19 Treatment Strategies for Refractory Bipolar Disorder

Essential Concepts

- The most common cause of treatment refractoriness in bipolar disorder is overuse of antidepressants.
- The most common scenario is rapid cycling in the context of constant and chronic antidepressant use.
- Antidepressants are *mood destabilizers*, counteracting the benefits of mood stabilizers. If a patient is "treatment refractory" but has always taken antidepressants, then the solution is to use prior mood stabilizers again in the *absence* of antidepressants.
- If a treatment-refractory patient has received only mood stabilizers while taking antidepressants, then lack of response to those mood stabilizers may have been due to antidepressant destabilization.
- A therapeutic trial of a mood stabilizer must happen in the *absence* of concomitant antidepressant use.
- Only a third of patients responds sufficiently to mood stabilizer monotherapy.
- Effective polypharmacy involves multiple mood stabilizers carefully chosen to provide the best combination for that individual.
- Emphasize mood stabilizers; minimize antidepressants.
- Noncompliance is an important factor. Once-daily dosing is simple and key.
- Antidepressants may be unavoidable in a small minority of patients, although at the cost of not being able to achieve stable euthymia.

ONE WAY TO BE WELL, MANY WAYS TO BE ILL

A key feature of bipolar disorder is its clinical complexity (Table 19.1). In unipolar depression or schizophrenia, patients are either well (euthymic or not psychotic) or ill (depressed or psychotic). In bipolar disorder, patients can be well in only one way (euthymia), but they can be ill in five ways (depression, mania, hypomania, mixed, and rapid cycling). Antidepressant effects, for instance, are correspondingly complex. In unipolar depression, antidepressants can lead to full euthymia, partial benefit, or no benefit. In bipolar disorder, antidepressants may lead to no benefit with continued unchanged depression, partial benefit with residual depression, temporary euthymia soon followed by a depression relapse, transient hypomania followed

TABLE 19.1. Treatment Scenarios in Refractory Bipolar Disorder

Scenario 1:
Step 1. Lithium (no response)
Step 2. Switch to valproate (25% improvement on YMRS)
Step 3. Switch to lamotrigine (25% improvement on YMRS)
Step 4. Combine lamotrigine and risperidone (45% improvement on YMRS)
Step 5. Add topiramate (60% improvement on HDRS)
Step 6. Add lithium (80% improvement on HDRS)

Scenario 2:
Step 1. Valproate (intolerant owing to weight gain)
Step 2. Switch to lithium (25% improvement in YMRS)
Step 3. Add ziprasidone (no added benefit)
Step 4. Add topiramate (no added benefit)
Step 5. Switch to carbamazepine (intolerant due to sedation)
Step 6. Switch to oxcarbazepine (50% improvement in YMRS)
Step 7. Add quetiapine (75% improvement on YMRS)

Scenario 3:
Step 1. Lithium (no response)
Step 2. Valproate (40% improvement on HDRS)
Step 3. Add lithium (65% improvement on YMRS)
Step 4. Add aripiprazole (85% improvement on YMRS)

Note: In scenario 1, gradual added benefit occurs with augmenting agents. In scenario 2, multiple agents are ineffective or not tolerated, alone or in combination, with the patient being unwilling to take many medications owing to weight gain. Creative combinations are needed. In scenario 3, valproate and lithium are most useful, but the final added benefit occurs with atypical neuroleptics.

by either euthymia or full mania, or immediate switch into a full mania. If none of these outcomes occurs, antidepressants can produce persistent euthymia. Similarly, traditional neuroleptic agents can have no benefit, produce only transient euthymia followed by depression, or cause an immediate switch into full depression, along with many other permutations.

Hence the cyclic complexity of bipolar disorder often makes it quite difficult to know if a medication is helpful or not. Mood stabilizers are a bit more straightforward at least in one sense: They either reduce cycling or they do not. But even to make this judgment, once must have an accurate longitudinal knowledge of the course of a patient's illness.

GENERAL STRATEGIES

It is my opinion that every patient with bipolar disorder who has some capacity for treatment response will respond to a specific combination of mood-stabilizing agents. The combination differs from person to person because of biological differences; it is like the numbers on a combination lock. We need to find the exact set of medications at the exact doses that will work for each patient.

This is not, as many patients believe, simply a matter of trial and error. The available options are not just any medications but rather only those proven mood stabilizers that actually treat this illness. We are constrained by science here; this has nothing to do with trial and error. As for which specific mood stabilizers work for which specific patient and at what dose, that is the art of medicine. The choice of medication combinations can be planned based on the available scientific evidence and subjective (but important) factors such as patient preference and side-effect variability from patient to patient.

Thus the process is not simply trial and error, unless one wants to ignore the science altogether; rather, it is a combination of the science and art of medicine.

KEY POINT

At best, only a third of patients with bipolar disorder will respond to a single established mood stabilizer such as lithium or valproate. Initial monotherapy trials are undertaken without surprise for not achieving complete remission. Most patients need two or more medications.

In essence, the clinician's goal is to achieve persistent euthymia. This is accomplished by finding the combination that strikes a balance at euthymia rather than tipping over into mania or depression. This balance usually is achieved (at least in bipolar disorder type I) with a combination of at least one primary mood stabilizer (e.g., lithium, lamotrigine, valproate, or carbamazepine; see Chapter 7) and one or more adjunctive mood-stabilizing agents (e.g., atypical neuroleptic agents or other novel anticonvulsant agents). We also must remember to focus on the long run.

FACTORS LEADING TO TREATMENT RESISTANCE

Treatment resistance is defined as long-term relapse despite adequate monotherapy with lithium or a comparable primary mood stabilizer and occurs in approximately two-thirds of patients with bipolar disorder. Numerous factors are associated with treatment resistance in bipolar disorder, the most important being excessive antidepressant use, misdiagnosis, concurrent substance abuse, and medication noncompliance.

Excessive antidepressant use in bipolar disorder has been discussed in some detail in Chapter 18. As noted there, a good deal of evidence exists pointing to the fact that antidepressants can act as mood destabilizers, counteracting the benefits of mood stabilizers. Antidepressants can promote rapid cycling, causing more and more mood episodes over time and thus worsening the long-term course of bipolar disorder. If used chronically and too aggressively, they can be a prime feature of a patient's lack of long-term response. Frequently, in consultation on patients who have a treatment-refractory history, I find that antidepressant use is the one constant in their previous treatments. Mood stabilizers come and go, often for only brief trials of months or less, but antidepressants of one kind or another are always in place for years on end. When obtaining a treatment history, it is important to note not only the drugs taken but also which drugs were taken together. Concurrent antidepressant use is often a major force behind apparent nonresponse to mood stabilizers.

In patients such as these, the first step in treatment is to stop antidepressants and try mood stabilizers without antidepressants. If lithium or valproate or other agents "failed" but the patient was always on an antidepressant, it is my opinion that the patient never had a therapeutic trial of mood stabilizers. A *therapeutic trial* is lithium alone, valproate alone, or

mood stabilizers in combination—*in the absence of* concurrent antidepressant use.

Another important contributor to treatment-refractory bipolar disorder is misdiagnosis. As noted previously, it appears that about 40% of patients with bipolar disorder in the United States are initially misdiagnosed as having unipolar depression. In these patients, antidepressants are given with many consequences. Patients develop more and more depressive episodes and usually have manic or hypomanic ones too. By the time bipolar disorder is finally diagnosed, usually about a decade after the patient first sought mental health treatment, the patient's illness may have become treatment-refractory. A 20-year-old with two mood episodes is much more responsive to lithium than a 30-year-old with ten mood episodes. We need to work to capture that 20-year-old correctly to avoid the dilemma of treatment nonresponse decades later.

Substance abuse is another important factor, and it is the rule rather than the exception in bipolar disorder. About 60% of patients with bipolar disorder also experience substance abuse at some point in their lives. Bipolar disorder is the most common axis I diagnosis associated with substance abuse, more common than unipolar depression. Frequently, the comorbid scenario has the following pattern: An adolescent begins abusing substances and increases use in his or her 20s. By the 30s, he or she intermittently seeks treatment, and clinicians note many depressive symptoms and possibly manic symptoms. Clinicians usually write off the mood symptoms as secondary to substance use, and no mood treatments are given. If they treat, clinicians are more likely to use antidepressants for depressive symptoms rather than mood stabilizers for manic symptoms partly because the depressive symptoms are often less vague and more prominent than the manic symptoms.

I strongly recommend the opposite approach. Depression can occur with many substances; mania, with few. It is reasonable to hold off diagnosing and treating unipolar depression if there is a chance to obtain a period of lack of substance use to assess secondary depression. Since many patients have bipolar disorder, the use of antidepressants indiscriminately also could worsen matters. On the other hand, secondary mania is infrequent, and if it happens, it only happens one to three times. However, someone with ten episodes of mania who also abuses cocaine cannot be legitimately diagnosed with mania secondary to cocaine. Substance abuse that is comorbid with bipolar disorder rarely resolves without treatment of the bipolar illness. Since most patients with bipolar disorder have substance abuse, this means that a reluctance to treat bipolar disorder in the setting of substance abuse would result in lack of treatment for most persons with bipolar disorder. This is obviously unacceptable. Yet it is my observation that manic symptoms in the setting of substance abuse often are left untreated.

Medication noncompliance is another major problem that contributes to lack of recovery in bipolar disorder. As mentioned previously, once-daily dosing is an important aspect of reducing noncompliance. Attention to the nocebo effect is also important, as is attention to side effects. Weight gain and cognitive problems are the most notable issues here. Patients need to be taken seriously in their side-effect concerns and must be informed of the limitations of their real options. The process is a yin and yang of compromise between clinician and patient.

Other features that contribute to lowered treatment response are mixed episodes, rapid cycling, psychotic features, and comorbid medical illnesses.

SPECIFIC STRATEGIES FOR TREATMENT-RESISTANT BIPOLAR DISORDER

It is important to remember that standard mood stabilizers used alone, such as lithium monotherapy, are at best effective in about a third of patients with bipolar disorder. Yet this fact does not mean that one should not use these agents in the other two-thirds of patients. Treatment response in bipolar disorder is an additive process in which one gradually finds the right combination. This means that one needs to add for efficacy, not subtract. One should subtract drugs only for side effects. In my opinion, one needs to subtract as well as add when three or more medications are used. For instance, if a patient is taking three mood stabilizers, then one ought to seriously consider dropping one of them when adding another. Sometimes four or even five mood stabilizers are needed, but not usually.

In any case, in refractory bipolar disorder type I, it is my strong belief that one of the four primary mood stabilizers should be the central core of treatment. These are lithium, valproate, carbamazepine, or lamotrigine. Carbamazepine has the added problem of multiple drug interactions, and thus it in many ways counteracts the benefits of polypharmacy by

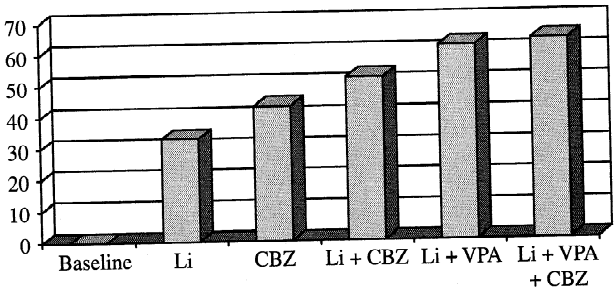

FIG. 19.1. Additive benefit of polypharmacy in bipolar disorder. Li, lithium, CBZ, carbamazepine, VPA, valproate. (From Denicoff et al., 1997.)

reducing the effects of added medications. Consequently, I lean toward the other three.

Polypharmacy with multiple mood stabilizers in refractory bipolar disorder is necessary and beneficial. Polypharmacy with antidepressants usually is not helpful. One study found clear gradual improvement with each step as lithium, valproate, and carbamazepine were combined (Fig 19.1).

In general, I do not distinguish between acute symptoms in the course of deciding on the polypharmacy regimens I use in refractory bipolar disorder. In almost any case, I choose from among the same list of mood-stabilizing medications, although some nuances are relevant. As shown in Figure 19.2, I begin with lithium or valproate. The choice of agent is primarily the patient's, not mine. I describe side effects and benefits and let the patient choose. One-third of patients can be expected to respond to one agent or the other. If appropriate, I also might recommend lamotrigine or carbamazepine. I would be particularly likely to suggest lamotrigine monotherapy for acute bipolar depression. In the other two-thirds of patients who are on lithium, valproate, or lamotrigine but partially responsive or not responsive at all, I usually add an atypical neuroleptic. If depressive symptoms are prominent, I might lean toward ziprasidone among the atypical neuroleptics. Despite the excellent studies supporting efficacy with olanzapine, sedation and weight gain often make it less palatable to patients. Risperidone is a good alternative, as is quetiapine. I might then combine lithium, valproate, and an atypical neuroleptic or possibly add a novel anticonvulsant such as topiramate to

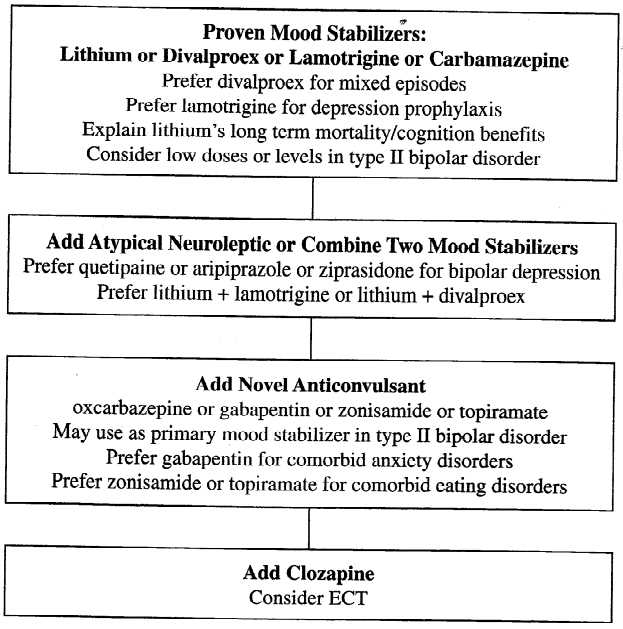

FIG. 19.2. Strategies for treatment-refractory bipolar disorder.

valproate plus an atypical neuroleptic. At this point, additive side effects can be a problem, and I often need to subtract as I add further. Oxcarbazepine is a good alternative to carbamazepine that is much better tolerated and has much fewer drug interactions in polypharmacy. Gabapentin can be added especially for insomnia or anxiety symptoms. Clozapine is useful at this point as a later resort owing to its toxicities. Newer anticonvulsants with less research, such as levetiracetam and zonisamide, also might be considered. This approach is the best method for treatment-refractory bipolar disorder, especially when the most prominent symptoms are manic, mixed, or rapid cycling. Table 19.1 outlines three treatment scenarios.

If the most prominent symptoms are depressive, I take the same approach, perhaps leaning toward agents with the most prominent antidepressant effects, such as lithium, lamotrigine, and perhaps quetipaine, ziprasidone, or aripiprazole. Nonetheless, in some patients (usually about 20%, in my experience),

refractory bipolar disorder is expressed as depressive symptoms that are insufficiently responsive to appropriate mood stabilizer polypharmacy. In such cases, it is appropriate to use antidepressants. I tend to emphasize paroxetine or bupropion because those two agents are the only standard antidepressants with a lowered acute mania switch risk in controlled studies. If paroxetine is not tolerable or acceptable, citalopram may be a good alternative owing to some open evidence of safety in terms of mania risk. I also like to use "antidepressant-like" agents with mild dopaminergic effects (see Chapter 18). If I use any of these antidepressants, I still try to taper patients off them after acute recovery. However, it is likely that in about 20% of patients, long-term antidepressant treatment may be needed for refractory bipolar depressive symptoms.

In other patients, antidepressants are needed earlier in treatment, usually for severe suicidality (i.e., with immediate intent and plan), but these situations usually need not lead to long-term antidepressant use. The antidepressants usually can be tapered off successfully after recovery from the acute depressive episode in these patients.

When antidepressants are inevitable, it is my experience that their benefits are usually suboptimal. More often than not, patients fluctuate around euthymia, sometimes hypomanic, sometimes depressed, but they are not usually stably euthymic. Sometimes it appears that this is the best achievable outcome in some patients, although certainly it is still an unsatisfactory outcome. Nonetheless, antidepressants might be of benefit by removing the most severe depressive symptoms and reducing suicidality.

Rapid-Cycling Bipolar Disorder

Essential Concepts

- Rapid-cycling bipolar disorder means four or more episodes in a year.
- It does not mean that someone simply has rapid "mood swings" (whether in the course of a day or days).
- The main feature of rapid cycling is depressive symptoms.
- Rapid cycling can be mistaken for chronic depression if brief hypomanic episodes are not identified.
- Avoidance of antidepressants is very important in the treatment of most cases of rapid-cycling bipolar disorder, particularly type I.
- Any single mood stabilizer is ineffective; contrary to common opinion, anticonvulsants are not more effective than lithium; and all are equal to placebo.
- Thus treatment almost always requires multiple mood stabilizers in the absence of antidepressants.
- Mood charting probably is most useful in diagnosing and following outcome in persons with rapid-cycling bipolar disorder.

Rapid-cycling bipolar disorder probably represents the most complex and confusing presentation of a mood disorder. It is commonly misunderstood to refer to any person with rapid "mood swings." This is an error. Rapid cycling has nothing to do with someone whose moods shift in minutes, hours, days, or even weeks. The definition of *rapid cycling* is the occurrence of four or more mood episodes in a year. These mood episodes can be of any variety; they could all be depression, or they could include hypomanic or manic episodes. They can each last 3 months, or one could last 9 months, followed by three hypomanic episodes lasting 5 days each, and both