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Steve Balt, MD
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Focus of the Month:
Bipolar Disorder

Learning objectives for this issue:
1. Prescribe and manage medications safely in pregnant and lactating women with bipolar disorder. **2.** Consider the evidence that bipolar disorder may be over-diagnosed. **3.** Describe the clinical interviewing strategy known as the "life course method" in diagnosing bipolar disorder. **4.** Integrate psychosocial methods into your treatment of bipolar disorder. **5.** Explain the management of bipolar depression. **6.** Understand some of the current findings in the psychiatry literature.

Treating Bipolar Disorder During Pregnancy and Lactation

Faina Novosolov, MD
Assistant director of clinical services
Women's Mood and Hormone Clinic
University of California, San Francisco

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

A 32-year-old pregnant woman with bipolar disorder, well-controlled on valproic acid (Depakote), comes into your office wanting advice on medications. What do you do? For both psychiatrists and patients, this can be an extremely high anxiety scenario, with concerns about the mother's—and now her baby's—well-being.

We know, for instance, that pregnancy itself can substantially increase the risk of recurrence of bipolar symptoms—as high as 71% (with or without treatment)—and stopping medications during pregnancy increases risk twofold compared to continuing them (Viguera AC et al, *Am J Psychiatry* 2007;164(12):1817–1824). In a case like this, a clinician can begin a conversation by saying: "There's no one right answer. We know that there are risks to treatment for the baby, but there are also significant risks to *no* treatment for both of you. Let's go through the risks and benefits of each so we can decide together what might be the best plan." This discussion should also include the mother's partner, if possible, as well as the mother's obstetrician and outside therapist, to make sure everyone involved is on the same page.

Be aware that mood shifts can happen very quickly with the hormonal variations of pregnancy. Visits with pregnant patients should be monthly at minimum, and sometimes weekly to biweekly during times of mood instability or medication changes. In this article I will discuss some of the most common medications in bipolar disorder, along with suggestions on how to manage them during pregnancy and lactation.

Lithium

Most psychiatrists are wary about using lithium during pregnancy because of the risk of Ebstein's anomaly, a tricuspid valve malformation. But lithium is actually one of the safest mood stabilizers in pregnancy—much safer

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A Note From the Editor

While bipolar disorder is something we all encounter in practice, views are mixed as to how best to diagnose and treat it. In this issue of *TCPR,* Drs Amos and James argue that bipolar disorder is over-diagnosed and the introduction of "soft" criteria may contribute to a worsening of this trend. On the other hand, Dr Baldassano argues that expanded criteria are necessary to treat certain populations more effectively, such as those with bipolar depression.

As with much in psychiatry, there are no easy answers—and, unlike the rest of medicine, no objective diagnostic tests—and even experts may interpret the same phenomena differently. What matters most is that we offer our patients the care they need, in a fashion that is motivated neither by ideology nor by a blind adherence to "evidence." We trust the reader to synthesize the views expressed here into a treatment approach that works best for his or her patients.

We hope you enjoy this issue and always welcome readers' comments. You can email us at info@thecarlatreport.com or visit our Facebook page to comment on any stories.

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than valproic acid. The risk of Ebstein's anomaly is 1 in 1,000 to 2,000 (0.05% to 0.1%) when using lithium in the first trimester, compared with 1 in 20,000 in the general population. So although there is a large relative risk, the absolute risk is still extremely low (Cohen LS et al, *J Am Med Assoc* 1994;271(2):146–150).

Lithium crosses the placenta, so you should aim for the lowest effective dose and monitor lithium levels throughout pregnancy. The downside is that monitoring levels throughout pregnancy and after delivery can get tricky (see table on page 5 for more).

Breastfeeding. Most clinicians don't recommend breastfeeding on lithium because of the theoretical risk of infant toxicity. However, if a woman chooses to do so, it's important to check lithium level, thyroid stimulating hormone (TSH), blood urea nitrogen (BUN), electrolytes, and creatinine in the infant immediately postpartum, at four to six weeks of age, and then every eight to 12 weeks for the duration of breastfeeding (Fowler S and Freeman M, *Lithium and breastfeeding;* http://bit.ly/aCokQC). Any testing of the infant is best done through cooperation with the child's pediatrician.

Valproic Acid (Depakote)

If possible, valproic acid should be avoided during pregnancy, especially in the first trimester, where it carries up to a 5% risk of neural tube defects. This makes it 50 to 100 times more teratogenic than lithium. Valproic acid is also associated with a two- to seven-fold increased risk of atrial septal defects, hypospadias, cleft palate, polydactyly, and craniosynostosis, and a 12- to 16-fold higher risk for spina bifida (Jentink J et al, *N Engl J Med* 2010;362:2185–2193). High-dose folic acid (4 mg to 5 mg per day) is often recommended. Even though in one study it didn't seem to lower the risk of these abnormalities, it did reduce the risk of miscarriage (Robinson GE, *Focus* 2012; 10(1):3–14). Vitamin K (20 mg per day) is also recommended in the last month of pregnancy for women taking valproic acid or carbamazepine (Tegretol) to avoid bleeding problems in the newborn.

Can valproic acid be restarted after the first trimester? That's not ideal either, as it can decrease vitamin K levels, and might also result in poorer cognitive function in the child when compared to other antiepileptic-drug monotherapies or no therapy at all (Meador KJ et al, *N Engl J Med* 2009;360(16):1597–605).

Breastfeeding. Valproic acid is considered relatively safe in breastfeeding, but even the low levels found in breast milk may contribute to liver damage. One questionable case of thrombocytopenia has been reported, so mom or physician should watch the infant for unusual bruising or bleeding. You may also want to check drug levels, platelets, and liver function in the infant.

Lamotrigine (Lamictal)

Lamotrigine looks very promising during pregnancy and breastfeeding and requires little monitoring. Multiple pregnancy registries have found that the overall risk of birth defects associated with first trimester lamotrigine use is 2.2%, well within the baseline rate of 2% to 3% (Robinson *ibid*). In 2006, the FDA issued a warning about the possibility of cleft palate with first-trimester lamotrigine use, based on one study that estimated the risk as 8.9 in 1,000 (versus a baseline risk of 0.5 to 2.16 in 1,000 in the general population). Later studies, however, found risks of 0.7% and 0.25%, while still another study showed no increased risk at all (Nonacs RM, *MGH Center for Women's Health* 2010; http://bit.ly/QXRQ8).

You may recall that estrogen can decrease lamotrigine levels by as much as 50%, both during oral contraceptive use and during pregnancy. Clinical monitoring should be sufficient, but be aware that the lamotrigine dose might need to be increased during pregnancy and decreased postpartum.

Breastfeeding. Lamotrigine is thought to be fairly safe, with only one reported adverse event, a case of a 16-day-old infant with apnea whose mother was taking lamotrigine at a whopping dose of 850 mg per day. Other studies have found no adverse events. Given these reassuring data, lamotrigine is a good option for breastfeeding, and certainly easier than lithium. We could switch all lithium patients to lamotrigine during breastfeeding, but there are certain scenarios where this might not be a good idea, particularly if mom has done well with lithium in the past and has been stable on lithium throughout the pregnancy, has severe depression or suicidality, or shows signs of mania or hypomania.

Carbamazepine (Tegretol)

Although it's not used much here in the US, especially during pregnancy, carbamazepine is one of the most widely used antiepileptic drugs in Europe, even among women of childbearing age. Data from a large European database found the risk for major congenital malformations to be 3.3%, only slightly higher than the 2% to 3% baseline risk. Spina bifida was the only specific birth

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Is Bipolar Disorder Over-Diagnosed?

James Amos, MD
Clinical professor of psychiatry
University of Iowa

Joan James, MD
Chief resident in psychiatry
University of Iowa

Dr. Amos and Dr. James have disclosed that they have no relevant relationships or financial interests in any commercial companies related to this educational activity.

Whether you work in a hospital or an office setting, you've probably seen many patients who come to you with a "history of bipolar disorder." We've seen it, too, in multiple settings at an academic medical center. Is this a new epidemic? Or a redefinition of what it means to be "bipolar"?

Some argue that bipolar disorder is actually under-diagnosed. They have support from abundant literature showing that bipolar disorder tends to present more often with depression than mania or hypomania (Judd LL et al, *Arch Gen Psychiatry* 2002:59(6):530–537). As many as 10% of patients with unipolar depression ultimately are shown to have bipolar illness instead, according to some experts (Goodwin GM et al, *Eur Neuropsychopharm* 2008:18(7):535–549). (See this month's Q&A with Claudia Baldassano for more on this.) In addition, a new emphasis on subthreshold mood symptoms and more rapid mood shifts has led some psychiatrists to promote the concept of a "bipolar spectrum disorder" (Youngstrom EA et al, *Curr Psychiatry Rep* 2010;12(6):479–489).

The pro-bipolar spectrum camp maintains that our definition of "bipolar" simply needs to be revised. Some have redefined "bipolarity" to include overactivity without mood changes; hypomanic episodes as short as one day; and a family history of mood disorder (Angst J et al, *J Affect Disord* 2003;73(1–2):133–146). Using these and other factors, loosely known as the "Zurich criteria," Angst and colleagues found that, among 5,000 patients in a current depressive episode, a surprising 47% met their redefined "bipolar" criteria, compared with only 16% using DSM-IV criteria (Angst J et al, *Arch Gen Psychiatry* 2011:68(8):791–799). In a separate study, when patients with major depressive disorder were asked about "subthreshold hypomania" symptoms, nearly 40% could be relabeled "bipolar" (Angst J et al, *Am J Psychiatry* 2010:167(10):1194–1201).

While it's important to remain vigilant about a history of manic and hypomanic symptoms, we think the problem of over-diagnosis is probably greater. For instance, in a 2008 study, Zimmerman and colleagues performed a comprehensive diagnostic interview on 700 patients, nearly 21% of who self-reported a history of "bipolar disorder." However, when using the gold-standard SCID (structured clinical interview), only 13% had the diagnosis; they also had more first-degree relatives with bipolar disorder than the others (Zimmerman M, Ruggero CJ et al, *J Clin Psychiatry* 2008:69(6):935–940). The authors hypothesized that over-diagnosis of bipolar disorder might be a consequence of efforts to improve recognition of it and avoid under-detection. In fact, the same authors studied 40 depressed patients previously diagnosed with bipolar disorder and found that, by the SCID, they had specific phobia, PTSD, drug abuse/dependence, or a personality disorder instead (Zimmerman M et al, *Compr Psychiatry* 2010;51(2):99–105).

"Subthreshold hypomania," assuming such a thing truly exists, is a condition that few clinicians are likely to take the time to diagnose properly—not to mention the fact that the criteria are broad and evolving. For instance, Appendix A of the Zurich interview includes nearly 40 items, such as "less sleep" and "more enthusiasm for work." The busy clinician will probably not take the time to ferret out the subtypes, and, instead, jump to the "bipolar" label. Furthermore, since "episodes" can last as little as one to three days under these criteria, it's no surprise that patients who describe their moods as "flipping every few minutes" might be diagnosed—or, more likely, misdiagnosed—bipolar.

Over-diagnosis can also occur when apparent mood episodes are defined as psychiatric when in fact they have a different etiology altogether. Decreased need for sleep, disorganized or racing thoughts, increased activity and agitation, and delusional thinking, even when they occur together, can represent a sort of "final common pathway" for medical conditions and other syndromes. The manic phenotype can occur in patients with agitated delirium, brain tumors, corticosteroid treatment, and of course substance intoxication (Bunevicius A et al, *CNS Spectr* 2008;13(11):950–958; Brooks JO and Hoblyn JC, *Am J Psychiatry* 2005;162(11):2033–2038). These other phenotypes can be distinguished by recognition of key features such as the fluctuating nature of consciousness in delirium, neuroimaging findings, and positive urine drug screens.

The growing public awareness of bipolar disorder, as well as media portrayals that have destigmatized the illness, have also contributed to a wave of individuals who "want to be bipolar" (Chan D and Sierling L, *The Psychiatrist* 2010;34(3):103–105). For many, it is less stigmatizing to be diagnosed with bipolar disorder than with another cause of mood swings, such as a personality disorder. Another source of over-diagnosis is "Dr. Google," ie, patients who have self-diagnosed from the Internet. Accurate or not, the label sticks for years—particularly when it appears in the patient's medical record—while treatment with multiple medications tends to reinforce the sticky label.

Unfortunately, physicians may also be susceptible to diagnostic shortcuts. When faced with limited time for diagnostic interviews and the pressure to prescribe by patients and their families, well-meaning clinicians may give the diagnosis after a single brief interview. Not uncommonly, we find that it was diagnosed on the basis of mood fluctuation over minutes, temper tantrums, and fleeting insomnia. The rapidly expanding repertoire of medications approved for bipolar disorder, and their relative

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defect significantly associated with carbamazepine monotherapy (Jentink J et al, *BMJ* 2010;341:c6581).

Breastfeeding. Most infants have had no adverse reactions during breastfeeding, but three cases of hepatic dysfunction have been reported. You may want to monitor infant carbamazepine levels, liver enzymes, and a complete blood count if your patient opts to breastfeed on it.

Topiramate (Topamax)

The data on topiramate looks better than for valproic acid, but worse than for lamotrigine. Topiramate monotherapy carries an overall birth defect risk of 5%; the risk of hypospadias is 5.1% and the risk of oral clefts 2.2%. Birth defects don't appear to be dose-related, so even a tiny amount could lead to trouble. According to the North American Antiepileptic Drug Pregnancy Registry, the birth defect risk is 2.8 times that of the general population (Robinson GE *op.cit*), prompting the FDA to change topiramate's pregnancy classification to category D.

Breastfeeding. There are very little data on breastfeeding, but based on one small observational study, infants had very low topiramate concentrations and had no adverse effects (Ohman I et al, *Epilepsia* 2002;43(10):1157–1160).

Antipsychotics

Typical antipsychotics do not appear to be associated with birth defects, but can contribute to neonatal withdrawal and extrapyramidal symptoms that can last up to several months.

Atypical antipsychotics are actually fairly safe and well tolerated in pregnancy. In fact, if you're trying to cut down a medication regimen to one or two medications to prepare for pregnancy, leaving a woman on an atypical antipsychotic alone can be a good choice. It often comes down to a toss-up between lamotrigine, an atypical antipsychotic, and lithium. The choice depends on past response, tolerability, and how reliable your patient might be with prenatal monitoring. For me, lithium is often a distant third because of the monitoring hassles.

Atypical antipsychotics do not seem to be associated with birth defects, but the weight gain associated with their use can increase the risk for neural tube defects, hypertension, and gestational diabetes. Therefore, you should try to use the lowest dose necessary and, as always with the atypicals, you should follow metabolic labs, blood pressure, and weight closely throughout pregnancy.

Breastfeeding. Data suggest that both typicals and atypicals are safe during breastfeeding and no long-term effects have been identified with either class (Robinson GE *ibid*). There is limited data on atypical agents and breastfeeding, but the data we have suggest that excretion into breast milk is minimal and adverse events are rare.

With clozapine (Clozaril), patients should avoid breastfeeding because of the potential risk of agranulocytosis or seizures in the baby. Breastfeeding on chlorpromazine (Thorazine) should also be avoided due to the risk of drowsiness in the baby—probably due to its long half-life (Winans EA, *J Hum Lact* 2001;17(4)344–347). In both cases, if you determine that staying on that particular medication is in the best interest of the mother, bottle-feeding may be the best choice.

Benzodiazepines

First-trimester benzodiazepine use has been associated with a very small (0.7%) increased risk of cleft lip and palate. However, it is fine to use them in the second and third trimesters and during breastfeeding (Nonacs RM, *MGH Center for Women's Health* 2007; http://bit.ly/JCXg5u). There have been some reports of baby withdrawal or over-sedation with these medications, but such symptoms are usually mild and self-limiting.

Breastfeeding. Lorazepam (Ativan) has a shorter half-life than other benzodiazepines and there is less risk of it building up in the baby and potentially causing lethargy.

TCPR'S VERDICT: When trying to pare down a medication regimen for bipolar disorder in pregnancy, stay away from valproic acid, and stick with lamotrigine or an atypical antipsychotic. Lithium isn't as bad as people make it out to be, but the monitoring can be taxing. And close follow-up—ideally involving the patient's partner and obstetrician—is valuable.

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ease of use, may also contribute to over-diagnosis. Unfortunately, in some cases the treatment may be worse than the symptoms themselves (Iordache I and Low NC, *J Psychiatry Neurosci* 2010;35(3):E3–4).

Ultimately, some patients become attached to their bipolar diagnosis. Is the patient's husband more likely to help with the kids when mom is having a "manic moment"? Helping them let go of a label and the associated treatment, which can include complex polypharmacy and side effect burdens, can include a number of psychotherapeutic approaches. Providing validation and education can be done even in busy psychiatry clinics. Motivational interviewing is a flexible yet powerful style for helping someone move toward change. And paying attention to the needs of the person behind the diagnosis is always a good idea.

TCPR'S VERDICT: We can avoid the trap of under-diagnosing or over-diagnosing bipolar disorder by maintaining a respectful skepticism and basing our diagnosis on serial evaluations over many follow-up visits to establish a longitudinal course of illness. Close attention to the evolving literature in this field may help shape our understanding of bipolar disorder and the best ways to diagnose and manage this condition.

Bipolar Medication Safety During Pregnancy and Lactation				
Medication	**Recommended supplements** (PNV = prenatal vitamin, FA = folic acid)	**During pregnancy**	**Teratogenicity (MCM = major congenital malformations)**	**Breastfeeding notes**
Lithium	PNV	Give dose BID; decrease or stop 7-10 days before delivery Level II U/S and fetal echo at 18-20 weeks check Li level, BUN, Cr and electrolytes monthly; check TSH mid pregnancy May need to increase dose in pregnancy and decrease dose postpartum	Ebstein's anomaly 0.05%–0.1% in 1st trimester	Breastfeeding not recommended; if necessary check infant Li level, BUN, TSH, electrolytes and Cr immediately postpartum, at 4-6 wks, then every 8–12 wks
Valproic Acid (Depakote)	PNV, FA, Vitamin K	Avoid in 1st trimester if possible	5% risk for neural tube defects Risk of poor cognitive function and lower IQ	Relatively safe in breastfeeding Check drug level, platelets, and liver function in infant
Lamotrigine (Lamictal)	PNV, FA	May need to increase dose in pregnancy and decrease dose postpartum	2.2% risk of MCMs and 0–0.89% risk of cleft palate in 1st trimester	Thought to be safe in breastfeeding
Carbamazepine (Tegretol)	PNV, FA, Vitamin K	Monitor serum concentration of unbound drug	3.3% risk of MCMs Odds ratio for spina bifida is 2.6	Relatively safe in breastfeeding Check drug level, CBC, and liver function in baby
Topiramate (Topamax)	PNV, FA	Limited data, but may want to follow levels	5% risk of MCMs and 5.1% risk of hypospadias 2.2% risk of oral clefts	Thought to be safe, but little data
Oxcarbazepine (Trileptal)	PNV, FA	Limited data, but may want to follow levels	2.8% risk of MCMs	Limited data, but no adverse events reported
Gabapentin (Neurontin)	PNV, FA	Limited data, but may want to follow levels	1.7% risk of MCMs	Limited data, but no adverse events reported
Typical Antipsychotics	PNV		Risk of neonatal withdrawal and EPS in neonate	Breastfeeding data are reassuring Avoid breastfeeding on chlorpromazine due to excessive sedation
Atypical Antipsychotics	PNV	Follow metabolic labs, BP, and weight	Risk of weight gain, which can lead to neural tube defects and diabetes	Watch baby for oversedation Avoid breastfeeding on clozapine, but if necessary monitor CBC in baby
Benzodiazepines	PNV	Avoid in 1st trimester if possible	0.7% risk of cleft lip or palate when used in 1st trimester; thought to be safe after that	Watch baby for oversedation and try to use lorazepam, or other BZD with a short half-life

Current Issues in Bipolar Disorder Diagnosis: The Life Course Method

Descartes Li, MD
Clinical associate professor of psychiatry
University of California, San Francisco

Dr. Li has disclosed that he has no relevant relationship or financial interest in any commercial company pertaining to this educational activity.

How should we diagnose bipolar disorder? It isn't always easy and current bipolar screening tools are problematic for a number of reasons. In my experience, the "Life Course Method" for clinical interviewing has proven to be effective. In this article, I'll explain the reasons why and offer tips for using this tool.

Current Screening Tools

Current screening tools for bipolar disorder have been somewhat disappointing. The Mood Disorder Questionnaire (http://bit.ly/LdTheP) (Hirschfeld RM et al, *J Clin Psychiatry* 2003;64:45–59) yields lots of false positives but misses some true bipolar cases (for a review, see *TCPR* June 2010). Similarly, the Bipolar Spectrum Diagnostic Scale (http://bit.ly/K85MEN) (Ghaemi N et al, *J Affect Disorders* 2005;84:273–277) has not found widespread acceptance, possibly because patients sometimes have difficulty understanding it.

The Mini-International Neuropsychiatric Interview (MINI) (http://bit.

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The Life Course Method

1. Start from the beginning of patient's history of mood/psychiatric problems
2. Divide history into epochs of time
3. Go chronologically forward with special attention to mood episodes and significant life events
4. For each mood episode, obtain prodromal symptoms, medications tried and their efficacy, adherence to medications
5. Get a story!

Q&A With the Expert

This Month's Expert

Psychosocial Treatment of Bipolar Disorder

David Miklowitz, PhD

Professor of Psychiatry
Director, Child and Adolescent Mood Disorders Program, UCLA Semel Institute
David Geffen School of Medicine, UCLA

Dr. Miklowitz has disclosed that he receives book royalties from Guilford Publications and John Wiley and Sons. He has presented one paid CME presentation for GlaxoSmithKline. Dr. Balt has reviewed this article and found no evidence of bias in this educational activity.

TCPR: Why should we as psychiatrists focus on the psychosocial aspects of bipolar disorder?

Dr. Miklowitz: There is evidence that life events, family distress, and antecedent adversity variables in childhood are related to the course of bipolar disorder. So as with any other psychiatric disorder, you have to consider the psychosocial triggers of episodes and to what extent those are related to how people respond to medications, whether they are compliant with medications, and their psychosocial functioning between episodes. As good as they are, the medications that we use are not always effective, particularly for depressive as compared with manic episodes. Paradoxically, some psychosocial treatments have more of an effect on depression than mania symptoms. So I think of the two as complementary; they are not substitutes for each other, but a good treatment program ought to be a combination of targeted psychosocial treatments and medication.

TCPR: So psychosocial treatment addresses the "big picture"?

Dr. Miklowitz: Right. The typical psychosocial treatment should be psychoeducational. We should focus on the factors that contributed to the most recent episode—be that manic, depressive, or mixed. We ask what the family or the patient can do to anticipate and hopefully minimize stressors that might trigger symptoms of the disorder. In addition, we should focus on whether a patient has accepted the diagnosis and the necessary pharmacological treatments.

TCPR: I think it is fair to say that ideally most doctors, when doing medication management, offer some psychoeducation about the disorder. But are you talking about something that is more in depth?

Dr. Miklowitz: I would make the distinction between education and psychoeducation. I think most doctors provide *education:* "You have a disorder; here are the signs and symptoms; the medication I am going to give you will do this or that; here are the side effects that you can expect; and this is the trajectory of improvement." But addressing the patients' affective reactions to that information requires a different level of understanding. We also want to know whether they believe what they're being told, whether they think it applies to them, and whether they believe that medications provide a route to better health and functioning.

TCPR: Beyond just laying the groundwork, is it important to have this sort of dialogue with the patient at every visit?

Dr. Miklowitz: Yes, as well as making the family a central part of psychoeducation. Family members are often the first to recognize a new manic episode or that the person is getting more depressed. They may also know if a patient is not taking his or her medications regularly. If family members are empowered with information about bipolar illness, they are in a better position to help during crises.

TCPR: Could you tell us more about the importance of involving family members in treatment?

Dr. Miklowitz: There are some major reasons to involve the family. Most patients live with family members. Parents or spouses are often major contributors to whether patients stay on regular daily or nightly routines, fill prescriptions, take medications, or get to their treatment appointments. They may play a key role in whether the patient abuses alcohol or other substances. We have some evidence that highly conflictual families can be a stress factor that contributes to recurrences (Miklowitz DJ, *Cur Direct Psychol Sci* 2007;16(4):192–196). Research on "expressed emotion" has shown in multiple disorders that if you have a family that is very critical, hostile, and overprotective, you are going to have a tougher time staying out of the hospital and staying relapse-free.

TCPR: Can you define "expressed emotion"?

Dr. Miklowitz: In research, you interview a parent, sibling, or spouse of a patient who has just had an illness episode. In one hour you count how many times they criticize the patient. Do they express hostility about the patient? Do they show any evidence of what we call emotional over-involvement? Along with expressing many criticisms of the patient, it is also common for high expressed emotion family members to be locked into back and forth verbal "negative escalation cycles" with the patient. They have a tough time walking away or calling for a time-out.

TCPR: What are the types of psychosocial treatments that psychiatrists can offer?

Dr. Miklowitz: Ours is called family focused treatment (FFT) and is a nine-month program that involves the family. It involves psychoeducation for the patient and family and communication/problem-solving skills training to reduce conflict and enhance the protective effects of family relationships. There is a program of CBT (cognitive behavioral therapy) for people with bipolar disorder as well. Like the CBT for depression, therapists encourage patients to identify and challenge negative cognitions. There is also "pleasant life event scheduling" for trying to get people reactivated during depression. Another type of psychosocial treatment is interpersonal and social rhythm therapy (IPSRT). The premise of that treatment is that triggers of recurrences often come in the form of changes in routines that lead to changes in sleep cycles. Patients can empower themselves first by regulating their daily

routines and keeping a fairly regimented lifestyle and anticipating when certain events are going to throw their system off kilter: a change in the seasons, for example.

TCPR: Can you outline what happens in the nine months of treatment in FFT?

Dr. Miklowitz: There are three stages spread out over 21 sessions. As a patient's mood episode is resolving, you meet weekly with the patient and family members (parents, spouse, siblings) for 12 weeks. As the treatment progresses and the patient stabilizes, you meet biweekly for another 12 weeks, and then monthly for up to nine months. Stage 1 is focused on psychoeducation. The family talks about what the patient's most recent episode and symptoms were like, and the patient describes the experiences of mania and depression from his or her perspective. Together, they examine triggers of past episodes and develop a relapse prevention plan. Stage 2 is focused on communication training, where the goal is to reduce family tension. Patients and families learn skills like active listening, conflict negotiation, and how to request changes in other people's behaviors. This is our more direct attempt to reduce expressed emotion. Finally, stage 3 is focused on problem solving. They are taught how to break big problems down to smaller problems. By that time in treatment the patient is often more stable and able to implement some of these strategies.

We should make the family a central part of psychoeducation. Family members are often the first to recognize a new manic episode or that the person is getting more depressed.

David J. Miklowitz, MD

TCPR: If the patient experiences an episode or is hospitalized during this process, does the treatment then restart from the beginning?

Dr. Miklowitz: Ideally when there has been a relapse, the patient and family come in as soon as possible and review what happened. Something about the relapse prevention plan didn't work. We try to put it in context and help the family realize that this is not a failure of the treatment or their efforts. It is just that this is a recurrent disorder and people have to expect that it will recur from time to time, but over time with their efforts there may be fewer of these, or the episodes may be shorter or less severe.

TCPR: Does this approach require special training on the part of the person doing the therapy?

Dr. Miklowitz: We are doing some research now to try to make it easier for practitioners to use this treatment. The current training process starts with a weekend workshop and then practitioners are supervised on two cases. We have written a book for practitioners that they can use as a guide (Miklowitz DJ. *Bipolar Disorder: A Family-Focused Treatment Approach.* Second Edition. New York, NY: Guilford Press; 2008).

TCPR: Is there is an age or a particular phenotype for which family therapy just doesn't work, or are their clinical presentations where you actually don't want the family involved?

Dr. Miklowitz: A good predictor of who will respond to FFT is the expressed emotion level of the family. The more conflict, hostility, or overprotectiveness, the more likely the patient is to show a big improvement in family therapy. However, I would not necessarily recommend this treatment for people if there is or has been physical or sexual abuse in the family. Also, sometimes a young person's issues have to do with drugs, alcohol, or sexuality and they are not comfortable talking about these things with a parent present. A lot of older patients just don't have families who are still involved in their lives. Probably 40% of adult patients in the community are disconnected from their families, but of course the proportion of young adult or adolescent patients without families is much lower. Sometimes we involve a friend, sibling or a roommate. In one case, we even involved an AA sponsor.

TCPR: Could family therapy or other psychosocial intervention take the place of medications?

Dr. Miklowitz: I don't think we have the data to answer that question. A group of researchers headed by Holly Swartz and Ellen Frank (University of Pittsburgh) is testing a version of interpersonal therapy as a substitute for medication for bipolar II patients. They have some early findings that suggest that interpersonal therapy and quetiapine have an equivalent short-term effect on depressive symptoms (Swartz HA et al, *Bipolar Disord* 2012;14(2):211–216).

TCPR: Are there specific aspects of the disease that make family therapy less promising?

Dr. Miklowitz: Someone who is acutely psychotic is not going to respond to any psychotherapy at that point. But somebody who has had psychosis and is recovering in a family environment is perfectly appropriate for this kind of approach. There are also people who are disconnected from their families because of substance abuse; their families don't want anything more to do with them and obviously this won't work for them. In general, bipolar patients with active substance abuse are harder to treat with psychotherapy and often need a more intensive chemical dependency program.

TCPR: Can you tell us what is new in your field and what you see in the future?

Dr. Miklowitz: The things that I am most excited about are studies of kids at risk for bipolar disorder. For example, we are conducting a randomized trial of kids, ages nine to 17, who have parents diagnosed with either bipolar I or II, and who are showing early warning signs of the condition. The participants may have already had a depressive episode or significant mood swings, but they are not yet bipolar. They are being randomized to either FFT or a comparison intervention, and the goal is to find out if we can prevent conversion to the full syndrome and reduce symptom severity. There are also studies on group mindfulness-based cognitive therapy that has been successful with recurrent depression. We are doing a trial with women who are either pregnant or in the postpartum, to teach mindfulness skills for coping with stress. In the long run, we are hoping to find that mindfulness-based treatment strategies are an alternative for women with mood disorders who are pregnant and don't want to take psychiatric medications. But we have a ways to go before we can show this.

TCPR: Thank you, Dr. Miklowitz.

Q&A With the Expert

This Month's Expert

Management of Bipolar Depression

Claudia Baldassano, MD

Assistant Professor of Clinical Psychiatry
University of Pennsylvania

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

TCPR: Dr. Baldassano, could you please share with us your definition of bipolar depression, and why we hear so much about it these days?

Dr. Baldassano: Bipolar depression is simply the term used when someone has a depressive episode in the context of having bipolar disorder type I or type II. We hear a lot about bipolar depression for two reasons. First, our bipolar patients suffer many more days with depression than they do with mania or hypomania. Many studies have found the ratio to be as much as three to one (Kuka RW et al, *Bipolar Disord* 2007;9(5):531–535). And second, it is very difficult to treat. We just don't have as many effective treatments for bipolar depression, and bipolar depression seems to be more resistant to treatment than unipolar depression. It seems to be an entity distinct from unipolar depression.

TCPR: Historically, the definition of bipolar depression is simple: a patient who has had a manic or hypomanic episode in the past presents with a depressive episode. However some literature lately is talking about bipolar depression in patients who present with depression *without* a clear history of mania or hypomania.

Dr. Baldassano: This is true and it is where this diagnosis becomes more difficult. Patients often enter into treatment with depression. Upon first presentation, unipolar and bipolar depression look the same, so you can't really distinguish the illness based on the depressive symptoms. Our job as psychiatrists is to try to understand what came before—what the longitudinal history is for the patient. This is especially challenging because often patients lack insight and it is not always easy to diagnose previous episodes of mood elevation, especially in type II bipolar where the elevations are hypomania rather than mania and often go unnoticed.

TCPR: If the presentations of bipolar and unipolar depression are clinically similar, if not identical, what is it about these depressions that is different?

Dr. Baldassano: A good illustration of this is the BRIDGE study (Bowden CL et al, *Arch Gen Psychiatry* 2011;68:791–799). The BRIDGE study was a multicenter, multinational study that looked at both prevalence and characteristics of more than 5000 people who presented with major depressive disorder. They found that many of them were actually undiagnosed bipolar disorder patients. They did this not through a systematic interview using DSM criteria, but with a set of "bipolar specifiers" they were able to diagnose a fairly large percent of this MDD cohort—47%, to be exact— as bipolar according to these "specifier" criteria, which look at factors like longitudinal history, family history, age of onset, and number of previous episodes. By comparison, when the researchers strictly applied just DSM criteria, they found fewer (about 16%) who were diagnosed with bipolar disorder. By the way, we don't know whether the 47% of patients with "bipolar-specifier" features would respond better to a mood stabilizer than to an antidepressant. In other words, we don't know whether their depression is more like bipolar or unipolar depression.

TCPR: Can you briefly explain how the results of that study guide your practice or how they should affect our practices?

Dr. Baldassano: What I always say to my residents is that when patients come in they give you a snapshot. But what a good clinician needs to do is create the photo album. And what is in the typical photo album of a patient who has bipolar disorder? I tend to look at five different dimensions: age of onset, course of illness, family history, treatment response, and comorbidities. We know our bipolar patients tend to present earlier with their first active episode; in fact, in the STEP-BD program, the mean age of onset was about 17 years of age (Perlis RH et al, *Biol Psychiatry* 2004;55(9):875–881). We also know that bipolar patients tend to have multiple recurrences of their illness and inter-episode recovery. Bipolar patients often have a loaded family history, including suicide, schizophrenia, substance abuse, anxiety, and unipolar and bipolar disorder (Serretti A et al, *Eur Arch Psychiatry Clin Neurosci* 2012;May 9:online ahead of print). And in terms of treatment response, our bipolar patients tend to have more treatment resistance, more failed antidepressant trials. I think it is very important to look at the longitudinal course of a person's illness, because it is essential to help you to parse out what is depression in the context of bipolar versus depression in the context of unipolar.

TCPR: So in a patient with depressive symptoms, even if they have never had a manic or hypomanic episode, if you still feel they may be bipolar, how do you approach treatment?

Dr. Baldassano: If I have a strong suspicion that a patient is bipolar, or if they have depression with one of the bipolar features I described earlier, then I am more likely to go ahead and treat with a mood stabilizer, for which we have more evidence. There is not an antidepressant that has shown in any large-scale study to be effective in the treatment of bipolar depression. (See for example, Sachs GS et al, *N Engl J Med* 2007;356(17):1711–1722. Editor's note: in this study, all patients were taking a mood stabilizer and the study medications were added.) So in an attempt to practice evidence-based medicine I am more likely to utilize mood stabilizers, which we have more evidence for. My second concern is switch rate: in placebo-controlled trials the switch rate

tends to be low associated with the more modern antidepressants such as the SSRIs, SNRIs, and Wellbutrin (Sachs GS ibid). However, if you look at observational data, which mirrors the real world, instead of clinical trials, you see higher switch rates. One study found self-reported switch rates in STEP-BD participants were as high as 44%. (Truman CJ et al, *J Clin Psychiatry* 2007;68(10):1472–1479).

Bipolar patients suffer many more days with depression than they do with mania or hypomania and bipolar depression is very difficult to treat.

Claudia Baldassano, MD

TCPR: In those rare circumstances when you give an antidepressant to a person with bipolar depression, do you always give some sort of mood stabilizer prophylaxis, too? And if so, which do you use?

Dr. Baldassano: Yes, personally I do, because bipolar disorder is a cyclical disorder. I prefer that patients are on mood stabilization to help reduce this cycle. There are two agents that are approved for acute bipolar depression: quetiapine (Seroquel) and the olanzapine/fluoxetine combination (sold under the brand name Symbyax). Also, there is a plethora of data supporting lithium in both acute treatment of bipolar depression and maintenance treatment. I also use lamotrigine (Lamictal), which has fairly robust data in prevention of bipolar depression, and is FDA-approved for this indication.

TCPR: Is there anything that makes you less or more likely to try an antidepressant in bipolar depression?

Dr. Baldassano: I am much less likely to add an antidepressant if someone has had previous manic switches with other antidepressants. In the Truman et al study I mentioned earlier, the odds ratio for a manic switch was as high as 7 or 8 if the patient had had a switch with previous antidepressants. I'm also hesitant to utilize an antidepressant in someone who has a history of rapid cycling, because research shows antidepressants in patients with bipolar rapid cycling can increase the cycles or cause more cyclic acceleration (Ghaemi SN et al, *Bipolar Disord* 2003;5(6):421–433). And I am less likely to use an antidepressant in postmania depression.

TCPR: Should we approach depressive episodes differently in bipolar II vs bipolar I?

Dr. Baldassano: I am equally hesitant to prescribe an antidepressant in bipolar 1 and bipolar 2 if there is any history of rapid cycling. My decision about using an antidepressant has more to do with proximity to their mood elevations and history of multiple mood elevations rather than type I or type II. This hasn't been well studied in the research.

TCPR: We're taught that one of the reasons a depressed patient may fail a trial of an antidepressants is because he or she is actually bipolar. While this is often true, is there a risk of doctors undertreating MDD because they are led to believe that their patient actually has bipolar depression?

Dr. Baldassano: Not responding to an antidepressant or having multiple antidepressant failures can be a sign of bipolar disorder. But just assuming that a patient who has failed an antidepressant trial is bipolar is a bit simplistic. If I have a patient who does not respond to a good therapeutic antidepressant trial, it may prompt me to take a step back and take a better longitudinal history or review their longitudinal history, or to get collaborative data from a family member. And I would look again at what I think of as the soft signs of the bipolar features: the course of illness, age of onset, and comorbidities.

TCPR: Thank you, Dr. Baldassano.

Current Issues in Bipolar Disorder Diagnosis: The Life Course Method

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ly/KWoXUN) (Sheehan DV et al, *J Clin Psychiatry* 1998;59 (suppl 20):22–33) uses the following screening question for mania/hypomania: "Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self?"

I rarely find questions like this to be useful. If the patient answers yes, I often end up asking about further symptoms of mania/hypomania, leading to variable or confusing answers—and I still don't have a good sense of whether the patient had a manic episode or not. A "no" answer, likewise, does not rule out a manic episode.

So are any of the current screening tools useful? You could always use the Structured Clinical Interview for DSM-IV (SCID-IV), the "gold standard" in diagnosis for clinical research studies, but it can take two to three hours to administer, and most clinicians do not have the training or time for this. On the other hand, more familiar scales like the Altman Mania Rating Scale and the Young Mania Rating Scale are intended only to rate intra-episode severity and monitor treatment response. They are not intended as screening instruments. (For a review of rating scales for mania, see Picardi A, *Curr Opin Psych* 2009;22(1):42–49.)

My experience in teaching psychiatric residents how to diagnose bipolar disorder led me to carefully observe the strategies of experienced clinicians. Expert clinicians seem to employ a strategy, or set of strategies, that I call the Life Course Method (not to be confused with the NIMH Life Chart Method, a tool to follow treatment outcomes in patients with bipolar disorder).

Clinical Pearls

- Use collateral information whenever possible
- Screen for mania in the time periods right before depressions
- Focus on behavioral activation or life events rather than on patient report of mood elevation
- Screen depressive episode for manic/hypomanic symptoms to diagnose mixed episodes

The Life Course Method: Get a Story

This method basically involves getting a good, solid clinical history from the beginning. I usually start with the question: *When did you first start experiencing mood symptoms?* Then I proceed chronologically, with special attention to mood episodes and significant life

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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

Low Dose Abilify Ineffective as Adjunct for MDD

Augmentation of antidepressants with antipsychotics has become a common practice, and aripiprazole (Abilify) has been FDA-approved at doses from 2 mg/day to 15 mg/day for this purpose. In a recent report, 225 patients with major depressive disorder (MDD) who had failed one to four antidepressant trials were studied to determine whether low dose Abilify really works.

Using the Sequential Parallel Combined Design (SPCD), a strategy designed to minimize placebo response, patients were randomized to receive adjunctive treatment with Abilify or placebo across two 30-day phases. Some patients received 2 mg/day in phase one with an increase to 5 mg/day in phase two. Others received a placebo in both phases, while still others received a placebo in phase one and 2 mg/day of Abilify in phase two. All patients continued to receive their original antidepressant throughout the trial, and no patients had a history of bipolar disorder or psychosis.

After 30 days, patients taking 2 mg/day of Abilify had only a slightly higher response rate (defined as a 50% decrease in MADRS score) relative to those taking placebo, 18.5% vs 17.4%, respectively—a difference of only 1.1%. When the dose was increased to 5 mg/day for another 30 days—while the placebo subjects continued taking placebo—response rates were also similar between groups, differing by only 4.3% (not statistically significant). Even when early-stage placebo responders were taken out of the analysis—to increase likelihood of finding a response in the Abilify group—the response rate to 2 mg/d Abilify was still only 18%, indistinguishable from placebo.

Dropout rates were low, reflecting generally good tolerability of low-dose Abilify when added to antidepressants. In fact, only constipation and dry mouth were significantly more common with Abilify. This was an investigator-initiated study supported by Bristol-Myers Squibb, which also provided blinded study medication (Fava M et al, *Psychother Psychosom* 2012;81:87–97).

TCPR's Take: The authors' primary conclusion is that Abilify is well tolerated at low doses. This is not surprising, since the average doses in the two trials to obtain FDA approval as an adjunctive antidepressant were above 10 mg/day, where akathisia and fatigue were common. However, lower doses—which are recommended by the manufacturer and frequently used by clinicians—were ineffective for depression. Based on these results, the authors suggest that Abilify's antidepressant effect may be restricted to doses over 10 mg, where, they point out, it acts more like a dopamine antagonist. This raises the question of whether a different antipsychotic might perform just as well.

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events. I like to divide the history into academic/occupational time periods, or epochs: *How was high school? How was college? Your first job?* Patients in their mid-twenties often have excellent recall for events during school years. Moreover, asking about whether an event occurred in freshman versus sophomore year of college is often easier than asking about 1994 or 1995. For older patients, life events such as marriage/divorce, job changes, periods of disability, or geographic relocations can help anchor the history. In addition, these life events may be concurrent with manic or hypomanic episodes. Behavioral changes, such as increased risky pleasurable behaviors or pressured speech, are often better markers for manic/hypomanic episodes than patient recall of mood elevations (Akiskal HS and Benazzi F, *J Clin Psychiatry* 2005;66:914–921), so ask for behavior changes first, then follow up with mood inquiries to nail down the diagnosis.

A sample series of questions might look like this: *Why did you move to Maine? So you decided to start lobstering, I see. What was your daily life like at that time? How about your mood? Did your [mood symptom] get so bad that you couldn't work? Why did you move back?*

I try to link events together into a life story to develop a baseline and trajectory for a person's life. A process of this kind can be quite memorable and I often literally get "where patient is coming from." Collateral information is helpful when I am at a loss to understand the patient, or am left with a bunch of symptoms that don't fit together. A family member who knows the patient well can confirm, clarify, or refute important details. Also, a review of mania/hypomania symptoms during depressive episodes sometimes yields a discovery of a mixed episode. Finally, I make sure to explore the period right before a depressive episode because sometimes the patient has forgotten about a mania that preceded it.

Advantages

A particular advantage of the Life Course Method is that most of what's important in treating bipolar disorder—triggers, age of onset, response to medications, number of episodes—are reviewed in the normal course of the interview, without having to memorize a list of questions. Remember to ask about functional impact of mood symptoms, keeping in mind that other diagnoses or co-morbidities (eg, substance abuse or anxiety disorders) may cause more impairment than mood complaints.

The Life Course Method makes the

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CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by August 31, 2013. 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. Valproic acid (Depakote) carries what risk of neural tube defects when taken in the first trimester of pregnancy (Learning Objective #1)?
   - [ ] a. 1%
   - [ ] b. 2%
   - [ ] c. 5%
   - [ ] d. 6%

2. Which of the following medications is not recommended during breastfeeding (LO #1)?
   - [ ] a. Lamotrigine (Lamictal)
   - [ ] b. Lithium
   - [ ] c. Carbamazepine (Tegretol)
   - [ ] d. Haloperidol (Haldol)

3. In a 2008 study in which Zimmerman and colleagues performed a comprehensive diagnostic interview of 700 patients, 21% of whom self-reported a history of "bipolar disorder," how many actually had the diagnosis (LO #2)?
   - [ ] a. 44%
   - [ ] b. 21%
   - [ ] c. 13%
   - [ ] d. 10%

4. The "life course method" of clinical interviewing suggests using which of the following strategies to get a thorough clinical history (LO #3)?
   - [ ] a. Beginning with the patient's year of birth, asking for details on particular years to gather a history (eg, "What was your mood in 1989?")
   - [ ] b. Working backward from the most recent episode to find a pattern
   - [ ] c. Starting with the question: "When did you first start experiencing mood symptoms?" and working chronologically forward, paying particular attention to certain life events (eg, "How was college?")
   - [ ] d. Giving patients a sheet of paper and asking them to plot their "ups and downs" over time

5. Family-focused treatment (FFT) traditionally takes place over how long of a time period (LO #4)?
   - [ ] a. 12 weeks
   - [ ] b. Six months
   - [ ] c. Nine months
   - [ ] d. One year

6. According to Dr. Claudia Baldassano, in patients with bipolar disorder, what is the ratio of days spent depressed vs. days spent manic (LO #5)?
   - [ ] a. 1 to 1
   - [ ] b. 3 to 1
   - [ ] c. 1 to 3
   - [ ] d. 1 to 5

7. According to Dr. Claudia Baldassano, which antidepressant is an effective treatment for bipolar depression (LO #5)?
   - [ ] a. There is not an antidepressant that has shown in any large-scale study to be effective in the treatment of bipolar depression
   - [ ] b. Imipramine (Tofranil)
   - [ ] c. Doxepin (Silenor)
   - [ ] d. Paroxetine (Paxil)

8. In the Fava et al study of low-dose aripiprazole (Abilify) as an adjunct for MDD, what was the 30-day response rate of patients taking 2 mg/day of the drug (compared to a 17.4% placebo response rate) (LO #6)?
   - [ ] a. 18.5%
   - [ ] b. 22.1%
   - [ ] c. 25.5%
   - [ ] d. 82.2%

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history much more memorable. Once the interview has been completed, a quick review of the patient's record can bring back the person's life story with surprising speed and vividness. If the interview is chronological, gaps in the history become quickly apparent and can be noted for future exploration. This method also often engages the patient in the interview process and begins the psycho-educational process, especially as patterns emerge and previously inexplicable mood symptoms are seen to have predictability.

Disadvantages

The Life Course Method can take a lot of time, so being efficient is critical. I advise inexperienced clinicians to obtain only enough information so as to confirm a diagnosis and obtain other relevant information, rather than spending a lot of time on florid manic episodes. I also recommend focus on the earliest symptoms of an episode, because these represent signals for future early intervention. However, the most important factor in improving efficiency is practice, and if possible, observation of expert clinicians.

TCPR'S VERDICT

No convenient, foolproof methods have emerged in routine screening for bipolar disorder. The Life Course Method is basically just good clinical interviewing with a longitudinal perspective. But it makes clinical interviewing memorable, engaging and (dare I say) fun.

Next month in *The Carlat Psychiatry Report*: Eating Disorders, including tips on assessing ED patients and an overview of binge eating disorder.

This Month's Focus:
Bipolar Disorder

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