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Controversies in bipolar disorder

TRUST EVIDENCE OR EXPERIENCE?

Confused by conflicting studies and opinions? 2 clinicians offer their perspective on how to manage real-life patients

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Today's buzzword in health care is evidence-based medicine. Most clinicians would agree that evidence from clinical research should guide decisions about treating bipolar disorder. In theory, randomized controlled trials should tell us how to manage bipolar patients and achieve therapeutic success.[1,2] But good theory does not always translate to good practice; many patients with bipolar disorder have poor outcomes, even when clinicians adhere to research-derived evidence.

The problem is that one well-designed study's conclusions may contradict those of another equally well-designed study because of differences in subject selection, comorbidities, dosages, outcome criteria, and other variables.[3] As a result, bipolar experts often disagree about issues as basic as antidepressants' role in managing bipolar disorder and whether recurrent major depression should be considered a form of bipolar disorder. This leaves the clinician with the task of interpreting not only conflicting research findings but also conflicting expert opinion.

This article conveys clinical impressions gained from treating approximately 10,000 patients with bipolar disorder over 16 years. We do not claim to have resolved the issues in dispute, but we hope our experience will help practicing clinicians. We examine the evidence and address controversies in bipolar disorder—such as subthreshold hypomania, manic switches, use of antidepressants, juvenile depression/bipolar disorder, and atypical depression—together with our opinions on each.

continued

Bipolar controversies

Clinical Point

In our patients, destabilization from antidepressant monotherapy rarely is as obvious as a sudden switch to mania

Box 1

A 'bipolar spectrum' matches our clinical observations

Proponents of the bipolar spectrum conceive of a continuum of bipolar disorders that encompasses classical presentations as well as softer variants. Some experts propose a unitary hypothesis of mood disorders, contending that most patients with recurrent depressive episodes have a form of bipolar disorder,[4] a position adopted by Goodwin and Jamison in the 2007 edition of their classic text on bipolar disorder.[5]

We agree with this view. Most of our patients with recurrent depression exhibit bipolar characteristics and respond preferentially to mood stabilizers. Many of these patients experience subthreshold hypomanic episodes.

Subthreshold hypomania: The rule, not the exception

DSM-IV-TR fails to capture variants of bipolar disorder that we see commonly in clinical practice. Depressive episodes in patients with soft forms of the illness can be disabling and protracted, but their subthreshold hypomanias are often briefer and milder than required for a diagnosis of bipolar II disorder.

During these episodes, energy increases, daytime sleepiness subsides, mood is brighter, and thought processes become clearer, allowing the patient to assume responsibilities and complete tasks left undone because of the preceding depressive episode. Our patients usually describe these brief interludes as feeling "normal." A clinician relying on a patient's response to questions about classical manic symptoms—euphoria, racing thoughts, increased sexual activity, overspending, etc.—may misdiagnose the patient with unipolar major depression.

Manic switches

Most patients with bipolar spectrum disorders (***Box 1***)[4,5] presenting with depression are misdiagnosed by clinicians[6] and treated with antidepressants.[7] But what is the effect of an antidepressant without a mood stabilizer in a bipolar patient? A few patients may benefit from antidepressant monotherapy (discussed below), but the predominant view in the literature is that antidepressants cause rapid mood cycling or a switch to mania or hypomania.[8]

In our experience, antidepressant monotherapy in a depressed bipolar patient usually, but not always, destabilizes the illness. However, the form that destabilization takes in our patients is rarely as obvious as a sudden switch to mania. If bipolar patients given antidepressants routinely switched to mania, we believe there would be fewer missed diagnoses of bipolar disorder.

Bipolar patients who enter our practice on antidepressant monotherapy exhibit, in approximate order of frequency, the following 3 forms of mood instability:

- worsening of depressive symptoms, sometimes accompanied by increased anxiety and agitation
- rapid improvement of depressive symptoms, followed by a depressive relapse
- fluctuating but incomplete antidepressant response (such as a patient who is paralyzed with severe depression and unable to get out of bed some days but on other days can function marginally despite less severe but still distressing symptoms—a condition some clinicians label "double depression").

The rarity of switching in our patients may be due in part to the frequency with which we prescribe selective serotonin reuptake inhibitors (SSRIs), because switching is more likely with tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRIs).[9]

Do patients on mood stabilizers require antidepressants?

The risk of antidepressant-induced mood dysregulation in bipolar patients (***Box 2, page 31***)[10] has led some bipolar experts to suggest avoiding antidepressants entirely or giving them only briefly to bipolar patients on mood stabilizers who experience breakthrough depression.[11] Sachs et al[12]

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found that although adding antidepressants to mood stabilizers did not increase the rate of switches to mania, antidepressants did not confer additional treatment efficacy. In our clinical experience, however, the combination of a mood stabilizer and an antidepressant benefits many patients.

Our experience comports with the findings of Altshuler et al,[13] who observed a significant depressive relapse rate in patients on mood stabilizers whose antidepressants had been discontinued. In the Sachs et al study,[12] mood stabilizers and antidepressants were initiated simultaneously, whereas in our practice we add antidepressants to mood stabilizers only when a mood stabilizer is ineffective in relieving depressive symptoms or when breakthrough depression occurs.

We do find, however, that antidepressants must be continued to prevent depressive relapse. Most of our bipolar patients maintain long-term stability during continuous treatment with an antidepressant combined with a mood stabilizer. These patients require periodic tweaking of medication dosages, supplementation with atypical antipsychotics, or addition of thyroid hormones, but they remain functional, rarely experience return of severe mood symptoms, and are able to avoid hospitalization.

Children, adolescents, and young adults with bipolar disorder

Akiskol[14] speculated that juvenile depression may be a developmental pathway to bipolar disorder. Geller et al[15] found that almost one-half of the patients in their study who as children had been diagnosed with major depression met criteria for bipolar disorder on follow-up assessment.

We agree that depression in a child or adolescent usually is a manifestation of bipolar disorder. If the family history and evidence of mood instability suggest a bipolar-spectrum disorder, we believe it may be safer to begin treating a depressed child or adolescent with a mood stabilizer than with an antidepressant.

In our opinion, reports of suicidal behavior in children, adolescents, and adults age <25 treated with antidepressants do not reflect an inherent problem with these medications. Rather, misdiagnosis of bipolar-spectrum disorders as unipolar depression leads to mood destabilization when antidepressants are used in the absence of mood stabilizers. Although FDA warnings on antidepressants in persons age <25 do not explicitly address inaccurate diagnosis,[16] physicians are cautioned to monitor patients for behavior characteristic of mood instability in patients with bipolar disorder.[17]

The age-25 divide is useful for distinguishing between unipolar and bipolar depression. We find that recurrent depressive episodes before the 25th birthday are usually bipolar, whereas depressive episodes that begin after the 25th birthday are usually unipolar. We believe there is a correlation between antidepressant-induced suicidality in children[18] and the earlier onset of bipolar disorder as compared with unipolar major depression.

Psychosis = schizophrenia?

Many of our patients with bipolar disorder describe "voices" that demean them or

Box 2

Antidepressant monotherapy: Always bad in bipolar patients?

Antidepressants in the absence of mood stabilizers usually make bipolar patients worse by destabilizing the illness. Some patients—especially those with soft features—appear to do well on an antidepressant, however.[10]

Although no longer suffering from severe depressive episodes, they usually can discern low-amplitude cycling—periods of increased activity and energy alternating with periods during which they experience a slight dampening of mood while remaining functional. For these patients, we prescribe very low dosages of selective serotonin reuptake inhibitors (such as sertraline, 12.5 to 25 mg/d).

Antidepressant monotherapy in bipolar patients is controversial for good reason, but it may be appropriate for a minority of patients.

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Clinical Point

We find that recurrent depressive episodes are usually bipolar before age 25 and unipolar with onset after age 25

Bipolar controversies

Clinical Point

Liothyronine augmentation often eliminates persistent low-level depressive symptoms in our patients on mood stabilizers

Box 3

Postpartum psychosis: Probably bipolar disorder

Postpartum psychosis is recognized by several commentators as a manifestation of bipolar disorder,[20,21] as is probably the case in many patients with postpartum depression.[22] We believe antidepressants should be used with caution in treating postpartum depression to prevent worsening of depressive symptoms or emergence of a psychotic bipolar episode.[23]

Andrea Yates—who drowned her 5 children while in a psychotic episode—was misdiagnosed with schizophrenia by some expert witnesses at her first criminal trail, an example of the practice of erroneously equating psychosis with schizophrenia and failing to take patient history into account. Her symptoms, professional accomplishments, past episodes, and family history should have suggested bipolar disorder.[24] ***(For more information on postpartum psychosis, see page 40.)***

We rarely have encountered a patient with postpartum depression or psychosis who does not have a history of (often undiagnosed and untreated) recurrent mood episodes. For most of these patients, a mood stabilizer may be a better choice than an antidepressant.

direct them to harm themselves or others; some insist that their TV or radio is speaking directly to them. A florid psychotic episode sometimes heralds the onset of bipolar disorder in a child or adolescent.

Although misdiagnosis of patients with bipolar disorder as suffering from schizophrenia is not as common as it was 25 years ago, it still occurs. Psychosis is now recognized as a prominent feature of bipolar disorder,[19] but some clinicians adhere to earlier diagnostic formulations that equate psychosis with schizophrenia (***Box 3***).[20-24]

The role of thyroid hormones

Adding a thyroid hormone—usually liothyronine—to an antidepressant has been demonstrated to accelerate,[25] augment,[26] and enhance[27] the therapeutic effect of antidepressants. Patients with mood disorders frequently have undiagnosed subclinical hypothyroidism[28] and may have:

- increased thyroid antibody levels[29]
- a rapid antidepressant response to thyrotropin-releasing hormone[30]
- an increased risk of antidepressant-induced rapid mood cycling.[31]

The American Association of Clinical Endocrinologists revised its recommended normal thyroid-stimulating hormone (TSH) range in 2002, setting the upper limit of TSH at 3.0 mU/L,[32] but conventional laboratory reference ranges still consider a TSH as high as 5.5 or 6.0 as normal. It is worth noting that even depressed patients with a normal TSH—below 3.0—may benefit from liothyronine supplementation. Cooper-Kazaz et al[27] demonstrated significant enhancement of antidepressant response to sertraline by adding liothyronine, even though subjects' baseline TSH was approximately 1.7 mU/L.

Patients in our practice with borderline or moderately elevated TSH often fail to respond optimally to bipolar medications. El-Mallakh and Karippott[33] describe chronic irritable dysphoria in bipolar patients taking antidepressants. Antidepressants can induce such symptoms, especially in the absence of a mood stabilizer, but we find that hypothyroidism often is the cause of chronic irritability and dysphoria in patients taking a mood stabilizer and an antidepressant.

Thyroid lab assessments and supplementation are an important part of our practice. Liothyronine augmentation often brings stability to our unstable bipolar patients and eliminates persistent low-level depressive symptoms in patients on mood stabilizers or mood stabilizer-antidepressant combinations. ***(For more information on thyroid function testing, see page 47.)***

Atypical depression and the bipolar spectrum

Depressive episodes are considered either "typical" (a category that includes melancholic depression—in DSM-IV-TR, major depression with melancholic features) or "atypical" (in DSM-IV-TR, major depression with atypical features). Atypical

features were originally associated with response to monoamine oxidase inhibitor antidepressants, whereas nonatypical depression was thought more likely to respond to tricyclic antidepressants.[34] The depression of bipolar disorder is usually atypical (***Box 4***), especially in patients with softer variants of the illness.[35]

We believe that depressed patients with atypical symptoms aggregate into groups according to the presence, severity, and character of interdepressive manic or hypomanic episodes. Some patients experience recurrent depressive episodes with intervening euthymia (recurrent major depression), whereas others experience depressive episodes punctuated by brief subthreshold hypomanic episodes. Patients in these groups occasionally tolerate or even benefit from cautiously managed antidepressant monotherapy. Patients with atypical depressive episodes alternating with frank hypomanic, manic, mixed, or manic-psychotic episodes usually require a mood stabilizer and may benefit from cotreatment with an atypical antipsychotic.

Akiskol and Benazzi[35] suggest that atypical depression may be a subtype of the bipolar spectrum. Our experience suggests that the bipolar spectrum is a continuum of degrees of risk for mood instability in persons with recurrent atypical depression.

Box 4

Atypical depression: Who sees 'leaden paralysis'?

DSM-IV-TR defines atypical depression as depression characterized by mood reactivity and at least 2 of these 4 features:

- hypersomnia
- increased appetite or weight gain
- leaden paralysis
- sensitivity to interpersonal rejection.

The term 'hypersomnia' is misleading. Many of these patients do not sleep excessively because work or school attendance prevents oversleeping. Instead, they experience an increased sleep requirement manifested by difficulty getting up in the morning and increased daytime sleepiness.

Increased appetite and weight gain (hyperphagia) often are present, but almost as often our patients report no change in appetite or weight or even anorexia and weight loss.

We rarely see a condition one would term 'leaden paralysis.' We also find that 'sensitivity to interpersonal rejection' is too narrow a construct. Our patients with atypical depression experience increased sensitivity to every stressor in their lives—work, school, family, and social stressors—not just interpersonal rejection.

Clinical Point

The depression of bipolar disorder usually is 'atypical,' especially in patients with softer variants of the illness

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Related Resources

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Drug Brand Names

Liothyronine • Cytomel
Sertraline • Zoloft

Disclosure

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Clinical Point

Our patients with atypical depression experience increased sensitivity to every stressor, not just to interpersonal rejection

Bottom Line

Be wary of the traditional paradigm: 'major depression—rule out bipolar disorder.' The frequency with which patients with bipolar disorder are misdiagnosed with major depression and receive inappropriate treatment suggests a different paradigm: consider a bipolar disorder diagnosis first, especially if a patient has a history of recurrent depressive episodes beginning in early life or has not responded well to previous antidepressant trials.