13 General Principles in the Treatment of Bipolar Disorder

Essential Concepts

- The treatment of bipolar disorder is based on two basic tenets: invariant use of mood stabilizers and infrequent use of antidepressants.
- Avoid the "poor man's mood stabilizer" regimen: a neuroleptic plus an antidepressant.
- The main mistake in the treatment of bipolar disorder is to focus on the short term, that is, acute depression or acute mania.
- The main focus should be on the long term: prevention of recurrences of depression or mania. Only mood stabilizers do this; antidepressants and antipsychotics do not.
- Acute treatment does not translate into long-term efficacy, and vice versa the "Happily Ever After" fallacy.
- Expunge from your thought processes the maxim, "If it ain't broke, don't fix it." Acute treatments for mania and depression should, as a rule, be stopped and not continued long term. In contrast, long-term mood stabilizers, as a rule, have little short-term efficacy.
- Most cases of bipolar depression can be treated initially with mood stabilizers, alone or in combination, without antidepressants.
- Antidepressant when used, should be limited mainly to the acute major depressive episode, with tapering of such agents after recovery from the acute depressive episode.
- The four primary mood stabilizers that should be used in patients with bipolar disorder type I are lithium, valproate, carbamazepine, and lamotrigine.
- Important adjunctive mood-stabilizing classes are the atypical neuroleptic and novel anticonvulsant classes.

- Atypical neuroleptic medications are *not* mood stabilizers and should not be used in bipolar disorder type I by themselves or in the absence of one of the preceding four mood stabilizers.
- Differentiate chronic depression in the long-term-treated person with bipolar disorder from existential despair. Two things heal despair: time and relationships not antidepressants.

The treatment of bipolar disorder is more complex than the treatment of unipolar depression. In unipolar depression, treatment decisions involve antidepressants and/or psychotherapy and, if the patient is insufficiently responsive, more of the same (i.e., more antidepressant, higher doses, combinations). In bipolar disorder, the nature of the illness is more complex. Whereas in unipolar depressions patients are either ill (depressed) or well, in bipolar disorders patients can be ill in myriad ways (e.g., depressed, hypomanic, manic, mixed, rapid cycling) but well in only one way (i.e., euthymia).

Treatments for mood symptoms in bipolar disorder are usually more likely to cause a different kind of illness rather than wellness. In bipolar disorder, the depressed patient who receives antidepressant medication frequently may become manic, and the manic patient who receives a neuroleptic frequently may become depressed. Even mood stabilizers, which are less prone to such extreme shifts of mood, often remove mania only to replace it with depression (although rarely the reverse). Hitting that golden mean is harder than even Aristotle, the son of a physician, might have presumed. In bipolar disorder, euthymia is an elusive goal. These general principles are meant to provide broad guidance about how to approach this matter, with supportive details provided in the following chapters:

1. *Acute treatment does not translate into long-term efficacy, and vice versa. Expunge from your thought processes the maxim, "If it ain't broke, don't fix it."*

Acute treatments for mania and depression should, as a rule, be stopped and not continued long term. In contrast, long-term mood stabilizers, as a rule, have little short-term efficacy. As discussed previously in Chapter 7 and again below (despite Food and Drud Administration indications for olanzapine and

aripiprazole in maintenance treatment of bipolar disorder), neuroleptics do not have robust evidence of prophylactic efficacy in bipolar disorder and thus do not meet that definition of a mood stabilizer. Also as discussed in Chapter 18, antidepressants are shown to be ineffective in prevention of depression in bipolar disorder. Both classes of agents are effective in acute mania and acute depression perhaps, but not in long-term prevention of mood episodes in bipolar disorder. In contrast, lamotrigine is the prototypic mood stabilizer that is ineffective in all acute phases (whether acute depression, mania, or mixed states, with multiple double-blind studies that show it to be equivalent to placebo in these settings). Similarly, lithium and divalproex are likely less robustly effective acutely for mania and depression than some antipsychotics and antidepressants. Yet these agents are much more robustly effective in prophylaxis than antipsychotics and antidepressants.

2. *Keep your eye on the long run. Bipolar disorder is a longitudinal illness. Always focus on treating the whole illness rather than simply acute depression or acute mania.*

Patients come to clinicians seeking help for their current symptoms, whether depressive or manic. It is up to the clinician to translate this human wish for immediate relief of symptoms into a medical diagnosis that can be treated. In the case of bipolar disorder, the diagnosis is of a longitudinal recurrent condition that never goes away. Sometimes clinicians avoid making this diagnosis because they do not want to saddle the patient with such a weighty label. Clinicians particularly avoid this diagnosis if they have any doubt about it.

Such reticence is unfortunate and goes against the Hippocratic oath. Physicians must be honest, courageous, and willing to detect and reveal serious illness. Treating more benign conditions that are not there is a disservice to patients. Bipolar disorder is a long-term, recurrent illness. One needs to focus on the long term not only to treat current symptoms but also to prevent future occurrences. Only mood stabilizers have such effects and should be used aggressively instead of acute treatments, namely, antidepressants and traditional neuroleptic drugs.

3. *Acute mania deserves aggressive treatment, but be prepared to scale back antimanic treatments in the maintenance phase.*

The first principle does not imply that clinicians should avoid treating acute mania or acute depression. In both cases, especially acute mania, the severity of symptoms requires

immediate relief. In the case of acute mania, patients can hurt themselves or others in serious ways. Clinicians need to do whatever they can to stop such symptoms, including hospitalization.

Acute mania generally responds quite well to treatment. Even untreated, the average acute manic episode resolves in about 2 to 4 months. Since it takes medications a few weeks to become effective, the treatment of acute mania really involves avoiding the extra month or few months of symptoms that would continue naturally. The episode will resolve, at which time the patient and clinician are faced with future treatment decisions. If many antimanic drugs were added during the acute phase, the patient usually begins to experience more side effects once the manic period is over. In the maintenance phase, faced with years or decades of treatment, patients rightfully want to reduce their medications to the minimum necessary. Clinicians need to be willing to work with patients on this issue, within the bounds of empirical knowledge and common sense. In general, the better the mood-stabilizing prophylactic treatment, the fewer manic episodes will occur, and the less need there will be to face the difficult circumstance of trying to reduce treatments after a severe manic episode.

4. *It is wise to be cautious with antidepressants.*

Antidepressants have not been proven to prevent depression in the treatment of bipolar disorder and may cause long-term rapid cycling with more and more mood episodes over time. Hence their use generally should be limited to only severe acute depression that either is accompanied by high suicidality or is refractory to multiple mood stabilizers. In my experience, only about 20% of patients with bipolar disorder need long-term antidepressant treatment, with another 30% or so needing only short-term antidepressant use. My approach is more cautious than is commonly the case; currently, about 80% of patients with bipolar disorder are treated with antidepressants, most of whom remain on these agents for the long term. I will discuss the risks of antidepressants in bipolar disorder in greater detail in Chapter 18.

5. *Don't chase your tail: Antidepressants given for depression often will cause mania or rapid cycling, which when treated with antimanic agents leads to depression.*

This principle follows from the first principle. Traditional neuroleptic agents seem to have a converse problem to

antidepressants. Just as antidepressants are associated with an increased risk of induction of acute mania, traditional neuroleptics are associated with an increased risk of induction of acute major depression. In other words, traditional neuroleptics are purely antimanic agents, not mood stabilizers. They bring the mood down from mania, but they keep moving it down into depression rather than stabilizing it near euthymia (just as antidepressants bring the mood up from depression but keep moving it up into mania). Only mood stabilizers can regularly treat mania without causing depression, and treat depression without causing mania. While atypical neuroleptic agents are associated with less risk of induction of acute major depression, such episodes do occur to some extent with these agents. Hence, if clinicians focus on the acute antidepressant and antimanic agents, patients with bipolar disorder are at some risk of simply switching from one phase of illness to another. Mood stabilizers must be the main focus of treatment to avoid such "chasing of the tail" in treatment.

CLINICAL VIGNETTE

The patient is a 40-year-old man who has been treated with multiple mood stabilizers and antidepressants and neuroleptics in the past but has never been stable for more than 3 months. He comes for evaluation complaining of depression. On questioning, he says that his current depression has lasted 2 months and was preceded by 2 weeks of hypomania, and two other 2-month depressive periods are noted in the past year, along with 1 week of mania. The diagnosis of rapid cycling is made. He is currently taking lithium, valproate, sertraline, bupropion, and olanzapine. All agents except lithium and valproate are discontinued over 2 weeks. He feels no better and no worse. Over the following month, his depression lifts gradually, and he is followed on lithium plus valproate. He experiences only one depression in the ensuing year, for which he received short-term treatment with paroxetine for 1 month. He is maintained long term on lithium plus valproate.

6. *Polypharmacy with mood stabilizers is appropriate in bipolar disorder.*

It follows that mood stabilizers should be used aggressively in the treatment of bipolar disorder. Numerous studies suggest that complete response to a single mood stabilizer, such as lithium, rarely exceeds about one-third of the population of persons with bipolar disorder. It is important to give all patients a chance at response to mood stabilizer monotherapy; however, in the majority, combinations will be needed.

KEY POINT

Addition of mood stabilizers in combination seems to lead to increased response in an almost linear fashion, with two or three mood stabilizers being associated with about 50% to 60% treatment response.

Consequently, polypharmacy with mood stabilizers can be appropriate in bipolar disorder but only if we focus on mood stabilizers and exclude antidepressants, for instance, as part of the regimen in most cases. Careful selection of combinations is needed to minimize the overall side-effect burden.

7. *Use atypical neuroleptic and novel anticonvulsant agents as your main classes of medications for bipolar disorder beyond standard mood stabilizers.*

In addition to the primary mood stabilizers (which by my definition include lithium, valproate, carbamazepine, and lamotrigine), polypharmacy with mood-stabilizing agents includes drugs with *adjunctive* mood-stabilizing effects. In other words, these agents have mood-stabilizing properties but only when combined with primary mood stabilizers, not when used alone.

The two major classes of adjunctive mood-stabilizing agents are the atypical neuroleptic agents and the novel anticonvulsant agents. By and large, these agents have been proven effective only in the acute depressive or manic phases of bipolar disorder, not in prophylaxis, and thus they cannot be termed mood stabilizers by conservative definitions of the term (see Chapter 7). Yet these agents appear to be more beneficial than standard antidepressants or traditional neuroleptic agents in that these newer classes tend to treat depression or mania with a low risk of switch into the opposite mood phase. Hence they have adjunctive mood-stabilizing benefits. This is not to say that further research may not show that some of these agents are primary mood stabilizers. Research already shows that lamotrigine is effective for acute bipolar

depression and the prevention of bipolar depression, which suggests that it likely is a primary mood stabilizer. Such data may be forthcoming with other agents but have not been demonstrated to date, which is why I would not recommend using these agents by themselves for bipolar disorder (at least type I). However, when added to some of the primary mood stabilizers, these classes can greatly enhance the treatment response in polypharmacy. Atypical neuroleptics and novel anticonvulsants have revolutionized the treatment of bipolar disorder such that most patients have much better treatment options today than a decade ago.

8. *Primary mood stabilizers, medications proven reasonably effective in the short- and long-term treatment of bipolar disorder, are lithium, valproate, carbamazepine, and lamotrigine.*

A conservative definition of a *mood stabilizer* is that it is an agent that is effective in acute mania or acute depression along with prophylaxis of those mood episodes. Only these agents have a reasonable amount of data to meet this definition (meaning controlled studies and sufficient clinical experience). In bipolar disorder type I, it is my recommendation that one of these four agents always be used as a primary mood stabilizer. In bipolar disorder type II, given the fact that there are much less data and that spontaneous mania does not occur, there may be room to be more liberal with one's definition of a mood stabilizer and allow other novel anticonvulsants (such as gabapentin or topiramate) to be used without any of the four proven mood stabilizers. In general, though, I believe that it is important to build the polypharmacy of bipolar disorder on one of these four medications. If they are neglected, treatment regimens are likely to be suboptimally effective, much like trying to build a house on an inadequate foundation.

9. *Avoid the "poor man's mood stabilizer regimen"—a neuroleptic plus an antidepressant.*

Many clinicians make the mistake of believing that neuroleptics are mood stabilizers, which I critiqued in Chapter 7. This mistake is understandable, given the Food and Drug Administration (FDA) indications of some neuroleptics for maintenance treatment of bipolar disorder, but I have reviewed why I think those indications are not scientifically valid in terms of meaning that those agents have long-term prophylactic efficacy.

Since many clinicians are not aware of or perhaps do not agree with these views, many patients with bipolar disorder are treated with neuroleptics in the absence of true mood stabilizers. Yet neuroleptics are simply antimanic agents and thus do not have much benefit for depressive symptoms. Consequently, clinicians tend to add antidepressants to them when depressive symptoms occur or persist. Patients then end up on this combination of a neuroleptic and an antidepressant, which I call the "poor man's mood stabilizer" because it is not the real thing. This combination usually does not lead to long-term stability and is best avoided.

CLINICAL VIGNETTE

A 32-year-old woman sought a second opinion owing to persistent yearly major depression in the fall, alternating with hypomania in the summer. She had received ziprasidone initially the previous summer, with improvement in hypomanic symptoms, but depression recurred in the fall. Escitalopram then was added, with improvement, but the patient again became hypomanic the following year. The patient had experienced two manic episodes in the past, with impulsive spending, but no prior hospitalizations or psychosis. She had two small children, was married, and was well educated. The consultant recommended discontinuing both agents and beginning treatment with lithium or lamotrigine. The patient preferred the latter so as to avoid weight gain. She brought the recommendations to her treating psychiatrist, who disagreed, stating that she already was taking a mood stabilizer, ziprasidone. Her husband called the consultant and asked why he should believe one psychiatrist over another. The consultant tried to explain that ziprasidone should not be seen as a mood stabilizer because it had no evidence of prophylactic efficacy. Yet the husband and patient thought it had helped her initially and thus thought it might continue to be helpful. The patient stayed on her regimen but continued to have one severe major depression yearly and intermittent hypomanic episodes. She transferred treatment to the consultant, both ziprasidone and escitalopram were discontinued, lamotrigine was continued, and she had one briefer and less severe depressive period the following winter, with no hypomanic symptoms. The following year, on lamotrigine monotherapy, she had no mood episodes at all.

10. *Use lithium for patients with suicidal symptoms, with appropriate safeguards.*

It is important to remember that only lithium, *among all psychotropic agents,* is proven to prevent suicide and reduce mortality (by suicide or cardiovascular disease) in psychiatric illness. Since the risk of suicide in bipolar disorder is serious (about 5% in patients who have never been hospitalized, 10% to 20% in those with more severe illness), lithium use should be considered for any person with bipolar disorder who has been hospitalized, made a suicide attempt, or otherwise possesses a serious risk of suicide. Lithium's antisuicide effect appears to be unrelated to its mood efficacy. In other words, even in individuals for whom it provides little or no benefit in the treatment of bipolar mood symptoms, lithium is still effective in preventing suicide. Appropriate safeguards are needed when overdose risk is acutely high, such as providing lithium in 1-month or less supplies and having family members control its supply beyond weekly dispensation.

TIP

Consider adding a low dose of lithium to any patient with a high suicide potential.

11. *Dose almost everything once daily.*

It is unfortunate that lithium and valproate are prescribed twice or thrice daily by most clinicians; there is no pharmacokinetic reason to do so. With lithium, once-daily dosing significantly reduces the long-term risk of chronic renal impairment. With all agents, medication noncompliance greatly increases with multiple daily dosing. Hence, as a rule, dose all medications for bipolar disorder once daily, with a few exceptions. The exceptions are carbamazepine, oxcarbazepine, gabapentin, topiramate, and ziprasidone, which need to be dosed twice daily. Avoid thrice-daily dosing if at all possible.

12. *Psychotherapies are effective to prevent relapse. Infrequent psychiatrist visits are inappropriate in the absence of concomitant psychotherapy.*

The main role of psychotherapies appears to be to enhance long-term mood stability rather than to assist with recovery from the acute manic or depressive episode. Specifically, cognitive behavioral therapy, interpersonal therapy, and family focused therapy appear to augment mood stabilizer benefits for prevention of future mood relapses. Further, these psychotherapies may enhance functioning in patients who have recovered from their mood symptoms. This is an especially important point because recent studies suggest that pharmacotherapies may lead to symptomatic improvement in bipolar disorder, but many of these patients still suffer from significant social and occupational impairment of functioning.

13. *Remember that the therapeutic alliance, even in brief but frequent visits with a psychopharmacologist, is itself a mood stabilizer.*

Often psychotherapy may not be feasible. The preceding kinds of therapy are often not practiced by many psychotherapists, or patients may not have the time or the funds to pay for psychotherapy. In this setting, the psychopharmacologist should keep in mind that brief 20- to 30-minute visits still can have an important psychotherapy component not only supportively, but also existentially, as the doctor and patient get to know, understand, and trust each other better. Unfortunately, in the managed-care era, where visits are reimbursed poorly, many doctors have responded by seeing more patients in less time so as to maintain or increase their income. Sometimes psychiatrists in private practice see so many patients that any one patient is in fact seen infrequently, often no sooner than every 3 months or longer (sometimes once yearly). In this setting, no therapeutic alliance can be established, and patients never develop trust in their doctors, nor do doctors ever understand their patients. Mistaken medication decisions tend to ensue, with poor treatment outcomes as a consequence.

Patients with bipolar disorder need to be seen frequently, especially when symptomatic, and the availability of the doctor for appointments in times of crisis itself has a mood-stabilizing effect, not to mention the existential rapport that grows with frequent visits over time. The key importance of this relationship cannot be underestimated.

14. *Psychotherapies are useful in young, newly diagnosed patients to help them come to terms with the illness.*

In newly diagnosed patients, empathic and insight-oriented psychotherapies may be useful in helping them to come to terms with the diagnosis of bipolar disorder. Since more stigma is associated with this diagnosis than with depression,

patients often need help to understand it, become educated about it, and come to terms with how the diagnosis relates to their sense of self and their own identities and values. In my experience, this (almost philosophical) psychotherapy is often helpful in enhancing a patient's insight, although it has been little studied.

15. *Noncompliance stems from lack of insight, side effects, and inconvenience. Educate, compromise as much as possible on side effects, and dose as many drugs once daily as possible.*

About half of patients with bipolar disorder do not possess insight into having manic symptoms. This lack of insight leads to medication noncompliance and is associated with poor outcome. Side effects also lead to noncompliance, particularly weight gain and cognitive side effects with many current mood-stabilizing agents. The inconvenience of multiple daily dosing and regular medication use also is a problem.

Clinicians need to educate patients about bipolar illness in a nonthreatening long-term manner so as to enhance insight. Side effects need to be taken seriously, and clinicians should compromise as much as possible on dosing and blood levels to show patients that treatment is a collaboration. The role of the clinician is to provide the patient with reasonable treatment options (e.g., avoiding antidepressants in rapid cycling and suggesting a few potentially effective mood stabilizers), with unbiased descriptions of the evidence for efficacy and likely side effects. It is then up to the patient to decide which medications to take and in which order. This process is both scientifically sound and most likely to promote compliance and a solid therapeutic alliance. Once-daily dosing, again, is another simple decision that will avoid unnecessary treatment noncompliance and can greatly enhance a patient's quality of life.

CLINICAL VIGNETTE

The patient is a 36-year-old woman who complains of recurrent depression in the setting of a diagnosis of bipolar disorder. She is treated with carbamazepine and venlafaxine and is attached to both medications. She admits that she wants to be better because she experiences one major depressive episode of marked severity yearly lasting 1 month and another period of milder depression yearly lasting 2 weeks. However, her current symptoms are much better than before treatment with these agents. The clinician is aware of the important

principle of being willing to compromise on as much as possible. The clinician knows that it is generally better to avoid telling patients with bipolar what to do; it is best to give them medically appropriate options and ask them to choose. The clinician explains the many drug interactions of carbamazepine and how it is decreasing the blood levels of venlafaxine. The clinician also explains the lack of evidence of efficacy and safety with venlafaxine in bipolar disorder compared with some other antidepressants. Over time, the patient agrees to tapering from carbamazepine to its similar analogue oxcarbazepine. She then agrees to gradual reduction of venlafaxine. This process of gradual transition takes 6 months. She feels generally the same on oxcarbazepine as on the previous combination. A year after initial evaluation, she consents to the addition of low-dose lithium to oxcarbazepine and no longer experiences more than a few days of depression at a time occurring two to three times a year.

It seems to me that physicians in particular appear to tell or try to tell their patients with bipolar disorder what to do. When someone asks, "What medication is the first-line choice for such-and-such?" this question implies that it is up to the clinician to decide what is the first-line choice. In fact, while clinicians might have opinions based on current literature or their own experience, it is not up to the clinician alone to decide the first-line choice. It is up to the patient, more so than the clinician; the patient must live with the decision and experience the side effects.

It is my observation that clinicians who try to make medication decisions for their patients usually end up with highly noncompliant patients. Involving the patient in the decision-making process reduces noncompliance because the patient is mainly obeying his or her own decisions.

There are obvious exceptions. Some patients will request that the clinician more or less autonomously decide on the choice of a medication. These days, most patients in the United States are not of this variety. Some clinicians may be used to less high-functioning populations, such as those with schizophrenia, in which it is more customary for treatment decisions to come mainly from the clinician. It is important not to take the same approach in patients with bipolar disorder, for they will resent it, and the therapeutic alliance will be deeply hurt.

16. *Settle in for the long haul; quick, easy responses are rare, but if the clinician and patient work together long term, most patients recover.*

The therapeutic alliance is essential to the treatment of bipolar disorder in particular because the process of treatment is a long-term process. Recovery is usually quite gradual, with the slow building of improvement on one mood stabilizer after another. There are few rapid prolonged treatment responses. Patients need to be educated to give up the idea of quick fixes.

TIP

A slow response to a medication for bipolar disorder is much better than a rapid response because the rapid response is likely to wear off, whereas the slow response is likely to persist.

Each patient who will respond has a biologically unique capacity to respond to a certain unique combination of mood stabilizers. For a few, it may be only one agent. For most, it is a combination of two or more. It is the job of the clinician and patient to work gradually to find that specific combination. In the process, many combinations will need to be tried and partially or completely discarded. The patient needs to avoid demoralization, and the clinician needs to avoid loss of confidence. For both, a strong therapeutic alliance is the mortar that will hold together the treatment edifice.

17. *Differentiate despair from depression in the long-term-treated patient.*

The most common long-term outcome of treatment for bipolar disorder is chronic subsyndromal depression, a low-level unhappiness, and failure to completely "get back to normal." This is usually interpreted by doctors as residual depression, symptoms of the depressive part of bipolar disorder. It is then often treated with more and more medications, particularly antidepressants, to no avail. More side effects ensue, with little benefit, leading to a decline in overall quality of life, and not infrequently, patients give up, stop medications altogether, and often lose the partial benefit they had earlier achieved with fewer medications.

I feel that frequently such patients are not "moderately depressed" but rather in despair, despair about all they have lost

in the past that cannot be regained—divorces, bank accounts, relationships, time. Two things heal this despair: time itself and relationships. The doctor needs to keep seeing the patient, without messing with the medications, without seeing the purpose of each visit as a medication change, but rather, after all that could be gained with the best mood stabilizers has been achieved, the goal of the doctor should be to simply *be* with the patient. Then, over time, despair gives way once again to hope, and the future of one's life can be lived without allowing the failures of the past to kill it beforehand.