7 What Is a Mood Stabilizer or Antidepressant? Definitions of Drug Classes

Essential Concepts

- The term *mood stabilizer* is often misunderstood to mean stabilization of mood wherever it happens to be.
- Most definitions of mood stabilizer involve antimanic and antidepressant effects.
- I believe that the best definition of a mood stabilizer is that it is an agent that has prophylactic (or preventive) efficacy. Acute efficacy, without preventive benefit, is insufficient.
- *Antidepressants* are often misunderstood as being agents that are effective for any kind of depression. In fact, standard antidepressants elevate the mood in general but are not necessarily effective or safe outside treatment of unipolar depression. Their efficacy in prophylaxis (or prevention) of recurrent depressive episodes is not as well established as their acute benefit.

WHAT IS AN ANTIDEPRESSANT?

Often, patients assume that antidepressants work for any kind of depression. The term *antidepressant* seems to imply that medications in this class should, simply put, treat depression. As clinicians, we have the important task of educating patients on this matter. The term *antidepressant* was coined by a psychiatric researcher in the 1950s as the new tricyclic agents (TCAs) and monoamine oxidase inhibitors (MAOIs) were being developed. Other competing terms were *thymoleptic* (Greek for "breaking mood") and *psychic energizer.* As pharmaceutical companies

and others began to use the term *antidepressant* more frequently, it gained common usage. In fact, it originated in studies of what came to be called *primary unipolar major depressive disorder.*

The most accurate definition of *antidepressant* is to say that it refers to an agent that is effective in treating primary unipolar major depressive disorder. This definition excludes bipolar disorder, as well as secondary depression.

KEY POINT

The term *antidepressant* refers to medications effective specifically for unipolar major depressive disorder. They may not be effective in bipolar depression or secondary depression.

In bipolar depression, the efficacy of antidepressants in acute depression has been only weakly established, and there is evidence suggesting lack of efficacy of antidepressants in prophylaxis of bipolar depression. In fact, some patients develop rapid-cycling mood episodes that are mostly depressive in character; paradoxically, antidepressants can *promote* depression in bipolar disorder. Hence the safety and efficacy of antidepressants in bipolar depression are far from established.

By *secondary* depression, I mean depressive illness owing to clear medical or other etiologies, such as poststroke depression or depression associated with hypothyroidism in a person with no previous illness. Antidepressants have not been proven effective in many of these secondary medical conditions. In some cases, such as vascular dementia, antidepressants appear to be less effective than in primary unipolar depression comparison groups. Usually the most effective treatments have to do with correcting the underlying medical conditions.

In summary, the best phrase for this class of drugs probably is *anti-unipolar major depressive disorder drugs,* but since the term *antidepressant* is more euphonious, it is used frequently. Clinicians should be clear that antidepressants are agents that are effective for unipolar depression, and their use in other conditions must be justified by a different caliber of clinical rationale.

WHAT IS A MOOD STABILIZER?

The term *mood stabilizer* is even more misunderstood. Its origins lie in a more distant haze than the roots of the term *antidepressant.* In the 1950s at least, clinicians used the term

mood stabilizer to refer to a combination amphetamine-barbiturate agent. What they meant by this term is unclear, but it seems relatively certain that clinicians did not mean that such an agent was specifically effective for patients with what would now be called *bipolar disorder.* Rather, the term *mood stabilizer* seemed to refer to effects in which mood would be elevated when depressed, along with some level of decreased mood lability.

When lithium became available and began to be used widely in bipolar disorder, the term *mood stabilizer* was applied to lithium, and then it began to take on its current connotations. Since lithium was studied mainly in acute mania, *mood stabilizer* came to imply antimanic benefits. However, a major difference between lithium and other antimanic agents, such as typical neuroleptics, was that lithium treated mania with less occurrence of postmanic depression than was observed with typical neuroleptics. Further, lithium was effective in treating and preventing depression in bipolar disorder, unlike tricyclic antidepressants.

Hence the term *mood stabilizer* came to include, at least in some quarters, the connotation of antidepressant and antimanic benefits, not only acutely but also in preventive maintenance treatment. The relevance of this definition was limited until recently because so few alternatives to lithium existed in treating bipolar disorder. The recent rise of new potential agents for bipolar disorder has invigorated a new discussion of what it means to be a mood stabilizer. It seems to me that four broad definitions exist, which I label strict, liberal, conservative, and simple (Table 7.1).

KEY POINT

The term *mood stabilizer* cannot and should not be applied to any agent that is effective in a specific phase of bipolar disorder. In other words, *antimanic* does not mean the same thing as *mood stabilizer.* Hence a neuroleptic, whether typical or atypical, is not a mood stabilizer based solely on efficacy in treating acute mania.

In the strictest definition, lithium sets the "gold standard." A drug would only be a mood stabilizer if it is proven effective in treating acute mania and acute depression and is in prophylaxis of mania and depression in bipolar disorder. Lithium is the only agent with double-blind evidence of efficacy in all four phases of bipolar illness. In Europe, regulatory boards follow something akin to this definition and will not approve an agent for acute mania without evidence of prophylactic efficacy as well. The problem with this strict definition is that it implies that every patient with bipolar disorder needs lithium treatment. While there are many benefits with lithium treatment (see Chapter 14), some patients do not respond to it, are unable to tolerate it, or simply refuse to take it.

The liberal definition, which in my opinion goes too far in widening the class of mood stabilizers, would argue that the term *mood stabilizer* should be applied to any agent that is effective in treating acute mania without causing depression or any agent that is effective in treating acute bipolar depression without causing mania. This definition takes out reference to prophylactic efficacy altogether. With this definition, olanzapine, risperidone, quetiapine, ziprasidone, and lamotrigine would be classified as mood stabilizers. All these agents have double-blind evidence of efficacy that meets this definition. However, since mood stabilizers will

TABLE 7.1. Definitions of *Mood Stabilizer*

Strict	
	Efficacy in acute mania, acute depression, and prophylaxis of mania and depression
	Only lithium meets criterion.
Liberal	
	Efficacy in acute mania without induction of depression
	All atypical neuroleptics meet criterion.
	Efficacy in acute depression without induction of mania
	Lamotrigine meets criterion.
Conservative	
	Antidepressant and antimanic efficacy
	Efficacy in two of the three phases of bipolar illness, one of which must be prophylaxis (acute mania, acute depression, prophylaxis)
	Lithium, valproate, carbamazepine, and lamotrigine meet criterion.
Simple	
	Efficacy in prophylaxis, irrespective of acute efficacy
	Lithium and lamotrigine meet criterion based on primary analyses of randomized studies.
	Divalproex and carbamazepine may meet criterion based on secondary analyses of double-blind, randomized studies and primary analyses of open randomized studies.

Note: All definitions of efficacy assume monotherapy, that is, use of the agent by itself, not solely as an adjunct to other agents.

be the core of treatments for bipolar disorder, these agents will be used in long-term treatment, often by themselves. If this definition is correct, such acute benefits need to translate into long-term benefits, which is not the case, either logically or empirically.

The conservative definition holds a middle position between the liberal and strict descriptions. In this approach, the term *mood stabilizer* is used for agents that possess antidepressant and antimanic efficacy. Another way of operationalizing this concept, which I have suggested in the past, proposes that the term *mood stabilizer* be applied to agents with monotherapy efficacy in two of the three phases of bipolar disorder, one of which must include prophylaxis (e.g., acute mania, acute depression, prophylaxis of mania or depression). To date, only four agents have reasonable amounts of evidence for efficacy along these lines: lithium, valproate, carbamazepine, and lamotrigine. These are also the agents that clinicians tend to use to the highest degree in long-term treatment of bipolar disorder.

Finally, what might be termed a *simple* definition, which I now prefer, is to equate a mood stabilizer with prophylaxis. If a drug prevents future mood episodes in bipolar disorder, then it is a mood stabilizer. While much simpler than all the preceding concepts, this view requires careful definition of what we mean by *prophylaxis*.

KEY POINT

Thus far only four medications have been shown to meet simple criteria as true *mood stabilizers:* lithium, valproate, carbamazepine, and lamotrigine.

WHAT IS PROPHYLAXIS?

Prophylaxis simply means prevention of episodes. However, owing to the complexities of the way pharmaceutical companies have designed some of their research studies, we will need to momentarily enter into the question in more detail. In fact, true prophylaxis differs from some other kinds of maintenance study designs. There are basically two varieties, what I call *true prophylaxis* and *relapse prevention;* others use the term *enriched design* for relapse prevention.

Thus, in a relapse-prevention study, patients initially must respond to the drug being studied (e.g., olanzapine or aripiprazole) before they enter the study. In other words, they are treated openly (unblended) with olanzapine for acute mania; those who respond to olanzapine for acute mania are then entered into the maintenance study, where they are then double-blind randomized to stay on olanzapine or stop it (switch to placebo). The outcome is usually timed to the first mood episode. The results of such studies, if positive, suggest that if a person responds to olanzapine for acute mania, then that person will do better by staying on it for the longer term. This is the meaning of the term *relapse prevention:* It only relates to people who use and benefit from the drug for the acute episode and is related to the question: "How long should they be maintained on the drug after the acute episode?" Such studies are, in a way, biased toward showing benefit for the drug being studied because only those who benefit initially from the drug enter the study.

True prophylaxis is different. In the only design that can demonstrate it, which has been conducted mainly in older lithium studies, patients enter the study in the euthymic state; they do not necessarily need to have been in an acute mood episode recently. Further, if they were acutely manic or depressed recently, they could have been treated with any medications, not just the one being studied (e.g., lithium). Thus, for instance, someone might be depressed, get better on an antidepressant alone, and then enter the lithium prophylaxis study, whereby that patient's antidepressant would be stopped and the patient would be randomized to receive lithium or placebo. In such designs, there is no bias in favor of the drug being studied. Further, if benefit is shown (as with lithium), then one can conclude that *anyone* would benefit with the drug for long-term treatment; one does not need to limit one's conclusion to people who benefit initially from the study drug for an acute episode.

To demonstrate the difference, suppose that someone went to the hospital for acute mania and improved with haloperidol. The inpatient doctors did not start a mood stabilizer. Two months later, I see the patient as a new evaluation in the outpatient clinic. I diagnose bipolar disorder, realize that haloperidol is not a mood stabilizer, and then decide to add a mood stabilizer for long-term prophylaxis. Even if I believe that olanzapine, for instance, is a mood stabilizer, the maintenance studies do not support the use of olanzapine in such a patient because the patient did not initially receive and benefit from olanzapine

for the acute mood episode. Only lithium would have evidence of benefit for such patients.

Thus, in general, lithium is the only drug that has been proven to be effective in true prophylaxis. This fact alone should highlight how far and away better proven lithium is as a mood stabilizer than newcomers (particularly among the antipsychotics).

WHY ANTIPSYCHOTICS ARE NOT MOOD STABILIZERS

I will now make perhaps the most controversial statement in this book, at least for clinicians: I believe that, after overuse of antidepressants, the biggest mistake clinicians make in treating bipolar disorder today is *overuse of antipsychotics*. This is occurring in particular because clinicians have made the mistake of believing that antipsychotics in general are mood stabilizers. They are not. While I am aware that most bipolar researchers also likely would not agree with me on this topic, I will explain my rationale and leave it to readers to judge.

Let me begin with a basic statement that cannot be criticized in any way scientifically and yet which gets enacted in daily practice all the time: Clinicians should not generalize mood stabilizer efficacy to the entire class of atypical antipsychotics, even if they believe the data in support of specific agents (to date, olanzapine and aripiprazole). This is simply unscientific and indefensible practice. The following vignette comes directly from my practice with minimal need for alteration on confidentiality grounds; the drugs used were exactly as described.

CLINICAL VIGNETTE

A 36-year-old woman came to me for evaluation. She described clear past manic and depressive episodes, with a diagnosis of bipolar disorder type I; she had been hospitalized recently for an acute psychotic manic episode 5 months previously. She had improved with ziprasidone 40 mg bid and was currently also taking citalopram 20 mg qd, which had been added 1 month after discharge owing to return of depressive symptoms. At the interview, she had mild depressive and moderate anxiety symptoms, much better than

previously but still notably below her normal baseline and interfering with her ability to take care of her two children. She had never received lithium or carbamazepine. Divalproex taken once for 2 weeks had led to excessive sedation. I recommended discontinuation of citalopram and initiation of lithium treatment. She said that she would discuss it with her husband, who then called me for clarification. I explained that lithium was the most proven mood stabilizer and that she was not taking a mood stabilizer. He replied, "Dr. X says ziprasidone is a mood stabilizer." I replied that there was not a single study that ever studied ziprasidone in any way for maintenance treatment of bipolar disorder, and thus it could not be claimed to be a mood stabilizer. Her husband replied; "Dr. X says it is; you say it is not. Why should I believe you?" The patient did not take lithium. Six months later, she had a severe depressive relapse despite continuing ziprasidone plus citalopram. She then came for treatment. Citalopram was stopped and lithium started, and the patient's depressive episode resolved quickly, followed by 1 year of normal mood.

This case highlights the major problem of clinicians thinking that atypical antipsychotics—all atypical antipsychotics—are mood stabilizers. Since they are not, patients often experience mood relapse, often of the depressive phase. This then leads to addition of antidepressants, despite evidence of lack of long-term benefit with those agents as well in bipolar disorder, resulting in what I call the "poor man's mood stabilizer": antipsychotics plus antidepressants. Clinicians should not be confused: A true mood stabilizer, such as lithium, is far and away more proven and, in my view, much more effective than a pseudo–mood stabilizer combination of antipsychotics plus antidepressants. In this vignette, the other clinician simply was wrong, making a claim that the pharmaceutical company could not legally make. Yet clinicians routinely practice in such a manner, with practically no supportive evidence.

The next issue is whether specific antipsychotic agents studied in maintenance treatment, such as olanzapine and aripiprazole, are mood stabilizers. In my view, the current evidence does not support the view that these agents are mood stabilizers.

Two separate issues are relevant: First, how long does a drug need to be studied to prove that it has maintenance or prophylactic efficacy? Second, do the research designs for

these drugs, studied in the relapse-prevention design, really prove prophylaxis?

Regarding the first question, one needs to assess the natural history of mood episodes. In unipolar depression, the average major depressive episode is thought to last 6 to 12 months. Antidepressants often show benefit within 2 months of treatment. Thus the first 2 months of treatment are in the *acute phase*, and 2 to 12 months is called *continuation treatment* because if the antidepressant is discontinued, the natural history of unipolar depression is such that the patient will relapse back into the same initial acute episode. After 12 months, the patient is in the *maintenance phase* of treatment, where mood episodes represent recurrence into new episodes (rather than relapse into an old episode). There is a consensus among unipolar depression researchers on these definitions.

In bipolar disorder, there has never been an attempt at such a consensus until recently, partly in response to criticisms about the olanzapine and aripiprazole studies. The acute phase of mania in bipolar disorder by natural history lasts 2 to 6 months untreated, and depression tends to last 3 to 6 months untreated. Thus, while the acute phase of treatment might again be about 1 to 2 months, the continuation phase extends to at least 6 months, and the maintenance phase of treatment cannot be said to begin until at least 6 months have passed.

In the case of olanzapine, as seen in Figure 7.1, olanzapine clearly was more beneficial than placebo, and the study lasted

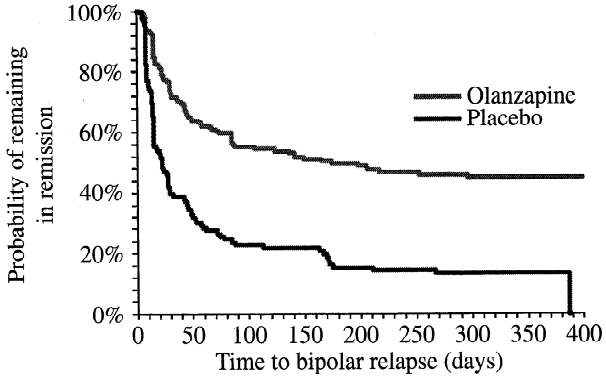

FIG. 7.1. Olanzapine versus placebo maintenance study. (From Tohen M, et al. *Am J Psychiatry.* 2006.)

12 months, which would seem at first glance to meet my maintenance criteria. However, all these studies used the relapse-prevention design; thus all patients in this study were treated initially with olanzapine openly for acute mania. Only those who responded for acute mania, for 2 weeks or more, were entered into this maintenance study. The vast majority of patients who entered the study had responded for only a few weeks to olanzapine for acute mania. This would put them at the beginning of the continuation phase of treatment when they entered the actual maintenance study. By inspecting the figure, you can see that the major difference between olanzapine and placebo occurred right at the beginning of the study. About 75% of patients in the placebo group relapsed within 2 months. After that time, only a few percent in the placebo group relapsed for the rest of the year. In other words, what one can conclude from this study is that if you get better with olanzapine for acute mania for 2 weeks, and then you stop it, you likely will relapse within 2 months. This is clearly relapse in the continuation phase into the same initial episode the patient experienced during the acute phase; it is nowhere near showing maintenance-phase prevention of new episodes 6 months or longer after the acute phase. It is, in other words, a discontinuation syndrome or a withdrawal syndrome masquerading as maintenance efficacy. In response to such criticisms, post hoc analyses of these data reportedly show benefit with olanzapine over placebo in the small leftover sample that continued treatment beyond 2 months; however, the fact remains that most of the difference between olanzapine and placebo was due to an initial withdrawal syndrome. Given that effect, I think that the claim of long-term maintenance efficacy is much weakened.

One might ask why the Food and Drug Administration (FDA) provided maintenance indications for these agents based on these studies. It is worthwhile to note that the FDA is not infrequently mistaken, having to withdraw previous indications. In the case of olanzapine in particular, the FDA has since very clearly stated that the design was highly flawed and that future studies would require much longer than just 2 weeks of stability before entering the relapse-prevention study. It is a source of unnecessary confusion, in my view, for clinicians to interpret FDA indications of these antipsychotics as similar to the same FDA indication of lithium for maintenance efficacy. The studies of lithium, conducted over decades, with replication by numerous researchers, contrast sharply with these flawed single studies of these antipsychotics conducted

by their manufacturers. The data hardly compare: Lithium's evidence as a mood stabilizer is far and away greater than that of aripiprazole or olanzapine. Yet clinicians make mistakes such as viewing them as equal or, even worse, concluding that other antipsychotics are just as good or even preferable to lithium. This kind of practice is quite unscientific and likely harmful to public health.

CONCLUSIONS

The most proven mood stabilizer remains lithium, far and away more proven than competitors. Antipsychotics are not mood stabilizers, in my view, and should be used only as adjuncts to proven agents such as lithium. Other likely mood stabilizers are divalproex, carbamazepine, and lamotrigine. In bipolar disorder type I, one of those four mood stabilizers should be the core of treatment, with all other agents used as adjuncts.

III

TREATMENT OF UNIPOLAR DEPRESSION