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Be a troubleshooter: systematically eliminate whatever is perpetuating manic, depressive, or cycling symptoms

When bipolar Treatment FAILS

What's
Your
Next
Step?

Marcelle Mostert, MD

Assistant professor of psychiatry
University at Buffalo, SUNY

Steven L. Dubovsky, MD

Professor and Chair, department of psychiatry
University at Buffalo, SUNY
Adjoint professor of psychiatry and medicine
University of Colorado, Denver

Ⓐ All phases of bipolar disorder can be difficult to treat, and patients remain symptomatic on average about half the time.¹ Not all bipolar patients who experience continued illness and disability are treatment-resistant (*Box 1, page 40*), but when symptoms persist you may ask yourself: Was treatment suboptimal or simply ineffective?

Patients with severe symptoms may be satisfied with a substantial decrease in symptoms, but any residual symptoms cause ongoing distress and lower the threshold for recurrences.² Finding the right combination of therapies for your patient is key to achieving an enduring response.

Future studies may tell us which treatments to combine and in what sequence for complex bipolar disorder, but—since most published studies exclude complex and comorbid cases—for now we must rely on limited controlled data and clinical experience. Using those resources, we offer comprehensive, practical recommendations for troubleshooting (*Box 2, page 41*)³⁻⁶ and getting better results when bipolar disorder does not respond to standard treatment.

Mania

When a patient with mania does not respond as expected, the next step depends on which antimanic agent you prescribed:



Bipolar disorder

Clinical Point

Double-blind studies of valproate in mania show the most beneficial clinical response at serum levels between 94 and 100 µg/mL

Box 1

What is 'treatment resistance' in bipolar disorder?

Some studies define treatment resistance as failure to respond to lithium, and in other settings it is viewed as failure to respond to ≥ 2 treatment courses. Because euthymia and normal functioning are important for long-term prognosis, we define treatment-resistance as failure to achieve both symptomatic and functional remission following an adequate course of therapy.

Effective strategies for treating bipolar disorder depend on:

- illness phase (later episodes are more difficult to treat than earlier ones)
- symptom complexity (mixed symptoms probably reflect more complex pathophysiology and are more likely to require combination therapies)
- predominant presentations (mania, depression, rapid and ultradian cycling)

Lithium can take a month to become fully effective for mania, which is why a benzodiazepine or antipsychotic is often added acutely to reduce agitation. Do not mistake neurotoxic interactions between lithium and antipsychotics for increased mania.

Although data vary on lithium's optimal serum level, adjust to approximately 0.8 to 1 mEq/L, if tolerated, when lower levels are not effective. Children and young adolescents may need higher serum levels (such as 1.5 mEq/L) because the difference between serum and brain lithium levels is greater in younger patients than in adults.

Consider the dosing schedule. Because lithium's elimination half-life with repeated dosing is 24 hours, most adults can take any formulation once daily—which improves adherence and reduces adverse effects. Children eliminate lithium more rapidly and need more frequent dosing.

Valproate. Empiric trials in bipolar disorder or epilepsy do not support the frequently reported "therapeutic range" of 50 to 125 µg/mL. Pooled data from three 21-day, double-blind studies of valproate in mania show a linear relationship between serum level and clinical

- whether symptoms are acute or chronic.

Unfortunately, the findings of and strategies used in clinical trials of refractory bipolar disorder are difficult to extrapolate to everyday practice. Most studies exclude patients with a history of treatment resistance, severe symptoms, and important comorbidities such as substance abuse. In addition, the usual primary endpoint is response ($\geq 50\%$ reduction of symptoms) rather than remission (minimal symptoms and no longer meeting criteria for the disorder). Very few studies address functional remission, which is necessary to reduce the risk of symptomatic recurrence.

In clinical practice, when initial treatment for bipolar disorder fails to produce remission, systematically addressing 5 questions (**Box 2**) can help direct your next step.

response, with the most beneficial response at >94 µg/mL.⁷ Better results—but more side effects—are seen with levels >100 µg/mL.

High loading doses result in more rapid control of agitation, probably as a result of sedation. In our experience, however, rapidly sedating patients may interfere with long-term adherence.

Carbamazepine, other anticonvulsants. Because they are less sedating, carbamazepine and other anticonvulsants might not appear to be rapidly effective for bipolar mania. If you wait up to a month, however, any antimanic effect will be obvious.

Antipsychotics are rapidly effective for mania. Higher doses work faster but produce more side effects. After an acute response, some patients can be maintained on a second-generation antipsychotic (SGA), but others do better on a standard mood stabilizer such as lithium or valproate.

Calcium channel blockers. Verapamil has been effective mostly for lithium-responsive mania in 27 of 30 studies. Nimodipine has been useful for more complex bipolar syndromes in a few studies using patients as their own controls.

To be effective for bipolar disorder,

5 questions to consider when bipolar symptoms persist

1 Is the patient taking anything that is making symptoms worse?

Antidepressants can induce mania, hypomania, and cycle acceleration in bipolar disorder, even when mood stabilizers are co-prescribed.³ Stimulants also may destabilize bipolar mood disorders; consider this possibility when patients taking stimulants for apparent attention-deficit/hyperactivity disorder at first appear to improve and then deteriorate.

Alcohol and cocaine can induce mania and depression. Cocaine is a potent kindling stimulus that could contribute to enduring mood instability.

2 Is the patient taking the medication?

Treatment adherence by bipolar patients may be as low as 35%.⁴ Ask outpatients what kinds of problems they have encountered taking medications, not whether they have such problems. Talk with the patient about adherence after each dosage increase, and be readily available. Prescribe extended-release pills for patients who have trouble keeping track of medications.

3 Is treatment adequate?

Adjust mood-stabilizer dosing until the patient responds or cannot tolerate the medication; complex cases often require combination treatment. Give the medication sufficient time to work; most mood stabilizers take ≥ 1 month to become fully effective.

4 Is another condition interfering with treatment?

Up to 70% of patients with refractory mood disorders have subclinical hypothyroidism. Look for:

- elevated thyroid stimulating hormone (TSH) with or without decreased thyroxine (T4)
- elevated TSH response to thyrotropin-releasing hormone (TRH).⁵

Also consider hypercalcemia from chronic lithium therapy,⁶ anemia, sleep apnea, posttraumatic stress disorder, substance use disorders, and personality disorders.

5 Am I ignoring psychotherapy?

Address psychosocial issues that influence the course of illness. Attend to patients' important relationships, loss, negative thinking, and biological and social rhythms.

however, calcium channel blockers require frequent, high dosing (such as verapamil, 120 mg 4 times daily, or nimodipine, 60 to 120 mg 6 times daily), which makes adherence difficult.

Augment or switch? If mania does not respond to an adequate dose of an antimanic drug given for a sufficient time, the next question is whether to augment or switch treatments. No studies have compared augmenting vs switching in any bipolar disorder phase, but it seems reasonable to:

- consider augmentation first when a patient has had a partial response to a given medication
- switch when a patient cannot tolerate or shows no response to a therapeutic dose of a given medication.

Combinations. Benzodiazepines such as clonazepam, 2 to 6 mg/d, or lorazepam, 4 to 8 mg/d, are often used to control agi-

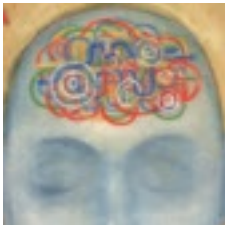
tation and insomnia in mania, usually as adjuncts to mood stabilizers (although improved sleep by itself can ameliorate acute mania in some cases). Adding an SGA may help when mania responds partially to a mood stabilizer.⁸

Combinations of lithium and carbamazepine or valproate can be more effective than either drug alone, but therapeutic doses of each usually are needed. Carbamazepine has been used successfully to augment a partial response to nimodipine.⁹ In a small open-label trial, adding oxcarbazepine to lithium, valproate or antidepressants improved response in some patients with mild refractory mania.¹⁰

Switching among anticonvulsants can be useful because their actions and side effects differ. Clozapine in a wide range of doses can be very effective for refractory mania,¹¹ but its use is difficult to monitor in highly agitated manic patients.

Clinical Point

Give medication sufficient time to work; most mood stabilizers take ≥ 1 month to become fully effective



Bipolar disorder

Clinical Point

Electroconvulsive therapy is the most effective treatment for mania, producing higher response rates than any drug

Other options. Electroconvulsive therapy (ECT) is the most effective treatment for mania, producing higher response rates than any antimanic drug.¹² In a study of repetitive transcranial magnetic stimulation (rTMS), 8 of 9 patients with mania refractory to mood stabilizers had a sustained response after 1 month of right-sided rTMS treatment.¹³ Conversely, left-sided rTMS can aggravate mania.

Bipolar depression

Continuing controversy about the best way to treat bipolar depression makes it difficult to know if treatment has been suboptimal or a patient is treatment-resistant.

Antidepressants. No antidepressant is approved (or recommended) as monotherapy for bipolar depression, and most experts recommend against prescribing antidepressants without concomitant mood stabilizers. Even so:

- Clinicians prescribing monotherapy for bipolar disorder choose antidepressants twice as often as mood stabilizers.
- Antidepressants are prescribed more frequently in combination with mood stabilizers than as monotherapy, although empiric trials have shown most antidepressants are not effective for bipolar depression.¹⁴

A recent report from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study¹⁵ found that adding bupropion or paroxetine to mood stabilizers was no more effective than adding placebo. Rates of mania induction also were no greater with antidepressants than with placebo, but the study lasted only 8 weeks. One interpretation of this finding is that when antidepressants do not induce mania and cycling, they also do not improve bipolar depression.

In many cases, an antidepressant seems to help at first and then induces a recurrence of depression, often mixed with dysphoric hypomanic symptoms. The recurrent episode improves when the clinician increases the antidepressant dose or changes to another antidepressant, only to be followed by another recurrence that may be interpreted as an incomplete antidepressant response.

Antipsychotics. Quetiapine¹⁶ and a combination of olanzapine and fluoxetine¹⁷ are approved for treating bipolar depression. The studies supporting this indication lasted only 8 weeks, however, and excluded patients with the kinds of complicated and comorbid mood disorders commonly seen in clinical practice.

Many patients dropped out before the studies were completed, and “screen fails” (patients with the diagnosis who were not enrolled in the study) were not reported. In addition, “remitted” patients remained symptomatic.

Therefore, FDA approval of this indication does not guarantee these medications’ long-term efficacy or safety for bipolar depression or that they are useful in patients with complex forms of bipolar depression.

Recommended approach. Treatment resistance of bipolar depression to multiple mood stabilizers—with or without an antidepressant—or to an antipsychotic may manifest as lack of response, partial response, or initial good response followed by relapse or recurrence. Sometimes depression improves but irritability or mood lability worsen.

No reliable controlled studies have addressed complex refractory bipolar depression, but clinical experience suggests 1 approach for all of these responses:

Reconsider possible hypothyroidism. A low-normal T4—especially if decreased over time—and a mid-range or high-normal TSH—especially if increased—may indicate that subclinical hypothyroidism is inhibiting a response to mood stabilizers and antidepressants.¹⁸

Stop the antidepressant. If your patient is taking an antidepressant, it may be ineffective, creating mixed dysphoric hypomania, and/or driving another recurrence of depression. This is especially likely if the patient shows an initial prompt antidepressant response, but depression returns with irritability, insomnia, restlessness, or other subtle symptoms of dysphoric hypomania.

Withdraw the antidepressant gradually; for example, you might reduce the dose by 10% every few weeks so that the agent is

What now? Treatment options for refractory bipolar depression

Treatment	Comment
Psychotherapy	Combine with somatic therapies for most patients with refractory mood disorders; adjunctive CBT, interpersonal and social rhythms therapy, or family-focused therapy speeded bipolar depression recovery in STEP-BD ²²
Bupropion	Generally accepted as first-line antidepressant; the relatively low doses used may explain this agent's lower risk of inducing mania compared with other antidepressants
MAO inhibitors	Can be combined with carbamazepine; ²³ tranylcypromine is best-studied antidepressant in bipolar depression and is especially useful for anergic states; ²⁴ selegiline also can be useful
Stimulants	Stimulants—such as methylphenidate, 15 to 30 mg/d—can be rapidly effective for lethargic, anergic depression (although evidence is limited); benefit wears off rapidly if mood is adversely affected
Pramipexole	Activating dopaminergic agent with rapid onset; investigational; has produced an antidepressant effect in patients with bipolar II depression when added to mood stabilizers ²⁵
Modafinil	May be useful for residual fatigue in major depression and medication-induced sedation; ²⁶ improved depressive symptoms when used as an adjunct ²⁷
Anticonvulsants	Anticonvulsants other than lamotrigine and carbamazepine-lithium combinations are considered later choices for bipolar depression; adjunctive zonisamide has been helpful in case series; ²⁸ gabapentin, pregabalin, and topiramate also can be useful adjuncts (although not supported by controlled studies in depression); adding levetiracetam may improve response ²⁹
NMDA antagonist	Investigational; memantine ³⁰ was effective in a small controlled study, and riluzole (indicated for amyotrophic lateral sclerosis) was helpful in a small open study ³¹

CBT: cognitive-behavioral therapy; MAO: monoamine oxidase; NMDA: N-methyl-D-aspartate; STEP-BD: Systematic Treatment Enhancement Program for Bipolar Disorder

discontinued across several months. Discontinuing an antidepressant too rapidly—even if it does not seem to be having any effect—can cause rebound depression that creates the mistaken impression that the antidepressant is needed.

Treat mood lability and mixed hypomania first. Antidepressant therapy may be more likely to destabilize mood if hypomania and mood cycling are present when you start the antidepressant.¹⁹ Older studies suggest that lithium and carbamazepine can improve bipolar depression, and a few small studies suggest nimodipine may be useful when depression is prominent. In our experience, valproate is not particularly helpful for bipolar depression, although it may reduce the risk of depressive recurrence.

Combine mood stabilizers. If a single mood stabilizer does not at least eliminate mood lability and other symptoms of acti-

vation, add a second agent. The combination of lithium and carbamazepine helps some depressed patients.²⁰ Patients with considerable mood instability or psychotic symptoms may benefit from an adjunct antipsychotic.

Introduce mood stabilizers gradually. These medications may work more rapidly against mixed manic symptoms than they do against depression, especially when the dose is raised too quickly. The result is rapid control of irritability, hyperactivity, agitation, and related symptoms but an apparent increase in depression as mixed elements of elevated mood and energy are filtered out.

Add an antidepressant? If gradual adjustment of mood stabilizers eliminates mixed symptoms and mood fluctuations but the patient is still depressed, cautiously add an antidepressant. Antidepressants

Clinical Point

Slowly withdraw antidepressant therapy to avoid rebound depression; you might reduce the dose by 10% every few weeks



Bipolar disorder

Clinical Point

Add psychotherapy to speed recovery from bipolar depression and to help most patients with refractory mood disorders

Box 3

Rapid and ultradian cycling: Complex disorders, complex treatment

Approximately 20% of bipolar patients are thought to experience rapid cycling, defined as ≥ 4 affective episodes/year separated by at least 2 weeks of euthymia between poles or with an immediate switch from one pole to the other.³² The prevalence of ultradian cycling—in which multiple brief affective episodes (usually subsyndromal or mixed) occur each day—is unclear.

Both cycling types probably represent stages in the evolution of bipolar mood disorders rather than distinct diagnoses. In many cases, mood cycling abates after months to years, but morbidity can be high and the wrong treatment may perpetuate mood cycling.

Complex mood cycling rarely responds to a single treatment, probably because its pathophysiology is complex. The need for polypharmacy may create the impression of treatment failure, but no one would expect a single medication to be sufficient for other complex illnesses such as cancer or AIDS.

may be less likely to destabilize mood after all mixed elements have been treated completely.

No empiric data support the choice of one antidepressant over another. Published experience suggests that lamotrigine, 25 to 200 mg/d, may be less likely to destabilize mood, especially in combination with an established mood-stabilizing regimen.²¹ Other medications have shown antidepressant effects in bipolar depression (*Table, page 43*).²²⁻³¹ Although clinicians often use serotonin reuptake inhibitors, this practice has no empiric support in refractory bipolar depression—and our experience has not been particularly positive. Fluoxetine's long half-life can perpetuate adverse effects long after the medication is withdrawn, and rebound depression is not uncommon when paroxetine or venlafaxine are withdrawn.

Some experts recommend discontinuing the antidepressant after depression remits

to avoid driving more recurrences,³ but others do not think continuing antidepressants is risky. Apparently some patients do well with continued antidepressants, and others do not. In our experience, patients who have had mixed symptoms or mood lability are most likely to deteriorate with continued antidepressant treatment. Whenever depression returns after an initial and especially rapid response to an antidepressant, consider withdrawing the antidepressant and maximizing mood stabilizers first rather than changing or augmenting the antidepressant.

Treat seasonal symptoms. Many bipolar patients are most likely to be depressed in winter, and seasonal affective disorder is common in patients with a bipolar mood disorder. Their depression may respond to artificial bright light, usually given in the morning. Light therapy can help normalize the sleep-wake cycle, although it also can induce hypomania.

Other options. ECT is the most reliably effective treatment for bipolar depression. Because it treats both poles of the mood disorder, ECT also can be a useful maintenance treatment. A comparison of rTMS and placebo in 23 bipolar depressed patients failed to find any benefit of active treatment.³²

Rapid and ultradian cycling

No controlled studies have compared single-drug or combination therapies for rapid and ultradian cycling (*Box 3*).³³ Thus, our recommendations for treating patients with cycling who have not responded to initial interventions are based on case series and clinical experience.

Keep a mood chart. When mood is labile, patients have difficulty recalling day to day—let alone week to week—which state predominated when. Use published mood charts or decide with the patient how to rate target symptoms such as depression, elation, irritability, increased or decreased sleep or energy, speeded up or slowed down thought, etc. Note medication changes on the chart to track whether an intervention was helpful, harmful, or neutral.

Reassess thyroid function. As many as 70% of patients with rapid cycling have subclinical hypothyroidism that contributes to mood instability.³⁴ Thyroid replacement is indicated for any degree of hypothyroidism—even if medically unimportant—in patients with refractory mood disorders.

Slowly withdraw antidepressants. Most patients with rapid cycling are taking antidepressants. If your patient is experiencing depressive symptoms while taking an antidepressant, this means the antidepressant is not working and there is little point in continuing it. For patients being withdrawn from multiple antidepressants, rotate dose decrements to help you monitor the effect of each reduction.

Combine mood stabilizers. After optimizing the dose of a single mood stabilizer, add a second one from a different class. In an open trial, adding oxcarbazepine, up to 2,400 mg/d, helped approximately one-third of 20 patients with refractory mood cycling.¹⁰ Lithium is generally considered less effective than anticonvulsants in rapid cycling, but at least one study showed it was equivalent to carbamazepine for this problem.³⁵ Lithium combined with other mood stabilizers may be more effective than lithium monotherapy in refractory bipolar states.

Other options to consider in combination with mood stabilizers:

- an antipsychotic, especially in the presence of psychotic symptoms, when mixed symptoms are present
- clozapine, which can be a highly effective adjunct for refractory mood cycling and mixed states³⁶ (but is a later adjunct because of required monitoring, common

adverse effects, and risk of interactions with carbamazepine and benzodiazepines)

- nimodipine, which has empiric support for complex mood cycling³⁷ and is well-tolerated with fewer interactions than other mood stabilizers (but cost and need for frequent dosing make it a second-line adjunct)

- supraphysiologic doses of thyroxine (≤ 0.4 mg/d, with T4 levels in the hyperthyroid range), which can improve response to mood-stabilizing regimens³⁴ (but risks of inducing hyperthyroidism make this intervention third-line).

ECT can be effective for refractory rapid cycling, but some patients need more treatments than are usually necessary for mania or depression.

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Clinical Point

In refractory cases, thyroid replacement is indicated for any degree of hypothyroidism, even if medically unimportant

Bottom Line

When bipolar patients do not respond adequately to therapy, ask yourself these questions: Are antidepressants or stimulants making symptoms worse? Is the patient adhering to medication? Is the treatment adequate? Is a comorbidity—such as subclinical hypothyroidism or substance use—interfering? Use psychotherapy to address relationships, loss, negative thinking, and biological and social rhythms that influence the course of illness.

continued



Bipolar disorder

Clinical Point

Clozapine can be a highly effective adjunct for refractory mood cycling and mixed states but is a later choice because of associated risks

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Drug Brand Names

Bupropion • Wellbutrin	Olanzapine/fluoxetine
Carbamazepine • Tegretol	• Symbiyax
Clonazepam • Klonopin	Oxcarbazepine • Trileptal
Clozapine • Clozaril	Paroxetine • Paxil
Fluoxetine • Prozac	Pramipexole • Mirapex
Gabapentin • Neurontin	Pregabalin • Lyrica
Lamotrigine • Lamictal	Quetiapine • Seroquel
Levetiracetam • Keppra	Riluzole • Rilutek
Lithium • Lithobid, others	Selegiline • Eldepryl
Lorazepam • Ativan	Topiramate • Topamax
Memantine • Namenda	Tranylcypromine • Parnate
Methylphenidate •	Valproate • Depakene, Depakote
Concerta, Ritalin, others	Venlafaxine • Effexor
Modafinil • Provigil	Verapamil • Calan, Isoptin, others
Nimodipine • Nimotop	Zonisamide • Zonegran

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