TCPR: What is the typical course of treatment?

Dr. Levy: We encourage specific actions that the patient might need to do in order to facilitate a better life for themselves. This may include working or going back to school. We find that within the first four to six months, there is often a reduction in symptomatology, most commonly reductions in suicidality, parasuicidality, and hospitalizations. However, the data still suggest that while those symptoms tend to be reduced, patients often continue to remain anxious, depressed, and even continue having difficulty with anger and negative emotions. The affects are still there; they are just not necessarily acting on them as much. Now, that has a huge benefit to patients. They find that when they don't engage in those behaviors any longer, they can maintain jobs and relationships with family, friends, and significant others. In the past, their behaviors would interfere with these activities and rela-

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Pharmacologic Treatment of Bipolar Depression
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study was sponsored by quetiapine's manufacturer, and the mean serum concentration of lithium was on the low end (0.61 mEq/L), just a hair within the clinically acceptable range of 0.6 to 1.2 mEq/L, and below the concentration that is often needed for efficacy in practice.

Lamotrigine (Lamictal) is a popular choice, primarily because of its lack of side effects relative to other treatments for bipolar disorder, and because, in my experience, it seems to keep people on the "happy" side of the mood spectrum, which is appreciated by patients who feel dulled on traditional mood stabilizers. Although data are mixed for acute bipolar depression, it does appear at least to be good at preventing future episodes, and is FDA-approved for maintenance treatment (Amman B et al, *J Psychopharmacol* 2011;25(10):1289–1294). However, it appears to have less efficacy for preventing mania. For this reason, I tend to use it only in combination with another mood-stabilizing agent.

Antidepressants. While there is little evidence supporting the use of antidepressants in bipolar depression, they are used quite frequently, particularly as adjuncts to a mood stabilizer. There are two issues that arise in the use of antidepressants in these patients: first, do they precipitate mania, and second, do they work to alleviate depression? The first issue remains controversial. Several studies have demonstrated that bipolar patients taking antidepressants do not switch into mania, but many of these were confounded by the patients taking mood stabilizers at the same time. For instance, the large and well-designed STEP-BD study found that neither bupropion nor paroxetine precipitated mania, although all patients were also on antimanic medication during the trial (Sachs GS et al, *N Engl J Med* 2007;356(17):1711–1722). Regarding efficacy, the same study showed no benefit of these medications in bipolar depression. That is not to say there are no outlier patients who will still benefit from an antidepressant during a bipolar depressive episode (see, for instance, Gijsman HJ et al, *Am J Psychiatry* 2004;161(9):1537–1547). However, for most bipolar patients, antidepressants are unlikely to provide much efficacy.

We've covered this very involved topic in prior issues of *TCPR* [see the July/August 2012 issue] and we will surely revisit it sometime soon.

Other Mood Stabilizers and Antipsychotics. Beyond those listed above, many of us have tried other mood stabilizers and atypical antipsychotics to treat our patients with bipolar depression. There is some evidence for valproate as monotherapy, but others are either inadequately studied or yield conflicting results (see Selle V et al, *Pharmacopsychiatry* 2014;47(2):43–52 for a meta-analysis and review). Aripiprazole (Abilify) has been effective as an adjunct to a mood stabilizer for minor depressive symptoms in an open-label trial (Schweitzer I et al, *Int J Bipolar Disorders* 2013;1(1):4) but was not effective as monotherapy for bipolar depression in two placebo-controlled studies (Thase ME et al, *J Clin Psychopharm* 2008;28(1):13–20).

TCPR'S VERDICT: Which meds for bipolar depression? If you're into FDA approval, lurasidone's your best choice—you'll likely avoid the potential metabolic effects of the other approved drugs. Off-label options include lithium and lamotrigine. And while not generally advised by experts or supported by the evidence, antidepressants are still used by many: just be sure to proceed with caution.

Recommended Metabolic Screening for Patients Taking Antipsychotics

If your patient is taking an antipsychotic with a risk of causing weight gain, especially olanzapine and quetiapine, but including risperidone and some others, you should regularly check for the possibility of metabolic side effects. The chart below is from guidelines developed in 2004 by the American Psychiatric Association (APA) and American Diabetes Association (ADA) (American Diabetes Association et al, *Diabetes Care* 2004;27(2):596–601):

Assessment	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose*	X			X		X	
Fasting lipid profile	X			X			X

* Hemoglobin A1c may be substituted when a fasting plasma glucose test is not feasible.
Note: More frequent assessments may be warranted based on clinical status.

Expert Interview: Dr. Baldassano

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TCPR: What kinds of issues do you see as patients are titrating their dose up?

Dr. Baldassano: The most common early side effects are gastrointestinal, such as nausea, queasiness, and cramping. I tell patients to stop increasing the dose if they experience these, and to wait until the symptoms go away before resuming the titration. Every once in a while, I will see a patient referred to me who is on an extended-release lithium who is having diarrhea, and an easy fix is to simply switch them to immediate-release once a day—this almost always works.

TCPR: How do you interpret lithium levels?

Dr. Baldassano: Before I evaluate the levels, I'll always ask the patient "was this a 12-hour blood level?" because many times it isn't a trough level and then the number is not useful. But I'm aiming for a lithium level of 0.8 or above, especially for bipolar depression, which, in my experience, tends to require higher blood levels for efficacy. I try not to go higher than 1.1 because most patients have side effects above that. If they are subtherapeutic, I will increase the dose, using the rule of thumb that every 300 mg addition leads to about a 0.2 increase in blood level in nongeriatric patients. Each time I increase the dose, I ask them to get another level after at least five days have passed. Generally I get patients therapeutic within a month using this procedure.

TCPR: What about follow-up labs after the level is therapeutic?

Dr. Baldassano: There are no official, specific guidelines on checking labs. I do another lithium level four to six weeks later, including a BUN, creatinine, and TSH. If they are new to lithium, I might check it one more time in eight weeks, and once I've established this person is doing well, and they have a consistent level, I may not check it again for six months. I usually check lithium twice a year, but in some very stable patients only once a year. Meanwhile, I'll check BUN/creatinine at the same frequency I check lithium levels, and I check TSH less frequently, usually once a year. One important thing to know about the thyroid is that if you see TSH increasing, then you have a discussion with the patient. Because about 3% of patients will develop permanent hypothyroidism, and this is more common in women. It can be reversible, if it's caught within six to eight months, but the patient has to stop the lithium.

TCPR: Thank you, Dr. Baldessano.

Expert Interview: Dr. Levy

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tionships and ultimately having the kind of life they desire.

TCPR: And then what happens after long-term treatment?

Dr. Levy: It's over the next six to 12 months that a lot of the personality change starts to occur—increases in reflectiveness and reductions in depression. The person is able to get into stable relationships, is able to get into disagreements with a loved one without throwing dishes, becoming suicidal, or something in between. So we start seeing life-enhancing changes at 12 to 24 months, and more consolidation around more stable affect and a more stable sense of oneself and others. I have seen people recapture really good lives—lives that are consistent with their interests and their abilities; and that are filled with the same capacity for what we might call "love and work" that the typical person has.

TCPR: Do you use any metrics or instruments to measure success?

Dr. Levy: It is our clinical experience that it can take three years before a patient is able to live the kind of life that they aspire towards. But even being in the middle of such a process is better than not having started it at all. In our treatment studies, we found that our patients went from an average of 2.5 to 4.1 on an 11-point rating scale measuring one's capacity to reflect on their own and others' motiviations and behaviors (Levy KN et al, *J Consult Clin Psychol* 2006;74(6):1027–1040). While 4.1 isn't where one might ultimately want to be with regard to reflectivity, it is a lot better than 2.5. A rating of 4 is within the range of "typical functioning" (a score of 5 is typical or average) and it does represent not only statistically significant change, but clinically significant change as well. It is on the road to more typical functioning.

TCPR: What are some of the biggest challenges in offering TFP?

Dr. Levy: What I have found is hardest for a therapist treating patients with BPD is to deal with all of the projections from the patient. In order to really treat borderline patients, a therapist needs to be able to manage these projections of malevolent intent that are put onto them by patients, and to tolerate them, and to recognize that the way a patient is "seeing" them is the patient's issue, and not really about the therapist. I see this as an issue of dealing with counter-transference. It is helpful to realize that you are being attacked because the patients have doubts about their own goodness. I think that therapists who successfully treat borderline patients just don't take this personally. Therapists who have a strong need to be liked by their patients or viewed positively by their patients often have a hard time treating BPD patients.

TCPR: Where can someone learn more about offering TFP?

Dr. Levy: Anyone could read any of the existing treatment manuals on their own to get a sense of TFP, but it is really important to be in supervision, for at least some amount of time. The American Psychiatric Association (www.psychiatry.org) and American Psychological Association (www.apa.org) offer workshops. The Personality Disorders Institute at Cornell (www.borderlinedisorders.com) and the Personality Studies Institute (www.personalitystudiesinstitute.com), a private organization in New York, offer Internet supervision as well as long-term seminars. In addition, there is the International Society of Transference-Focused Psychotherapy (http://istfp.org), which lists certified teachers of transference-focused psychotherapy across the world, and many of those individuals can be engaged for supervision.

TCPR: Thank you, Dr. Levy.

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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.

DEPRESSION

NSAIDs May be Effective for Depression

Inflammation is hot, both literally and figuratively. The medical literature is replete with studies implicating inflammation as a possible root cause of diseases as varied as heart disease, cancer, Alzheimer's disease, depression and, of course, arthritis. A recent meta-analysis of all randomized controlled studies for depression yielded some intriguing results.

Researchers scoured the literature and located 14 randomized, placebo-controlled trials assessing the efficacy of anti-inflammatory treatment for depressive symptoms or depression, involving 6,262 participants. Ten trials evaluated the use of non-steroidal anti-inflammatories (NSAIDs) in almost 4,300 patients and four investigated cytokine inhibitors (in just over 2,000 patients). The NSAIDs included celecoxib (Celebrex), ibuprofen, and naproxen, and the cytokine inhibitors included etanercept (Enbrel), adalimumab (Humira), ustekinumab (Stelara), and infliximab (Remicade). These tongue-twisting cytokine inhibitors are expensive biological agents approved to treat various inflammatory illnesses.

While some studies tested the effects of NSAIDs when added to antidepressants, most were studies primarily of patients with arthritis with depressive symptoms who were treated exclusively with anti-inflammatories. Not all patients met criteria for major depression.

Results. In general, patients assigned to anti-inflammatories improved significantly more than those assigned to placebo. The overall effect size for all treatments was -0.34, which is considered a small to moderate effect. In a subanalysis, the authors found that the single most effective medication was celecoxib when used as an add-on to antidepressants—though this covered only four trials with a total of 132 patients, much fewer than the over 6,000 patients in all studies. The four studies on cytokine inhibitors showed a trend toward an antidepressant effect, but it was not significant. In terms of adverse events, neither the NSAIDs nor the cytokine inhibitors produced more side effects than placebo. However, the studies were relatively short (six to 12 weeks) and some gastrointestinal and cardiovascular side effects sometimes take longer than that to appear (Köhler O et al, *JAMA Psychiatry* 2014;epub ahead of print).

TCPR's Take: NSAIDs might be effective in treating depressive symptoms, with effect sizes similar to standard medications, and with no more side effects than placebo. Celecoxib may be particularly promising. If you decide to give these meds a try, here are the doses typically used in the studies reviewed: celecoxib 200 mg to 400 mg a day, ibuprofen 800 mg three times a day, and naproxen 500 mg twice a day. Be careful though: using any of these for depression is off-label, and side effects may emerge over the many months or years of treatment typical in major depression.

PTSD

Study Shows Relationship between 'Mini-Strokes' and PTSD

Transient ischemic attacks (TIAs)—commonly referred to as "mini-strokes"—don't leave people with any permanent neurological symptoms, but in some individuals they may lead to post-traumatic stress disorder (PTSD) for the event, according to a new study.

The study followed 108 patients who were treated at a German hospital for TIA. Three months after the diagnosis, they were asked to answer a series of questionnaires to self-assess for PTSD, anxiety, depression, quality of life, coping strategies, and medical knowledge. According to the Posttraumatic Stress Diagnostic Scale, 32 patients (29.6%) were classified as having PTSD—a rate 10 times higher than the general German population (prevalence of 2.9%). They also had more depression and anxiety, as well as reduced mental and physical quality of life.

As to why some TIA patients develop PTSD and others do not, researchers said they could not rule out metabolic changes that can occur up to three days after TIA, or the sudden experience of neurological symptoms, which itself may be a major trigger. Other contributors may be the experience of acute pain during the TIA, or the fear that the TIA may be a precursor of stroke.

To prevent the development of PTSD after TIA, researchers recommended prevention efforts, including training patients to develop adaptive coping strategies and briefing them about the realistic stroke risk following a TIA (Kiphuth I et al, *Stroke* 2014;45(11):3360–3366).

TCPR's Take: It's well known that even a mild stroke can cause psychological consequences such as depression and anxiety. This study shows that TIAs—which are even more "mild," at least neurologically speaking—can also be sufficiently traumatic to produce PTSD in some patients. While the diagnosis of PTSD in this study was made by a single written questionnaire, the results support the idea that a subset of TIA patients experience significant psychological distress and might benefit from screening and preventive measures.

DEMENTIA

Personality May Influence the Risk for Alzheimer's

It's commonly known that the risk of developing dementia is related to education level, history of head trauma, family history, and genetics. But could personality also play a role? It just might: a group of Swedish and American researchers has found that women who test high on a "neuroticism" scale in middle age may have a higher risk of developing Alzheimer's disease (AD) later in life.

The research was based on an unusually long-term prospective study

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CME Post-Test

This CME post-test is intended for participants only seeking AMA PRA Category 1 Credit™. For those seeking ABPN self-assessment (MOC) credit, a 25 question pre- and post-test must be taken online. For all others, 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 score at least 80% correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by December 31, 2015. 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. The FDA has approved how many medications for the treatment of depressive episodes of bipolar disorder (Learning Objective #1)?
   [ ] a) One [ ] b) Three [ ] c) Seven [ ] d) Twelve

2. Most people with bipolar disorder spend more time in a depressive episode than they do in a manic or hypomanic state—on average nearly how much more time in bipolar II (LO #1)?
   [ ] a) 10 times more [ ] b) 17 times more [ ] c) 23 times more [ ] d) 40 times more

3. According to Claudia Baldassano, MD, what is the single most common comorbid condition in patients diagnosed with bipolar disorder (LO #2)?
   [ ] a) Psychosis [ ] b) Eating disorders [ ] c) ADHD [ ] d) Anxiety

4. According to Dr. Baldassano, when patients self-report a diagnosis of bipolar disorder, what initial step does she take (LO #2)?
   [ ] a) Proceed with treatment based on that diagnosis
   [ ] b) Review their history and not assume they have the disorder
   [ ] c) Speak to the clinician who made the original diagnosis
   [ ] d) Speak to the patient's family about the diagnosis

5. Which of the following describes transference-focused psychotherapy (TFP) for borderline personality disorder (LO #3)?
   [ ] a) TFP is done in group therapy and takes place twice weekly
   [ ] b) TFP is a face-to-face individual therapy that must be done daily
   [ ] c) TFP is individual therapy that takes place twice weekly for about 50 minutes
   [ ] d) TFP takes place in sessions that last several hours

6. In a recent meta-analysis of 14 randomized controlled studies assessing the efficacy of anti-inflammatory treatment for depressive symptoms or depression, which medication was most effective (LO #4)?
   [ ] a) Celecoxib [ ] b) Ibuprofen [ ] c) Naproxen [ ] d) Prednisone

7. A group of Swedish and American researchers found that women who possess which of the following personality traits in middle age may have a higher risk of developing Alzheimer's disease later in life (LO #4)?
   [ ] a) Neuroticism [ ] b) Extroversion [ ] c) Perfectionism [ ] d) Pessimism

8. Transient ischemic attacks (TIAs)— commonly referred to as "mini-strokes"—can lead to what mental disorder in some individuals (LO #4)?
   [ ] a) ADHD [ ] b) Bipolar disorder [ ] c) PTSD [ ] d) SAD

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Research Updates

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(38 years) in which 800 women, ages 38 to 54, were selected at random from the population of a Swedish city in 1968. They were given a full psychological examination at baseline, with subsequent evaluations every six to eight years until 2005.

At baseline, the women were assessed for both neuroticism and extroversion using the Eysenck Personality Inventory. While neuroticism is not a term in common use clinically, in personality research it lives on, and describes people who are anxious, tend to be somaticisers, are emotionally reactive, and are prone to feeling excessively guilty. The extroversion scale measures sociability and positive affect. In addition to these baseline tests, all subjects were evaluated every six to eight years on their level of distress, defined as any stress lasting one month or longer in situations relating to work, health, or family. "Stress" was defined as feelings of irritability, tension, nervousness, fear, anxiety, or sleep disturbances.

During the 38 years of follow-up, dementia was diagnosed in 153 women, 104 of whom had AD. The authors focused on AD because the numbers for other dementias were too small to find any associations.

The upshot of the study is that the most risky combination of personality traits is having high neuroticism and low

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This Month's Focus:
Bipolar Disorder and Psychotherapy

Next month in *The Carlat Psychiatry Report:* Risk Management

Research Updates

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extroversion. Women with this combination had double the chance of developing AD (16/63, 25%) than those with low neuroticism and high extroversion (8/63, 12.5%). The association between neuroticism and Alzheimer's was partly mediated by the fact that neuroticism led to a greater degree of subjective distress (Johansson L et al, *Neurology* 2014;83(17):1538–1544).

TCPR's Take: This research shows that "unopposed" neuroticism (that is, neuroticism that isn't modified by a healthy dose of extroversion) is statistically associated with developing AD. It doesn't prove that being neurotic causes AD but, rather, that the trait of neuroticism may be simply a precursor of a purely biological disease called Alzheimer's. So when a middle-aged woman in your practice worries that she will develop dementia, you can reassure her that a positive and extroverted personality reduces her risk. But if she exhibits anxiety, guilt, somatic complaints, and negative affect, this study may give you—and her—more of a reason to work on these symptoms.