NOS. I use the phrase *bipolar spectrum* to loosely refer to these patients, as opposed to type I or type II bipolar patients. These bipolar spectrum patients mainly suffer from major depression, but they also tend to have a number of signs that are atypical for unipolar depression but typical for bipolar disorder. These features of bipolarity are described in detail in Chapter 4.

The Bipolar Spectrum

Essential Concepts

- The bipolar spectrum consists of features of bipolarity besides the classic kind found in DSM-IV in the criteria of bipolar disorder type I.
- A proposed new diagnosis, *bipolar spectrum disorder,* occurs in persons with severe major depression but not spontaneous hypomania or mania and yet with many signs of bipolarity.
- The most important signs of bipolarity are a family history of bipolar disorder in a first-degree relative and antidepressant-induced mania/hypomania.
- Other useful signs of bipolarity include brief, recurrent, atypical psychotic or postpartum major depressive episodes.
- Treatment often can begin with low-dose standard mood stabilizers (e.g., lithium or valproate), followed by novel anticonvulsants alone or in combination with the standard mood stabilizers.

The bipolar spectrum concept has been used at least three different ways in recent literature. At one level, it reflects a broad definition of any bipolar condition from classic forms of type I disorder to type II and not otherwise specified (NOS) forms. This is what Kraepelin meant with his concept of "manic-depressive illness." At another level, the bipolar spectrum can reflect any atypical form of bipolar disorder; for instance, the term may be applied to type II and NOS conditions only, excluding type I bipolar disorder. At a third level, the term may be applied to any condition that may be bipolar in some fashion but is not diagnosable or recognized by current DSM-IV criteria. This way of looking at it conceptualizes the bipolar spectrum concept as an overlap between more classic presentations of unipolar depression or bipolar disorder. Since DSM-IV recognizes type I and type II disorders with specific criteria, this last use of the term *bipolar*

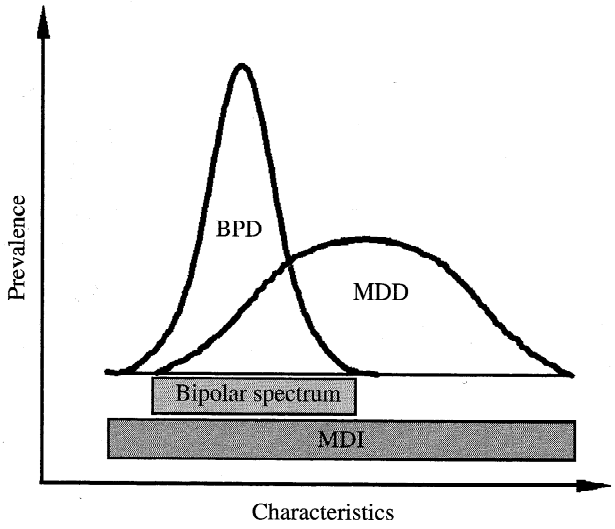

FIG. 4.1. Different concepts of the bipolar spectrum. (Reprinted with permission from SN Ghaemi, RJ Baldessarini, The manic-depressive spectrum and mood stabilization. *Psychother Psychosom* 2007;76:65–69.)

spectrum may be a way of trying to be more specific and detailed about the throwaway bipolar NOS category in DSM-IV. The possible varieties of perspectives on the bipolar spectrum are suggested in Figure 4.1.

In this chapter, when I refer to the *bipolar spectrum*, I mean the second definition: anything but bipolar disorder type I. I also will use the phrase *bipolar spectrum disorder* to refer to a potentially useful diagnosis for many patients whom we now label *NOS* without providing specific criteria for this essentially wastebasket category. This may prove important because of the implication that antidepressant and mood stabilizer use may differ in bipolar spectrum patients compared with standard bipolar type I or unipolar depressed patients.

Another way of visualizing the bipolar spectrum can be seen in Figure 4.2. In this definition, I conceive the bipolar spectrum as part of a continuum of mood disorders, between classic type I bipolar disorder and classic unipolar depression. This is what clinicians tend to see in practice. Despite the utility of our categorical diagnoses for teaching and research, practitioners

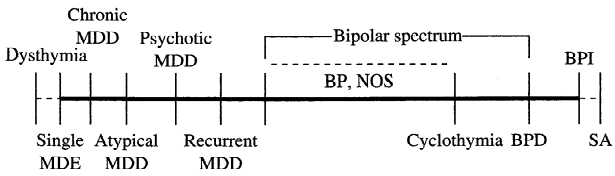

FIG. 4.2. The affective spectrum.

frequently find that many patients do not fall neatly into these categories. By taking a continuum perspective and viewing our diagnostic categories as classic extremes on a spectrum, we can reconcile the existence and utility of these diagnostic categories with the fact that many patients share features of more than one category and fall in the middle of the continuum. In a community-based practice setting, more patients might be found to fall in the middle of the continuum in the figure—in the bipolar spectrum—than at either end of classic bipolar disorder type I or classic unipolar depression.

It may be useful to label classic bipolar disorder type I with a moniker to separate it from the rest of the bipolar spectrum. Terrence Ketter has suggested *Cade's disease* in honor of the discoverer of lithium. By bipolar disorder, most clinicians mean Cade's disease. In this discussion, I want to keep Cade's disease separate from the rest of the bipolar spectrum, but I also want to emphasize the need to think seriously about the probable existence of this bipolar spectrum that is not describable in classic terms used for bipolar disorder type I, (or Cade's disease).

Another way of looking at the bipolar spectrum is to try to characterize the features of those persons who fall in the middle of that continuum. In this approach, we would create another category that captures many, though not all, of the persons who fall in between the classic categories of bipolar disorder type I or unipolar depression. Frederick Goodwin and I have tried to do this in Table 4.1, labeled "Bipolar Spectrum Disorder."

CHARACTERISTICS OF THE BIPOLAR SPECTRUM

The primary feature of the bipolar spectrum is that it consists of a mixture of symptoms that are not classic for unipolar depression or bipolar disorder type I. We might call these

TABLE 4.1. Bipolar Spectrum Disorder: A Proposed Definition

A. At least one major depressive episode
B. No spontaneous hypomanic or manic episodes
C. Either of the following, plus at least two items from criterion D, or both of the following plus one item from criterion D:
   1. A family history of bipolar disorder in a first degree relative
   2. Antidepressant-induced mania or hypomania
D. If no items from criterion C are present, six of the following nine criteria are needed:
   1. Hyperthymic personality (at baseline, nondepressed state)
   2. Recurrent major depressive episodes (more than three)
   3. Brief major depressive episodes (on average, <3 months)
   4. Atypical depressive symptoms (DSM-IV criteria)
   5. Psychotic major depressive episodes
   6. Early age of onset of major depressive episode (younger than age 25)
   7. Postpartum depression
   8. Antidepressant "wearoff" (acute but not prophylactic response)
   9. Lack of response to three or more antidepressant treatment trials

Source: Reprinted with permission from SN Ghaemi, JY Ko, FK Goodwin, *Journal of Psychiatric Practice* 2001;7:287–297.

features of bipolarity (Table 4.2). The main utility of these features is that they allow us to go beyond obsessing about whether or not a patient experienced manic or hypomanic symptoms in the past. DSM-IV sets up this dilemma by making the diagnosis of bipolar disorder solely dependent on manic symptomatology. Clinicians are often forced to forego the bipolar diagnosis because mania/hypomania is so difficult to identify with accuracy and reasonable certainty. Yet phenomenology is only one of four diagnostic validators (see Table 1.2), the other three being family history, course, and treatment response. I will focus on the other validators, as

TABLE 4.2. Features of Bipolarity

1. Phenomenology of manic symptoms
2. Phenomenology of depressive symptoms
3. Course
4. Family history
5. Antidepressant treatment response
6. Mood stabilizer treatment response

well as look at the diagnostic relevance of the phenomenology of depression (as opposed to focusing only on the phenomenology of mania) (refer to Appendix A for a bipolar spectrum diagnostic scale).

Manic features are the least useful. In classic bipolar disorder type I, euphoric mood is often present. In more subtle presentations, one might observe only mood lability, colloquially called *mood swings*. The diagnostic relevance of this mood lability is controversial. In some research, such mood lability appears to be a sign of bipolarity because it later predicts the development of diagnosable bipolar disorder. However, in clinical practice, the specificity of mood swings to bipolar disorder seems limited in my experience. My opinion is that we need to examine where the mood lability begins and ends. Often, by "mood swing," a patient means that his or her depressed mood swings from mildly depressed to more severely depressed or perhaps from a period of normal mood to a period of depressed mood. This kind of mood lability appears to be very nonspecific. It simply reflects the variability of depressed mood on an hour-to-hour basis. On the other hand, mood lability where the mood swings above the euthymic baseline to a euphoric state would seem more relevant to bipolarity. Yet, if this happens, I don't see the utility of using the term *mood lability* or *mood swing* instead of simply noting that euphoric mood occurs. In this sense, we are not saying anything different from the classic definition of mania. Mood swings from depression to irritability are similarly nonspecific and difficult to interpret. Perhaps future research will clarify this issue, but at this point, my inclination is to put little weight on mood lability per se, separate from the presence of euphoric mood.

The phenomenology of depression is much more important for the concept of the bipolar spectrum.

KEY POINT

Conventional wisdom is that one cannot distinguish bipolar disorder from unipolar depression based on depressive symptoms. This clinical assumption is not supported by empirical research.

Psychotic features of depression are more common in bipolar than unipolar depression, as are atypical features (e.g., increased sleep, increased appetite, leaden paralysis).

Postpartum depressive periods are more common in bipolar than unipolar illness in some studies. Melancholic and chronic depressive periods are more common in unipolar than bipolar depression. As with all features of bipolarity that characterize the bipolar spectrum, these differences are not pathognomonic, but they are differences nonetheless.

The course of depressive illness is also a key bipolarity factor. Depressive episodes never recur in about one-third of patients with unipolar depression; they recur in almost all patients with bipolar disorder. Hence the greater the number of depressive episodes, the more characteristic this feature of the course would be for bipolar disorder rather than for unipolar depression. The average major depressive episode lasts 6 to 12 months in unipolar depression by untreated natural history; it lasts 3 to 6 months in bipolar depression. Hence the shorter the duration of the depressive episode, the more characteristic it would be for bipolar as opposed to unipolar depression. The mean age of onset of bipolar disorder is 19 years; of unipolar depression, about 30 years. The earlier the age of onset, the more likely it is that the illness is bipolar rather than unipolar.

KEY POINT

To give a sense of the immense impact of age of onset, it suffices to note that the chance that a unipolar depressed 30-year-old will develop mania or hypomania in the future is about 10% to 20%. However, the likelihood that a 12-year-old with solely major depressive episodes will continue to have a solely unipolar course is 50%.

That child has a 50% chance of switching diagnostically to bipolar disorder in a decade. The clinician could flip a coin to determine the diagnosis based solely on age of onset.

Again, none of these phenomenologic or course features are pathognomonic, and they certainly can occur in persons with unipolar depression. Yet the more features of bipolarity present, the more relevant is the diagnosis of a bipolar spectrum illness rather than simple unipolar depression. For example, imagine a patient whose illness began at age 15 years and who has brief episodes (mean 2 months) that are highly recurrent (3 times yearly, 20 overall in lifetime), usually atypical and sometimes psychotic. This person would be

highly unusual in our understanding of the nature of unipolar depression. To label this person with the diagnosis of unipolar depression, as we currently do, stretches the unipolar diagnosis to a point of heterogeneity that appears quite excessive. Rather, it seems to make more sense to stretch our currently rarefied, pure, but tiny conception of bipolar disorder and take it into the concept of a bipolar spectrum patient such as this hypothetical person.

Other features that are relevant are family history and treatment response. In some respects, these features are more definitive than phenomenology and course of depressive illness partly because certain features of the family history and treatment response appear to be more specific to bipolar illness in some studies.

Family history is key. The whole distinction between unipolar depression and bipolar disorder dates to empirical genetic studies from the 1960s. The strongest evidence for differentiating the two conditions comes from genetics: Those who experience mania also possess a family history of mania; those who experience depression only do not have a family history of mania.

KEY POINT

A family history of bipolar disorder should be extremely rare in persons with unipolar depression; in fact, such a family history throws strong doubt on the presumed unipolar diagnosis.

Too often I observe among clinicians a lax attitude toward this subject. The family history is almost always duly recorded, but its impact on diagnosis is practically ignored. Much greater weight is given to phenomenology, such that a person with solely depressive episodes is diagnosed unipolar, and the fact that this person's mother may have had bipolar disorder is dismissed with a shrug. It bears repeating that it should be exceedingly rare to find a family history of bipolar disorder type I in a first-degree relative of a person with unipolar depression. If found, the patient is likely to have a form of bipolar spectrum illness.

Treatment response is also important. History of effects of antidepressants can be more diagnostically valuable than treatment history with mood stabilizers. The most valuable finding is antidepressant-induced acute mania or hypomania. A number of studies now show that antidepressant-induced

mania/hypomania occurs in 20% to 50% of patients with bipolar disorder type I, about 5% to 20% of persons with bipolar disorder type II, and less than 1 percent of patients with unipolar depression. Thus, DSM-IV notwithstanding, the empirical evidence suggests that this finding is almost pathognomonic of bipolar illness.

Other aspects of antidepressant response are also revealing. Clinical tolerance is extremely important. In one study, about 60% of patients with bipolar disorder develop tolerance to antidepressants, compared with 20% of patients with unipolar depression. This means that the patients respond initially, become euthymic rather than manic, and then lose that response after 6 months or longer. They experience an acute, but not a prophylactic or preventive, benefit. They improve from their acute depression initially, but later relapse.

Conversely, only about 20% of patients with bipolar disorder relapse into depression on discontinuation of antidepressants after recovery from the acute depressive episode compared with 60% of unipolar depressed patients who appear to experience withdrawal depression after stopping antidepressants.

Patients with bipolar disorder also may be more refractory acutely to treatment with antidepressants as compared with those with unipolar depression. The empirical evidence for this statement is not definitive, although it is suggestive.

Perhaps most important from a practical standpoint is that antidepressants appear to be associated with induction of a rapid-cycling course in about a third of patients with bipolar disorder, as discussed previously. This association can be subtle and difficult to recognize without a careful and accurate treatment and descriptive history of the course of a patient's mood disorder.

Hence, in sum, a number of poor outcomes with antidepressant treatment appear to be more common in bipolar than unipolar depression and can be suggestive of the bipolar spectrum.

Response to mood stabilizers also suggests possible bipolar illness. There is some evidence that lithium may be effective in unipolar depression, but there are suggestions that other mood stabilizers such as valproate, lamotrigine, and carbamazepine may be more effective in bipolar than unipolar depression.

In the definition we suggest for a *bipolar spectrum disorder*, Frederick Goodwin and I try to synthesize these findings and weight them differently based on the amount of evidence supporting the association between these various findings and bipolar illness. It has not been validated empirically, but I present it here for clinicians, who then can determine whether it proves useful clinically in their experience. In this definition, I place the most emphasis on family history and antidepressant-induced mania owing to the greater apparent specificity of those findings for bipolar illness. The other features, while relevant, need to be present in greater number to diagnose bipolar spectrum disorder.

CLINICAL VIGNETTE

The patient is a 45-year-old man who presents for a consultation for refractory depression. He reports having had depression "all my life," although, on further questioning, it becomes apparent that he also experiences periods of feeling relatively well, apparently near euthymic. As best as can be determined, he has experienced at least five periods of depression in between periods of wellness, with the depressive episodes beginning at age 17 and most recently occurring for the past 4 months. The average depressive episode lasts 2 to 4 months, with atypical symptoms of increased sleep and increased appetite. He has not responded to full therapeutic trials of three antidepressants, including two in combination. He has never received lithium augmentation. Once he responded to fluoxetine, but then he relapsed into another depressive episode 9 months later despite continuing fluoxetine. Resumption of that agent has not led to benefit with later depressive episodes. On questioning, he reports that his aunt was hospitalized for schizophrenia in the 1960s and later was rediagnosed with bipolar disorder in the 1980s, responding well to lithium. After consultation, lithium was added to his current antidepressant with gradual response and maintenance of benefit at 2-year follow-up.

Hyperthymic personality is a final bipolar feature that deserves special mention. Most patients' personality styles can be divided roughly into three arbitrary cutoffs on a normal distribution, with most individuals falling in the middle at *normothymia*. These persons sleep about 8 hours nightly, they are neither extroverted nor introverted, they work a moderate amount, and they are generally well rounded and show evidence of good equanimity. At one end of the normal

curve, there are other persons who are called *dysthymic* in their personality style (as opposed to the DSM-IV diagnosis, which is not a personality-related definition). These persons need more sleep (about 10 to 12 hours nightly), tend to be shy and introverted, are somewhat low in their energy level chronically, and have a melancholic tint to their feelings. At the other end, there are persons with *hyperthymia,* who might be called chronically hypomanic, except that hypomania is, by definition, brief and episodic. Patients with hyperthymia tend to be the life of the party, jokesters, humorous, gregarious, and extroverted, and they tend to be high-energy persons, workaholics, and highly successful occupationally and tend to need less sleep (about 6 to 7 hours nightly or less). These persons often show evidence of bipolar disorder in family members. Sometimes, persons with hyperthymia will also experience recurrent major depressive episodes, always recovering to their hyperthymic baseline. Unlike patients with bipolar disorder type II, these persons do not experience a euthymic baseline that approximates normothymia. Hyperthymia has been shown to be a predictor of antidepressant-induced mania.

At a practical level, these features of bipolarity add up to make an individual less likely to respond to antidepressant medications by themselves and more likely to respond to the addition of mood-stabilizing agents, either with antidepressants or in monotherapy. Also, many of these bipolar features tend to cluster together. As stated earlier, the individual with hyperthymic personality frequently has a family history of bipolar disorder type I, has experienced antidepressant-induced mania, and demonstrates evidence of brief, recurrent, atypical major depressive episodes. Such persons do not possess classic unipolar depression and, in my experience, best fit the profile of the bipolar spectrum individual with consequent mood stabilizer treatment (with or without antidepressants).

PRACTICAL RELEVANCE

Why go to all this effort to diagnose the bipolar spectrum? These patients do not respond as uniformly or as completely to antidepressants as do patients with unipolar depression, and they appear to respond best either with mood stabilizers alone in low doses, putative mood stabilizers (such as novel anticonvulsants), or combinations of those agents with standard antidepressants in low doses. The clinician is not guided

by much in the way of empirical research because researchers usually confine their studies to DSM-IV diagnoses. This discussion is based mainly on my clinical experience, supplemented with the limited available research.

KEY POINT

All other things being equal, if I diagnose bipolar spectrum illness (not type I), I prefer to begin treatment either with low-dose lithium or valproate or with a novel anticonvulsant, all in monotherapy, in the absence of standard antidepressants.

The use of low-dose standard mood stabilizers such as lithium or valproate may be particularly relevant in these patients because they frequently do not want to take these mood stabilizers owing to the fact that they usually have not experienced mania. Yet it is important to recognize that most of the research on therapeutic blood levels for lithium and valproate are limited to acute mania. These "therapeutic" levels may not apply in other circumstances (such as the elderly and children; see Chapter 26). Such levels also may not apply in some cases of patients who do not have bipolar disorder type I (i.e., acute mania). Thus, by definition, this discussion of a possible bipolar spectrum raises the question of what appropriate mood stabilizer blood levels would be for these patients. There are very few data to rely on here. In one study, over 80% of patients with cyclothymia responded to a mean level of valproate of 32.5 mg/dL. It seems to me that it may not be unreasonable to try low-dose lithium or valproate initially in patients who might meet our criteria for bipolar spectrum disorder. If patients respond, they can avoid the increased side effects associated with higher levels. If patients do not respond, the doses can be raised to full therapeutic levels. If the patient objects or refuses, the standard mood stabilizers can be dropped in favor of the novel anticonvulsants.

If a standard mood stabilizer fails or is refused at either "low" or "therapeutic" levels, I think that it is reasonable to start with any novel anticonvulsant. I lean toward gabapentin, dosed initially at 300 mg qhs, then gradually raised to 300 mg bid, and increased in 300-mg intervals every 4 to 7 days to a therapeutic range of 600 to 1,800 mg per day (usual dosing 900 to 1,200 mg per day). If gabapentin is ineffective or not tolerated, I usually try topiramate next (25 mg qhs, increased to 25 mg bid, and increased 25 mg per day every week to a dose range of 100 to

200 mg per day). If topiramate is ineffective or not tolerated, I then would go to lamotrigine (25 mg qhs, increased weekly no faster than 25 mg per day per week in once-daily dosing to a dose range of 50 to 200 mg per day). I tend to hold off on lamotrigine in this population compared with other novel anticonvulsants owing to the risk of Stevens-Johnson syndrome. In bipolar disorder type I, I would use lamotrigine before the other agents owing to its much more extensive evidence of efficacy. But again, in the bipolar spectrum, one has to function based on minimal data, and my inclination is to lean toward the safest agents first and then move to the agents with more efficacy data but somewhat greater risk.

Antidepressants can be used at any point. In patients with an extensive history of poor response to antidepressants, I would avoid antidepressants while trying the preceding mood stabilizer trials. I might even combine mood stabilizers (such as low-dose lithium plus gabapentin or lamotrigine plus topiramate) before adding antidepressants. In other patients without a history of refractoriness to antidepressants, I would be willing to use antidepressants earlier in treatment, either right after trying one mood stabilizer or even combined with a mood stabilizer from the beginning in some cases. If antidepressants are used, it is important to use as low a dose as possible, usually half the dose used in unipolar depression, and avoid tricyclic antidepressants and stimulants in particular.

CLINICAL VIGNETTE

The patient is a 33-year-old woman who has been diagnosed with depression since age 23. She has been treated with four antidepressants (fluoxetine, sertraline, bupropion, and venlafaxine). She did not respond at all to bupropion or sertraline and experienced a brief hypomanic episode on venlafaxine. She has never experienced spontaneous mania or hypomania, according to her and her family. Fluoxetine worked best for her ("I never felt better") without any clearly identifiable hypomania, but its benefit wore off after 1 year. Her first major depressive episode at age 23 occurred postpartum. Most of her depressive periods are characterized by atypical features of increased sleep and appetite, and the episodes usually last about 4 months. She has experienced six episodes. She has a first cousin who was recently diagnosed with bipolar disorder and two siblings diagnosed with

"depression." Her grandmother was diagnosed with schizophrenia in the 1950s and treated with electroconvulsive therapy (ECT) with good benefit.

This patient has many of the clues of bipolarity, yet she cannot be officially diagnosed with bipolar disorder type I or type II because of lack of spontaneous manic or hypomanic episodes. This is the kind of patient who heuristically I find it useful to see as a bipolar spectrum patient. She was treated with csitalopram plus lithium with excellent improvement, and she was able to maintain her benefit for over 5 years.