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

courses would be considered rapid cycling. At some level, rapid cycling reflects mood episodes, some of which usually are 3 months in duration or longer, occurring frequently over the course of a year. Thus, to diagnose rapid cycling, one must have a 1-year time frame of history in mind.

While a patient with rapid cycling may experience rapid mood lability over hours (sometimes called *ultradian cycling*) or days (sometimes called *ultrarapid cycling*), such lability is not by itself diagnostic of rapid cycling. The four episodes over a year must be established. Conversely, persons with non-rapid-cycling mood disorders may experience mood lability over days to weeks, an observation that is not of clear diagnostic or therapeutic significance.

It is important to define what I mean by the term *mood swings*. Used colloquially, *mood swings* means that one's mood simply shifts from one state to another. Such a description may or may not be diagnostically informative. For instance, describing a mood swing, a patient might say that he or she went from feeling very down for a few hours to feeling okay (average, euthymic). He or she may mean that he or she went from feeling down for a few hours to feeling irritable. Or perhaps he or she means that he or she went from feeling down to feeling elated. These experiences all can be termed *mood swings*, but they are very different. Only mood swings that lead to 4 days or longer of a hypomanic episode or 7 days or longer of a manic episode really can be seen as related to bipolar disorder.

KEY POINT

In unipolar depression, one can have mood shifts from depression to euthymia or irritability without any other manic symptoms. These "mood swings" have nothing to do with mania or bipolar disorder.

If other manic symptoms occur with irritable mood for days to 1 week or longer, then the mood swing may be part of a hypomanic or manic episode. If elated mood is present and appears to be above the euthymic baseline, other manic symptoms usually can be unearthed (currently or historically), and a diagnosis of bipolar disorder can be made. I want to emphasize, though, that mood swings are not by themselves diagnostic and frequently can occur in unipolar depression. They should lead to a careful examination with

the patient of what is actually occurring and should *trigger*, rather than conclude, the search for a bipolar diagnosis.

WHY NOTHING, INCLUDING ANTICONVULSANT TREATMENT, IS EFFECTIVE

Rapid cycling was defined based on early studies with lithium, where nonresponders were found to have four or more episodes in a year. Thus, by definition, lithium is not effective in rapid cycling. Many clinicians have come to believe, therefore, that other agents, particularly anticonvulsants such as divalproex, are more effective than lithium for rapid cycling. This belief was put to the test recently with the first randomized comparison of the two drugs, and the verdict was that divalproex was very similar to lithium. In other words, it too is basically ineffective. Other studies also find carbamazepine to be no better than lithium, and two randomized studies (one unpublished) find lamotrigine equivalent to placebo for rapid cycling.

TIP

Contrary to common belief, anticonvulsants are not more effective than lithium in rapid-cycling bipolar disorder. This is a generally treatment-refractory condition: No single mood stabilizer is effective by itself. Thus multiple mood stabilizers are needed.

So nothing works, as least by itself, with the exception of antidepressant discontinuation, as described below. Thus, in rapid cycling, we need to use multiple mood stabilizers, in the absence of antidepressants, and we need to be very patient. Over time, sometimes years in my experience, this approach to treatment leads to gradual and sometimes complete improvement.

THE NATURE OF THE RAPID-CYCLING COURSE

Rapid-cycling bipolar disorder, then, is a condition in which four or more mood episodes occur in a year in someone who has experienced at least one manic or hypomanic episode in their life. Remember that all the mood episodes in a given year

can be depressive; they need not be manic or hypomanic (although usually at least one such episode can be identified in a given year). On the other hand, rapid-cycling is rare in unipolar depression. In other words, if a patient never experiences even a single manic or hypomanic episode, it is unlikely that he or she will experience a year in which the major depressive episodes are brief and occur four separate times. The lack of relationship between unipolar depression and rapid cycling is due mainly to the fact that major depressive episodes in unipolar depression last 6 months to a year on average if untreated. Rapid cycling is more common in bipolar disorder because depressive episodes are more brief, as are manic periods.

Rapid cycling was almost unheard of before 1960. Although Kraepelin, Bleuler, and others were painstakingly descriptive writers, they rarely describe cases along the lines I have just defined. The first descriptions date to the 1970s, when Dunner and Fieve noted that many patients who failed to respond to lithium appeared to experience four or more episodes in a year. This subgroup was found to occur in about 20% of patients with bipolar disorder, and this finding has been replicated since in numerous studies, leading to the inclusion of the rapid-cycling course in DSM-IV in 1996.

Why was rapid cycling absent in the psychiatric literature before 1960 and present in 20% of patients from then onward? One cannot ascribe it to poor research because our predecessors in the early to middle 20th century were more descriptive than we are, and we still rely to a great extent on their observations. What changed in 1960? (The exact year, of course, is only an approximate indication of the historical epoch to which I refer.) Are there any secular factors that might be relevant? While the election of President Kennedy and the birth of the American Football League are unlikely to be related to the rise of rapid cycling, one factor that is, in my opinion, noteworthy is the rise of psychopharmacology. Antidepressants and antipsychotics began to be used widely into the 1960s and 1970s. Antidepressants in particular have been implicated in the induction of rapid cycling in about one-quarter or more of patients with bipolar disorder, as discussed in Chapter 18, a rate that by itself might be completely sufficient to explain the prevalence of rapid cycling.

The association between antidepressants and rapid cycling was first reported by Wehr and Goodwin in 1975 and confirmed by Wehr and his associates in 1979 and by Kukopulos and his colleagues in 1980. Yet this clinical observation of immense importance went largely unnoticed for over a decade and is still resisted in some quarters. Wehr, Kukopulos, and their associates agreed that discontinuation of antidepressants was the most important clinical decision in the management of rapid cycling. In most patients, the rapid-cycling course would go away after stopping antidepressants. In a minority, the rapid cycling might not go away, leading to the conclusion that excessive antidepressant use may have led to a permanent rapid-cycling state.

Based on the available clinical literature and my own experience, I find that certain clinical approaches have proven helpful to me:

1. Antidepressants are basically contraindicated in these patients, except for a small minority (in my experience, not likely more than 10%) in whom they may be needed (intermittently or continuously) for intractable depressive symptoms.
2. Multiple mood-stabilizing drugs usually are required, with atypical neuroleptics being a key ingredient in most cases.
3. Longitudinal assessment of episodes is most helpful. Patient mood charting and some ability to follow frequency of episodes are necessary to assess outcome. Minimal therapeutic trials for rapid cycling are 3 months or longer in duration in many patients, as opposed to 2 months or less for depression and 1 month or less for mania.
4. Focusing on the long run is the key to clinical success. Overreaction to short-term depressive symptoms or mood swings only complicates the long-term treatment.

HOW TO ASSESS AND FOLLOW RAPID CYCLING

Rapid cycling is often a difficult course to conceptualize without a visual aid. Patients often make vague statements that are too difficult to operationalize so as to allow a rational assessment of treatment response. Such statements may be along the following lines, in response to questions regarding past mood symptoms. I place my comments in parentheses after the statement to indicate how they might be assessed diagnostically:

- "My moods are all over the place." (This statement is too vague to be very informative diagnostically.)

- "Sometimes I'm up; sometimes I'm down; there's no rhyme or reason." (This statement can be fleshed out by getting a sense about the frequency and relative duration of *sometimes*. The patient is focusing on potential causes or triggers of mood episodes, which is not highly relevant diagnostically, although such triggers may be useful clinically. Diagnostically speaking, the potential causes of episodes do not matter once a single secondary episode has been ruled out; what matters is the simple description of what happened symptomatically during the episode. Often patients tend to focus on speculations about cause rather than describing their symptoms straightforwardly.)
- "I'm depressed all the time." (Many patients with rapid-cycling bipolar disorder focus on the depressive moods, which, though usually longer and more severe, are not present every single day of their lives. Especially if currently depressed, such patients overemphasize the extent of their depressive symptoms when initially asked about mood. In further questioning, one needs to challenge this statement. Often patients will then admit brief hypomanic or even manic, episodes. Remember that patients can be depressed 340 days out of the year, but if they have three interruptions with 4 days of hypomania each, then such patients not only have bipolar disorder, but they also are diagnosable with rapid-cycling bipolar illness rather than a year-long major depressive episode. This distinction would alter treatment decisions markedly.)

To get around many patients' tendency to overemphasize their depressive periods and to underreport mood cycling, many investigators find that a mood chart can be a helpful diagnostic aid. The concept of mood charting dates back to Kraepelin, when he made a card summarizing the history of a patient that provided decades of overall information about the patient's mood phases. Later, Adolf Meyer emphasized the utility of making a life chart to follow the course of a patient's illness, with special attention to life events that led to psychiatric symptoms.

Recent investigators, most notably Gabriele Leverich and Robert Post, have combined these two historical sources to create a *life-chart methodology* (LCM) for bipolar disorder. They emphasize its usefulness for rapid-cycling bipolar disorder. The LCM can be used retrospectively to record a patient's history and prospectively to follow a patient's course. It can be rated by the patient or by the clinician. In my opinion, the greatest evidence of validity is a prospective clinician-rated

LCM (avoiding the pitfalls of patients' lack of insight or poor memory). In patients with good insight, prospectively rated self-report mood charts can be useful to the clinician. I include in the appendix such a prospective daily mood chart that can be rated by a patient; it is derived from the work of Gary Sachs and mildly revised by me. In this appendix I provide the clinician-rated LCM and the patient-rated mood chart as two aids in diagnosing and following the course of bipolar disorder in general and rapid cycling in particular.

KEY POINT

Aids such as mood charting can be crucial in helping to follow treatment response in rapid-cycling bipolar illness, where mild improvement can be hard to detect in a global sense but may be more obvious in a mood chart.

Further, worsening of illness may seem vague and unclearly related to any specific factors in standard clinical interviews, whereas mood charts can more clearly establish potential relationships. For instance, associations between antidepressant use and worsened rapid-cycling bipolar illness are most obvious in mood charting and very difficult to detect or reconstruct accurately from standard clinical interviews.

Unfortunately, when patients are most ill, such as when they are in a severely depressed episode, or when their moods are cycling rapidly, they are often unwilling or unable to fill out their self-report mood charts. This factor makes the clinician-rated mood chart all the more important. The LCM comes with specific instructions and can be used as an integral part of clinical interviewing, especially for rapid-cycling bipolar disorder. Let's see how we can apply these methods and our rules for treating rapid-cycling bipolar disorder to an instructive case.

CLINICAL VIGNETTE

The patient is a 34-year-old white woman. The patient's chief complaint is, "I'm always depressed." She reports either not responding to many antidepressants or responding for a while but then becoming depressed again. She has taken fluoxetine, sertraline, paroxetine, citalopram, and venlafaxine. Her best response was with fluoxetine, but it wore off after

6 months. She tried it again three times with the same effect of temporary response each time. Her doctors thought of the potential of a bipolar component at one point, and she received lithium with her antidepressants for 3 months without any benefit that she noticed. She gained weight and had trouble with her memory and wanted to stop it. Valproate also produced no benefit after 2 months of treatment, again with antidepressants.

This is the kind of patient in whom a careful assessment of brief mood swings to hypomania needs to be made. Although she complains about and mainly experiences depression, it is key to know if she has ever had mania or hypomania to determine if she has unipolar or bipolar depression. Further, we need to know the frequency of her depressive or manic episodes to determine if she has rapid cycling or not. This issue is really quite important. It is not enough to know about the patient's current mood state or to have a general sense of a patient's history. It is really necessary to try to provide the answers to the questions in Table 20.1. In many cases, the patient and his or her friends or family are unable to provide

TABLE 20.1. Questions Clinicians Need to Answer to Adequately Assess Rapid-Cycling Bipolar Disorder

1. At what age did the first major depressive episode begin?
2. At what age did the first manic or hypomanic episode begin?
3. How many major depressive episodes have occurred? When?
4. How many manic or hypomanic episodes have occurred? When?
5. When was the last major depressive episode? What is the longest they will last?
6. How long do the major depressive episodes typically last?
7. When was the last manic or hypomanic episode?
8. How long do the manic or hypomanic episodes typically last? What is the longest they will last?
9. How many mood episodes have occurred in the past year?
10. Assess associated medications during periods of mood episodes. Did mood episodes increase in frequency during periods of antidepressant use?
11. Assess associated substance abuse during periods of mood episodes. Did mood episodes increase in frequency during periods of substance abuse?

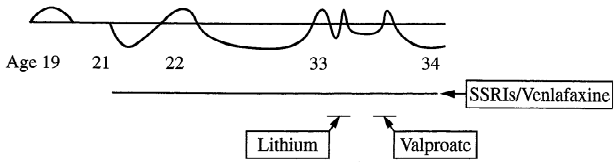

FIG. 20.1. Graphic summary of lifetime mood episodes.

such information. But this does not absolve the clinician from trying to obtain it. In the case of this patient, answers to the questions in the table provided a life history that could be summarized graphically (Fig 20.1).

I find that it is frequently useful to draw some kind of graphic summary of the mood episodes in the lifetime history of a patient with bipolar disorder. Such a summary, while only a one-dimensional, rough approximation of the realities of a person's life, provides information visually that is quite difficult to grasp in words. Drawing rough periods of medication use also provides a visual understanding of the overall treatment and the especially important point of overlap among treatments (e.g., mood stabilizers always used with antidepressants may be less likely to be effective than when used without antidepressants). One also might get a sense of whether the patient's rapid cycling appeared to worsen with antidepressants by making this visual figure. Without the visual image, I find it is very hard to ask patients to make these judgments, and as the interviewer, I fail to get a seamless longitudinal sense of the patient's history.

In the patient in the preceding vignette, my first move is to stop the antidepressants. Clearly, antidepressants have not been sufficiently effective for her. Further, she has never had a period of time in which she did not use antidepressants since she began treatment. Her rapid cycling could be driven by antidepressant use; the only way to know is to stop the antidepressants. Given that she is currently depressed, she is quite willing to stop her current ineffective antidepressant treatments.

Further, this patient was referred to me with the history that she has been refractory to multiple antidepressants as well as lithium and valproate. My impression initially was that she had never received a fair trial of a single mood stabilizer. This was so because she always was taking an antidepressant, which might have been destabilizing her mood and counteracting any potential benefit from her mood stabilizer.

Hence, after stopping the antidepressant, I would give her a trial again of either lithium or valproate alone. In this case, she wished to take valproate owing to concerns about acne with lithium. She took valproate (1,000 mg qhs, level 75 ng/dL) for 1 month with moderate benefit in her depressive symptoms. She experienced some sedation, which resolved. Her weight increased by 3 pounds. She felt that her depression was too problematic to wait longer, so we then decided to make another intervention. At this point, reviewing the algorithm shown in Chapter 19, I could either combine valproate and lithium, or I could add an atypical neuroleptic. She chose to add an atypical neuroleptic but wanted to take one with a lower chance of weight gain, given the already present risk of weight gain with valproate. I offered her risperidone or ziprasidone, and she chose risperidone to avoid any cardiac risks. We added risperidone 0.5 mg qhs. (I generally start at quite low doses in women with rapid cycling to minimize the risks of side effects.) We then moved to 1 mg qhs after 1 week and waited for 2 weeks. She reported moderate improvement, but that 1.5 mg qhs was too sedating, and we went back to 1 mg/d with benefit. She ultimately remained on valproate and risperidone with long-term benefit.

SPECIAL TOPICS