Clinical Case Conference

Treating Bipolar Illness: Focus on Treatment Algorithms and Management of the Sleep-Wake Cycle

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Some patients with bipolar illness are fortunate enough to have a relatively uncomplicated course (for example, responding to lithium monotherapy with extended periods of stability); however, data indicate that this course is probably the exception rather than the rule (1–6). Instead, for many patients with bipolar disorder, the management of their illness presents substantial challenges for both patient and physician. Historically, an important factor contributing to this challenge has been the relative dearth of mood-stabilizing medications. For approximately 20 years, the only treatment approved by the Food and Drug Administration for treatment of acute mania or maintenance treatment of bipolar disorder was lithium carbonate. Then, researchers suggested that anticonvulsant medications (first carbamazepine and, later, divalproex) might have mood-stabilizing effects, and in 1995 divalproex was approved for use in acute mania. Now, the possible mood-stabilizing effects of other medications, including newer anticonvulsants and atypical antipsychotic medications, are being studied. The hope is that the number of medications approved for maintenance mood stabilization as well as acute treatment of patients with bipolar disorder will soon increase.

In addition to mood-stabilizing medications, many patients with bipolar disorder are treated with antidepressants. Indeed, many patients with bipolar disorder are ultimately treated with complex medication regimens, including mood-stabilizing medications, antidepressant medications, and sometimes sedative and/or antipsychotic medications (7, 8). The complexity of these regimens, as well as the advent of evidence-based medical practice, has resulted in the development of treatment guidelines and algorithms for the treatment of bipolar illness as well as for other psychiatric illnesses (9–13). Treatment algorithms organize scientific results and expert consensus into recommended treatment sequences that the practitioner can follow. The initial steps in these sequences are based on controlled studies, and later steps in the algorithm are based on consensus opinions of researchers and clinicians.

The case described here is of a patient with bipolar disorder whose treatment generally conformed to the recommendations of current treatment algorithms for patients with bipolar illness. However, as both patients and clinicians are well aware, the course of a patient's illness depends on a number of factors other than the medications that he or she is prescribed. Specifically, in bipolar illness, as well as in other psychiatric illnesses, there is evidence that life stresses can influence the number and timing of episodes (14, 15). In the case of bipolar illness, there is further evidence that sleep deprivation may be a mediating link between stress and manic episodes particularly (16). In addition, a large body of literature indicates that not only the duration of a depressed patient's sleep but also its timing can have a clinically significant impact on the patient's mood (17–20). Therefore, there are several reasons why a bipolar patient's sleep-wake cycle merits careful monitoring, and there is reason to believe that stabilizing the sleep-wake cycle can have beneficial effects on the patient's course. As the following case demonstrates, however, such stabilization can be difficult to achieve.

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CASE PRESENTATION

Ms. A is a 42-year-old woman who was first diagnosed with bipolar illness at age 23, when she was hospitalized with a manic episode shortly after her graduation from college. The patient's symptoms at that time included almost total insomnia, agitation, racing thoughts, grandiosity, and a mood that fluctuated between euphoria and irritability. She was treated with lithium, 600 mg t.i.d., in the hospital, which yielded a blood level of 0.9 meq/liter and caused remission of her acute symptoms.

When she was able to give an accurate past history, the patient stated that she had had depressive symptoms in childhood and adolescence, consisting of intermittent episodes of depressed mood, hypersomnia, hyperphagia, and decreased concentration. In addition, she had taken a small overdose of aspirin after breaking up with a boyfriend at age 16. However, she was ashamed of the overdose and concealed it, so that she received no treatment. The patients' family history was remarkable for a paternal grandfather who was alcoholic and had committed suicide and for untreated depressive symptoms in her mother.

After discharge, the patient continued to take lithium, although the dose was lowered to 600 mg b.i.d., yielding a blood level of 0.6 meq/liter. Side effects included a fine tremor and some difficulty retrieving words. She reacted to the diagnosis of bipolar disorder first with disbelief and then with self-deprecatory thoughts (e.g., wondering what she might have done to precipi-

tate the illness, etc.). However, she responded well to education and support and was consistently compliant with her treatment. She remained stable over the next 10 years, with the exception of occasional week-long periods of mild dysphoria and social withdrawal.

Ms. A maintained steady employment in the hotel industry. Although she established several long-term friendships with both men and women, she never married. She maintained a close relationship with her sister, brother-in-law, and nieces. When asked whether remaining single was distressing to her, she expressed some sense of loss. However, after considerable discussion, she declined the opportunity to enter more intensive therapy, stating that, except when she was clinically depressed, she was basically satisfied with her life situation. She said that her treatment goals were to learn as much as she could about her illness and to use the medication as effectively as possible to keep her mood swings under control so that she could work productively and enjoy her relationships with her friends and family.

After this extended period of stability, Ms. A began to develop more severe depressive episodes, interspersed with mild hypomanic episodes and periods of euthymia. During the hypomanic episodes, she experienced decreased hours of sleep and increased productivity. During the depressive episodes, which lasted for up to a month, she was unable to get out of bed and reported substantial suicidal ideation. Therefore, a series of antidepressants were added to the lithium. The first of these, imipramine, precipitated a manic episode that remitted with nighttime sedation and withdrawal of the antidepressant. Fluoxetine, venlafaxine, and bupropion all seemed to cause only temporary remission of depressive symptoms.

At this point, the patient's physician asked her to begin completing daily mood logs. An examination of these logs revealed that Ms. A was experiencing rapid cycling. Specifically, a mild hypomanic episode developed each time a new antidepressant medication was introduced or the dose was increased. During these episodes, which typically lasted about a week, the patient slept only 5 hours a night and experienced increased energy and social activity. These hypomanic episodes typically were followed by severe depressive episodes, lasting approximately 2 weeks, and occasional euthymic periods. In an attempt to decrease this rapid cycling, divalproex was added to the lithium. Divalproex was gradually increased to a dose of 1000 mg h.s., yielding a blood level of 70 mg/liter. However, this combination was still insufficient to control the patient's severe depressive episodes, so sertraline, 100 mg/day, was added. This regimen resulted in her reverting to a pattern of mood cycling characterized by mild hypomanic and depressive symptoms interspersed with periods of euthymia. With these symptoms, the patient was able to function at an acceptable, albeit not ideal, level.

The patient continued to take sertraline, lithium, and divalproex for approximately 3 years. During that time, in an attempt to minimize the patient's side effects, her medication regimen was altered so that she took all of her medication at bedtime. However, in addition to continued (although mild) symptoms, the patient complained of substantial weight gain and difficulty getting to work on time in the morning. The latter problem resulted from her inability to fall asleep until 1:00 or 2:00 a.m. and her difficulty awakening before 9:00 a.m.

Treatment Algorithms

This patient's care was consistent with the recommendations of several treatment guidelines and algorithms for patients with bipolar disorder (9–13). Monotherapy was used first; published clinical trials on the treatment of acute mania (e.g., references 21 and 22) used single medications only. However, many patients need combination therapy in the maintenance phase of treatment (8). For example, in the case of lithium monotherapy, approximately 60% of acutely manic patients respond initially, but only about half of these (or 30% of the original group) have sustained mood stability (1–4, 6). Unless the patient's clinical status is so acute as to necessitate more aggressive treatment, the decision to add a second medication is typically made after the first one has been used for a minimum of 4–8 weeks at an adequate dose, confirmed by therapeutic serum levels.

Because this patient experienced severe depressive episodes on lithium, an antidepressant was added to her medication regimen. Although controversy exists in the literature, the consensus among researchers and clinicians is that antidepressant medication can precipitate manic episodes and, therefore, that it is contraindicated to treat a bipolar patient with an antidepressant in the absence of a mood stabilizer. However, as this case demonstrates, antidepressant-induced manic episodes can occur even when the patient is treated with a mood stabilizer, although such episodes are generally less severe than spontaneous mania (23).

In addition to the risk that antidepressants might induce mania, Wehr and Goodwin (24) were the first to suggest that these medications could shorten the duration of bipolar cycles. This contention also remains controversial, but considerable anecdotal evidence and some research data exist to support it (25–28). Establishing a connection between antidepressant treatment and cycle acceleration is challenging for both the researcher and the clinician. As in this patient, the proximate result of antidepressant treatment is frequently remission of depressive symptoms; when the patient worsens weeks later, the possible connection between her relapse and the earlier change in treatment is difficult to establish. Prospective mood ratings can be very helpful in this regard, as well as in identifying mood variation temporally linked to the menstrual cycle.

Generally, one attempts to minimize the use of antidepressant medications in patients with bipolar disorder, especially in those whose cycles appear to be shortened by such treatment. However, as this case demonstrates, the elimination of antidepressant medication from a patient's regimen is not always possible, and the addition of a mood stabilizer sometimes, but not always, controls the patient's symptoms (27, 28). This patient is not unusual in that two mood stabilizers, as well as an antidepressant, were needed to minimize her mood cycling.

Few controlled studies have tested combinations of mood stabilizers, but a recent review (7) noted the frequent use of such regimens and supported their safety. In addition, several case series in which patients were followed longitudinally support both the limited efficacy of monotherapy and the clinical improvement that frequently occurs when multiple mood stabilizers are prescribed. Treatment algorithms for hypomania or mania all begin with monotherapy (lithium, carbamazepine, or divalproex); this first step is based on controlled studies. By the second step, all of the treatment guidelines and algorithms for bipolar disorder advocate the use of combination medications; here, the algorithms rely on a consensus among academic experts

and clinical practitioners because the relevant data are not available (29).

In trying to understand the clinical observation that many patients appear to do best on combination therapy, it has been suggested that the distinct therapeutic actions of different mood stabilizers may lead to synergistic physiological activity that complements their shared therapeutic effects (30, 31). For example, for some patients, the frequently used combination of lithium and divalproex is more efficacious than treatment with either of these agents alone. It has been suggested that the symptoms of bipolar disorder result from an inability to modulate neuronal excitation (30, 32). If this is true, then the synergistic effect of lithium and divalproex might result from the fact that lithium acts on the inositol phosphate second messenger system to stabilize neuronal excitability, while divalproex increases γ-aminobutyric acid (GABA)-ergic inhibitory activity (among other actions), thereby dampening aberrant neuronal excitation through a different physiological mechanism (30, 33).

The crucial point is that our patient progressed through an orderly sequence of treatments. This sequence began with monotherapy, followed by the addition of an antidepressant to treat severe depressive symptoms, the discontinuation of the antidepressant and addition of a second mood stabilizer because the antidepressant appeared to worsen the patient's cycling, and, finally, the reintroduction of an antidepressant because the combination of the two mood stabilizers did not control her depressive symptoms. Ideally, the clinician managing such a complex treatment regimen should make adjustments gradually, since clinical observations suggest that rapid discontinuation of medications can hasten relapse. Data addressing this point specifically are available for lithium (34–37), but there is anecdotal evidence that rapid and frequent changes in other mood-stabilizing and antidepressant medications may also have destabilizing effects in patients with bipolar disorder. A gradual, systematic approach to symptom management requires patience on the part of both patient and physician.

The Sleep-Wake Cycle

Although Ms. A appeared to be relatively stable for a number of years on a regimen of lithium, divalproex, and sertraline, it should be noted that she continued to have some degree of cycling and was not functioning optimally. Therefore, it might have been appropriate to consider medication adjustments sooner than was attempted. In addition, the role of supportive psychotherapeutic techniques in contributing to the mood stability of patients with bipolar illness is a neglected area that is now receiving more study (38, 39). The therapeutic technique developed by Frank et al. (39) is based in part on the hypothesis that stabilizing the sleep-wake cycle of patients with bipolar disorder will help to prevent relapse.

Indeed, like Ms. A, many patients with bipolar disorder have difficulty maintaining a stable and adaptive sleep-wake schedule. Ms. A's delayed schedule, in which both bedtime and awakening are shifted to later than normal, is not unusual in patients with severe bipolar illness. In particular, many patients with rapid cycling bipolar disorder (defined as four or more episodes of mania, hypomania, or depression in a year) complain about inability to get up in the morning (40). The reasons for this "phase delay" are unclear. Since humans have an endogenous circadian period that is somewhat longer than 24 hours (41), individuals who are not forced to awaken at a specific time each morning tend gradually to shift their bed and awakening times later. Patients with severe bipolar illness may be less likely than normal subjects to have stable employment and, therefore, may tend to follow a "weekend" schedule all week long. Medication effects may also be relevant, since lithium appears to delay the timing of both melatonin secretion and activity in rodents (42, 43). In addition, patients with rapid cycling bipolar disorder tend to have diurnal variation in the direction of their mood switches, so that they generally switch "up" into hypomania between when they awaken in the morning and when they go to sleep at night (while typically switching "down" into depression between bedtime and awakening the next morning) (44). Unfortunately, this means that patients may be feeling most energized at precisely the time when they should be retiring for the night.

Whatever its cause, a schedule that is phase-delayed (shifted later) can be problematic for patients with daytime jobs. In addition, it may contribute to the persistent depressive symptoms that are seen in many patients with rapid cycling bipolar disorder, since there is evidence that sleeping in the morning hours may increase the probability that the patient will be depressed, while wakefulness at that time can have antidepressant effects (19, 45). To minimize the phase delay, it can be helpful to advise patients to avoid physical exercise and exposure to bright light in the evening hours (both of which exacerbate a delayed sleep-wake schedule [46, 47]) and not to undertake cognitively arousing activities in the evening. Exercise and bright light in the morning can be potent phase-advancing techniques, but the safety of the latter in patients with rapid cycling bipolar disorder is unclear (48).

After approximately 3 years of treatment with sertraline, lithium, and divalproex, the patient began once again to experience depressive episodes severe enough to hamper her performance at work. At this point, the decision was made to add lamotrigine to her regimen in an attempt to treat her depressive symptoms without increasing her mood cycling. The dose of lamotrigine was gradually increased to 200 mg/day. This intervention was successful in once again reducing her depressive symptoms to intermittent, brief episodes of mild dysphoria and fatigue.

The patient was then transferred to a job that necessitated her working occasional evening and night shifts in the hotel. On days when she worked late shifts, she typically became hypomanic and was unable to sleep when she arrived home. After several days of little sleep, she would finally "crash," sleep excessively, and wake up depressed, only to resume the pattern after she once again became sleep-deprived. Despite the adverse effects of this irregular schedule, the patient was reluctant to give up her new position, since it represented an advancement opportunity for her. Therefore, an attempt was made to manage the increased cycling, first by withdrawing the sertraline and then by adding olanzapine at bedtime. Unfortunately, these interventions were insufficient to control her symptoms, and, eventually, with the help of a letter from her psychiatrist, the patient's employer allowed her to retain her new position without being required to work irregular shifts. Once her sleep-wake schedule was regularized, her mood cycling diminished. She was able to withdraw from olanzapine and, with her psychiatrist, was beginning to consider tapering her lithium dose.

DISCUSSION

Several open trials and case series (49–52), as well as a recent double-blind, placebo-controlled trial (53) provide preliminary evidence that lamotrigine, an anticonvulsant approved for use in epilepsy, may be an effective treatment for bipolar depression and/or for rapid cycling bipolar disorder. A mood-stabilizing medication with potent antidepressant properties would be a particularly welcome addition to the therapeutic armamentarium, since lithium, divalproex, and carbamazepine all appear to be more reliable antimanic than antidepressant agents (54–56). However, further studies are needed to define the range of psychotropic efficacy of lamotrigine and the other new anticonvulsant medications.

When clinicians prescribe lamotrigine, it is critical that the initial escalation of dose be slow, since there is a greater risk of rash when the medication is given more quickly than the recommended dose escalation during the first 8 weeks (55). At the recommended rate of dose escalation, the risk of rash in adults is approximately 10% for allergic rashes and 0.1% for Stevens-Johnson syndrome or toxic epidermal necrosis (57). Since the risk of rash is significantly higher in children, lamotrigine is contraindicated in children under 16 years of age (57; 1999 edition of *Physician's Desk Reference*). The risk of rash may also be increased by combination therapy with divalproex (which slows the metabolism of lamotrigine) and decreased by the administration of carbamazepine (which accelerates it) (57). When lamotrigine is not given in combination with other anticonvulsants, the recommended regimen is 25 mg/day for 2 weeks, followed by 50 mg for 2 weeks, followed by 100 mg for 2 weeks and 150 mg for 2 weeks (1999 edition of *Physician's Desk Reference*). Recommended dosing strategies for combination therapies with lamotrigine may also be found in the 1999 edition of *Physician's Desk Reference*.

Several other anticonvulsants approved for the treatment of epilepsy are currently being evaluated as possible mood stabilizers. For example, case reports and reports of series of patients treated with gabapentin indicate that it may have antimanic as well as antidepressant properties and may be helpful for both sleep disruption and anxiety (e.g., references 58–61). Because it is excreted by the kidney without first being metabolized by the liver, gabapentin does not have problematic drug-drug interactions, and it is generally well tolerated if introduced slowly, i.e., starting at 200–300 mg/day and increasing in 100–300 mg/day increments (62). However, the efficacy of gabapentin in bipolar illness has not been established in a placebo-controlled trial, and a recent double-blind add-on trial (63) failed to demonstrate a significant effect on manic or hypomanic symptoms. Other anticonvulsants include topiramate, whose mood-stabilizing properties are currently being studied; its apparent side effect of weight loss may be helpful to patients taking agents that cause weight gain (64, 65). Thus, several new anticonvulsant medications are under study for the treatment of bipolar disorder. It will be important for researchers to define the unique clinical properties of each agent, so that its appropriate role in the treatment of bipolar illness can be defined.

Although the risk of tardive dyskinesia has caused the use of typical antipsychotics to fall increasingly into disfavor in the treatment of patients with bipolar disorder, the advent of atypical antipsychotics has added a new class of medications to the treatment armamentarium. In several open studies and a few controlled studies, clozapine and risperidone have shown promise as mood-stabilizing agents in some patients. Clozapine, in particular, has shown significant mood-stabilizing capability in patients with bipolar disorder (66). One randomized trial in patients with treatment-resistant bipolar disorder (67) found that adding clozapine was associated with significant improvement over 1 year. Open, naturalistic data indicate that risperidone may have mood-stabilizing properties, although some case series found a greater risk of mania when the medication was used as monotherapy in relatively high doses (e.g., 6–8 mg/day) (for a review, see Keck et al. [68] or Frye et al. [66]). This issue is currently being evaluated in blinded, controlled clinical trials. In addition, data are accumulating that olanzapine may have mood-stabilizing properties apart from its antipsychotic efficacy (for a review, see Keck et al. [68]). In a recent placebo-controlled trial (69), olanzapine treated acute mania effectively, regardless of whether the patient had psychotic symptoms. Other new atypical antipsychotic medications, including quetiapine and ziprazidone, are also being evaluated for potential utility in the treatment of bipolar illness (70). Thus, the role of atypical antipsychotic medication in the treatment of bipolar illness is currently being addressed in controlled studies and treatment guideline research. At the current time, although atypical antipsychotic medications cannot be considered first-line treatment in bipolar disorder, it is reasonable to consider their use, either alone or in conjunction with mood stabilizers, in patients with continued breakthrough cycling.

As in the case of Ms. A, patients with brittle bipolar illness are frequently unable to tolerate work schedules that include rotating shifts; they may even become hypomanic or manic after a single night of sleep deprivation. Recent data (71) indicate that, in outpatients, disrupted sleep secondary to psychosocial stressors is a common precipitant of manic episodes. Such disrupted sleep schedules may occur in the context of jet lag, school examinations, and in the postpartum period; indeed, it is possible that postpartum sleep disruption contributes to the high rate of relapse in women with bipolar disorder during that time (72). Acute sleep disruption, and the instability that results from it, can frequently respond to the short-term use of sedative medication. As in the case of Ms. A, however, chronic sleep disruption often requires a life-style intervention that allows the patient to maintain a stable sleep-wake cycle, once again reinforcing the principle that optimal medication management may be necessary but not sufficient to achieve mood stability in a patient with severe bipolar disorder.

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