

Difficulties in Diagnosis and Management of Bipolar Disorder: Three Case Presentations

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© Bipolar disorder is associated with significant problems in patient management, including misdiagnosis, noncompliance, and comorbid substance use disorders. This article describes strategies for the management of difficult cases, with particular emphasis on the choice of therapeutic agents, such as mood stabilizers and atypical antipsychotics, for optimal control of symptoms and psychosocial interventions for reinforcement of therapeutic interventions. Special attention is given to the relationship between bipolar disorder and substance use disorders.

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Bipolar disorder is well known among clinicians as an illness associated with many problems in patient management. One of these problems is noncompliance with treatment. As Goodwin and Jamison¹ and Jamison et al.² have pointed out, for every patient who follows the prescribed treatment regimen, there is at least one who does not, either by taking too much or too little medication or by refusing to cooperate at all. The consequences of noncompliance are roughly equivalent to those of untreated or inadequately treated bipolar disorder—recurrent, intense episodes accompanied by personal chaos, substance use, hospitalization, social disruption, and even violence and suicide. Fortunately, noncompliance can be reversed through patient education and psychotherapy. The careful choice of therapeutic agents also plays a role in limiting noncompliance by effectively intervening in patients' symptoms.

NONCOMPLIANCE

Patients have many reasons for failing to comply with prescribed medication regimens. One study by Jamison et al.² identified the reasons patients with bipolar disorder gave for their noncompliance and compared them with the reasons clinicians considered most important. Patients cited their dislike of having their moods controlled by medication, feeling depressed, and the side effects of

medication as the most important reasons for their noncompliance. Clinicians felt that bipolar patients stopped taking their medication because they felt well and saw no need to continue and because they missed the highs of hypomania. Both patients and clinicians agreed that a common reason for noncompliance was the patients' refusal to accept the chronic nature of their illness.

The many issues impinging on compliance with therapy are most clearly seen in direct clinical practice. The following example of long-term outpatient therapy with a young woman diagnosed with bipolar disorder illustrates some of the difficulties clinicians routinely face in their management of patients whose compliance is erratic. This particular case is one whose course has been punctuated by repeated episodes of noncompliance precipitated by side effects and the patient's wish to deny the chronic nature of the disease.

A Noncompliant Patient

Ms. A was a 21-year-old white student living at home while attending a local college when her parents first brought her in for treatment. They described her behavior as falling somewhere between manic and hypomanic, and they were especially concerned about her indiscriminate sexual behavior over the past 2 to 3 months. By her own account, Ms. A's symptoms had included little or no sleep for 2 weeks, racing thoughts, an inability to concentrate on schoolwork, and markedly deteriorating performance in school. The patient seemed unconcerned about her situation and thought that her parents were overreacting. While she showed no psychotic symptoms, Ms. A demonstrated some grandiosity and poor judgment, stating that the reason she was not doing well in school was that she was so smart she could do well without studying. The deterioration in her school performance suggested that this clearly was not the case.

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Ms. A's parents were unusually conscientious about bringing their daughter in for evaluation because they had a strong family history of bipolar disorder: Ms. A's maternal grandfather had had bipolar disorder, as had an aunt living in the same city, who had been in and out of hospitals for many years. Because of their experience with the disorder, the parents recognized the symptoms of a manic episode and realized that immediate intervention was desirable, even though the patient herself saw no reason for concern and did not think she needed treatment. As it happened, the patient was entirely dependent on her parents, despite her age; she lived with and was supported financially by them. The parents were therefore able to put a good deal of effective pressure on Ms. A to agree to take medication and follow through with treatment, whether she thought she needed it or not.

Initial course of treatment. Neither the patient nor her parents wanted her to be hospitalized, although her symptoms warranted such an intervention. Thus, the initial treatment plan was to try to manage her manic symptoms on an outpatient basis. Although Ms. A refused to believe that there was anything wrong with her, she did agree from the start to take medication because she remembered clearly how disruptive the disorder had been in her aunt's life. She had always identified with her aunt and wanted to avoid a similar experience.

The initial treatment regimen, including lithium (starting at 300 mg t.i.d., titrated to 600 mg b.i.d.) and clonazepam (1 mg h.s.), addressed the presenting symptoms of agitation and sleep deprivation. The patient responded well enough to the combination that the clonazepam dose was tapered after about 4 weeks. She remained stable on lithium treatment for about 6 months. Unfortunately, over that 6-month period Ms. A gained weight, a lithium-related side effect she found extremely upsetting. Despite extensive nutritional consultation on diet and exercise, beginning when the weight gain first became apparent, Ms. A continued to gain weight until she had put on 25 lb (11 kg). She was very unhappy with the weight gain and began to comply only intermittently with her medication. Not surprisingly, hypomanic symptoms recurred.

Management issues. The case of Ms. A illustrates 2 of the reasons patients give as most important for their failure to comply with treatment for bipolar disorder: their dislike of having a chronic disorder and their irritation with the side effects of medication.¹ Ms. A was only 21 years old when she had her first manic episode, and her life until then had been mostly successful. It was very difficult to convince her not only that she had a mental disorder for which she was going to have to take medicine but also that she was very possibly going to have to take it for the rest of her life. She appeared able to accept the situation at first, but the weight gain undermined her tolerance. From that point on, she became thoroughly disenchanted with lithium.

Treatment options. Finding an effective substitute for lithium that would not cause weight gain proved to be a challenge in this case. Five possible options were identified:

1. switch to valproate,
2. add a second mood-stabilizing agent in order to lower the dose of lithium,
3. switch to an atypical antipsychotic agent,
4. switch to carbamazepine, and
5. add topiramate.

Discussion. The first option, switching to valproate, is not recommended in a case like this because, like lithium, valproate can cause weight gain. The second option, adding a mood stabilizer in order to lower the lithium dose and so limit the risk of weight gain, will work only if weight gain is a dose-dependent phenomenon, which is not always the case. Switching to an atypical antipsychotic, option number 3, is possible even when there are no psychotic symptoms, because antipsychotics can have a prophylactic effect as well as a mood-stabilizing one. Unfortunately, several of the atypical antipsychotics, such as olanzapine and clozapine, also cause weight gain. Although option 4, switching to carbamazepine, is a reasonable option, carbamazepine has complex drug-drug interactions and can cause a number of unacceptable adverse events, including skin rash, blood dyscrasias, and somnolence. Thus, its usefulness is limited in cases in which noncompliance is likely. The most appropriate choice for this patient is therefore the fifth one—adding topiramate (100 mg b.i.d.)—always bearing in mind that topiramate should only be given to a woman who does not want or intend to get pregnant while taking it. Topiramate has been shown to cause weight loss and may have additive mood-stabilizing properties as well.

Update. Ms. A is now about 26 years old, married, and doing fairly well. Consistently, though, she has tried to stop taking her medication whenever she feels things are going well, on the grounds that “everything is fine; I’m okay, so what do I need medication for?” Her current medication regimen consists of gabapentin (600 mg t.i.d.). She has taken gabapentin successfully for over a year without any manic episodes, even though it is intended for use in conjunction with another agent and is not generally used as a first-line mood stabilizer. She is very pleased with the medication and that, of course, is the best reason to hope she will continue to comply with therapy.

BIPOLAR DISORDER AND SUBSTANCE ABUSE

The relationship between bipolar disorder and substance use has been of interest to clinicians and researchers for some time. Feinman and Dunner³ have discussed this complex and common relationship. The National In-

stitute of Mental Health Epidemiologic Catchment Area (ECA) study reported in 1990 that in the United States, 37% of people with an alcohol disorder also had a mental disorder and that 53% of people who reported a non-alcohol drug disorder also had a mental disorder.⁴ In the ECA study, bipolar disorder was more likely than any other psychiatric disorder to co-occur with substance use, and that finding has since been replicated a number of times.⁵⁻¹⁰ As Brady and Sonne⁵ have pointed out, for example, 6 of 20 patients hospitalized with bipolar disorder also met the diagnostic criteria for drug or alcohol abuse, and more than half of all people with bipolar disorder have a substance use disorder at some point in their lives.

A number of theories exist to explain the strong association between substance use and bipolar disorder; these were reviewed in detail by Sonne and Brady in 1999.⁶ Some of these theories suggest that patients use drugs and/or alcohol as a form of self-medication or that substance use unmasks previously undetected affective instability. While acknowledging that the relationship between the disorders will always be complex and intricate, the authors observed that the course of bipolar disorder is inevitably adversely affected by substance use, particularly by precipitating states of mixed mania and increasing the number of hospitalizations. The diagnosis of bipolar disorder is also made more difficult by co-occurring substance use because, as Brady and Lydiard⁸ and others^{6,7} have noted, the effects of chronic drug and alcohol use can mimic nearly any psychiatric disorder.

Most experts agree that the most troubling consequence of coexisting bipolar disorder and substance use is the negative impact of the substance use on the clinical course of the bipolar disorder. Feinman and Dunner³ found that substance use can worsen the course of bipolar disorder, as demonstrated in higher rates of suicide and panic attacks among patients with both disorders. The authors also noted that patients with both bipolar and substance use disorders are more likely to be rapid cyclers, perhaps because of the long-term effects of drugs on the duration of the cycles. Describing a small study based on patient self-reporting, Sonne and colleagues¹¹ found that people with bipolar disorder complicated by substance use have a worse course of illness than most, with earlier onset of mood disorder and more irritable and dysphoric mood states than patients with only one of the disorders. Such patients are twice as likely to experience more rapid mood swings and to require significantly more hospitalizations.

The difficulties associated with treating patients whose bipolar disorder is exacerbated and complicated by chronic or episodic substance use are clearly demonstrated in clinical practice. The following account of a challenging patient with concomitant bipolar and substance use disorders illustrates many of the difficulties associated with the care of these dually diagnosed patients.

A Substance-Abusing Patient

Mr. B is a 36-year-old white man who works as a house painter, although his employment has been sporadic over the past 5 years. He was admitted to an inpatient unit while in a mixed manic episode characterized by agitation complaining that the devil had been talking to him about all the bad things he had done in his life. He also complained of sleeplessness for a week, racing thoughts, and suicidal ideation. At admission, his urine drug screen tested positive for marijuana. He had been drinking to excess for some time and had been noncompliant with his medications, which at the time were valproate and a conventional neuroleptic. His chart indicated that he was non-responsive to lithium, although it was not clear whether this meant that he was truly nonresponsive or simply so noncompliant that psychiatrists had stopped prescribing it for him.

Mr. B's substance use history began around the age of 15 or 16, when he started to drink and to experiment seriously with marijuana, cocaine, and hallucinogens. Although he had no family history of affective disorder, he did have a strong family history of alcoholism. By age 28, he met DSM-IV criteria for alcohol dependence with escalating dose tolerance and withdrawal symptoms,¹² and he was probably polysubstance-dependent well before he had his first diagnosed affective episode at age 18. The complexities of the relationship between substance use and first-episode mania have been studied by Strakowski and fellow researchers¹⁰ and are clearly seen in Mr. B's case. It seems likely that Mr. B's early drug and alcohol use interacted with an innate vulnerability to affective disorder to trigger full-blown disease, consistent with Strakowski and colleagues'¹⁰ finding that a subgroup of patients exists in whom alcohol abuse is necessary to precipitate affective disorder.

Since his first episode of bipolar disorder, Mr. B has been hospitalized about 10 times. As Goldberg et al.⁷ have observed, a history of multiple hospital admissions is typical of the bipolar substance user, whose substance use interferes with the ability to maintain remission. Each of Mr. B's admissions was precipitated by episodes of mixed mania, and he also has experienced several severe episodes of suicidal depression. Every hospitalization followed a period of noncompliance with prescribed therapy as well, and each was preceded by periods of binge drinking or drug taking, sometimes with cocaine or marijuana, always with alcohol. Mr. B has never demonstrated any particular interest in abstaining from substance use. It is entirely possible that the only times he has abstained since first beginning to use drugs and alcohol as a teenager have coincided with his periods of hospitalization. While in the hospital, Mr. B invariably has a good response to valproate (1000 mg b.i.d.), which has the double benefit of stabilizing his mood by controlling affect and making his withdrawal from drugs and alcohol more comfortable. This

dual effect on withdrawal symptoms as well as mood has been noted by Brady et al.¹³

Management issues. As all experienced clinicians know from firsthand experience, substance-using bipolar patients are the most challenging patients to deal with. No single answer exists for all cases. The best we can hope for is to come up with an effective therapy through trial and error. There are, however, some useful rules of thumb that we can all follow.

- Lithium is rarely useful for substance-using bipolar patients because they tend to be both forgetful and noncompliant. This is the kind of patient who says, "Oh, I missed my dose yesterday, so I think I'll take double today to make up for it." The therapeutic window for lithium is far too narrow to allow for such unpredictable dosing.
- Lithium is also problematic in this population because bipolar substance users tend to be impulsive and careless, given to spontaneous overdoses while intoxicated.
- Valproate is a useful therapy in bipolar patients who abuse alcohol, provided their liver function test (LFT) results are no greater than twice normal.
- Even more important than LFT results in alcoholic patients who take valproate is the platelet count, because alcohol and valproate both decrease the platelet count.

Treatment options. A reasonable selection of therapy options for Mr. B, in the hospital and stabilized on valproate treatment, would include the following:

1. switch to carbamazepine,
2. switch to an atypical antipsychotic,
3. add a second mood-stabilizing agent,
4. switch to a depot neuroleptic, and
5. use psychosocial interventions targeting compliance.

Discussion. Option 1, carbamazepine, is rarely a preferable remedy for bipolar patients. Carbamazepine has not been approved for the treatment of mania, and carbamazepine has significant side effects on the liver, platelet count, and cytochrome P450 isoenzyme 3A4. As Nemeroff¹⁴ reminded us recently, carbamazepine is not necessarily effective in bipolar patients. All in all, carbamazepine is not a good choice in this case. Option 2, an atypical antipsychotic such as risperidone or olanzapine, is probably a good choice for a patient like Mr. B, who is unlikely ever to be successfully treated with a single agent. Although option 3, the addition of a second mood stabilizer, is not likely to prove effective with a noncompliant patient like Mr. B, option 4, the depot neuroleptic, may well prove to be helpful in such a noncompliant bipolar patient.

Psychosocial interventions. Option 5 represents the implementation of a customized set of psychosocial inter-

ventions that are essential if noncompliant patients like Mr. B are to continue their treatment outside a hospital. In this case, the simultaneous targets of the approach were the patient's noncompliance and his substance use: Mr. B needed specialized treatment for his substance use disorder, and he also needed constant reinforcement and encouragement to comply with his medication regimen. The hallmark of this approach is the recruitment of any and all resources in a patient's environment that might help or induce the patient to comply—including such strategies as using financial inducements and supportive housing designed for the mentally ill to compel adherence to the treatment plan.

NONCOMPLIANCE COMPLICATED BY MISDIAGNOSIS

Bipolar disorder is misdiagnosed quite often, chiefly because clinicians find it difficult to differentiate the symptoms of mania from the symptoms of schizophrenia or schizoaffective disorder, as Goodwin and Jamison¹ have pointed out. The symptoms of bipolar disorder frequently mimic those of other disorders, including schizophrenia. Diagnostic errors may occur because both bipolar disorder and schizophrenia share a number of symptoms, including delusions, incoherence, inappropriate flat affect, and hallucinations of various types, as noted by Evans.¹⁵ Such a confusing symptom picture is made more so by the further complication of substance use.

Misdiagnosis generally leads to missed opportunities for early therapeutic intervention. The following account, a striking example of such a situation, shows how difficult it can be to pinpoint the symptoms of bipolar disorder when they have been blurred by substance use. The added challenge of managing such a patient in the face of chronic noncompliance makes the clinician's task that much more difficult.

A Misdiagnosed Patient

Mr. C, a 42-year-old African American construction worker, has a 20-year history of psychiatric hospitalizations. His first admission took place when he was 21; he presented with symptoms of psychosis that included delusions, paranoid thinking, sleeplessness, agitation, and aggression. Although his urine tested positive for marijuana, Mr. C denied drug use. During this first hospitalization, Mr. C responded well to treatment with haloperidol and benzodiazepines. His symptoms resolved fairly rapidly, and he was able to return to his job.

Mr. C remained stable for 3 years after this first hospitalization, despite discontinuing his medication soon after discharge and never appearing for outpatient follow-up. During this period, he maintained his work and got married. At age 24, he was readmitted to the hospital with symptoms similar to those seen at the first admission. On

this occasion, his urine tested positive for both marijuana and cocaine, and this time Mr. C acknowledged that he had been using drugs and alcohol for many years, with a sharp escalation during the previous 2 months. Once again, he stabilized quickly on antipsychotic and benzodiazepine therapy.

Over the next 10 years, Mr. C was hospitalized 8 times with psychosis, and each time, his urine tested positive for cocaine and/or marijuana. With each readmission, his stays became longer and his symptoms resolved less and less completely. He lost his job and went on disability. Consistently, the diagnosis was schizophrenia and substance abuse, and repeated attempts to address the substance abuse proved unsuccessful.

In 1994, Mr. C attempted suicide and was admitted to the hospital, severely depressed and with only minimal psychotic features. His urine tested negative for all drugs, and he acknowledged that he had been feeling so depressed that he did not even feel like taking drugs. On this occasion, Mr. C was treated with both an antipsychotic and an antidepressant, and it took several months for his mood to return to baseline. He remained drug-free for an entire year. In 1995, he was readmitted following a period of noncompliance with medication. He was once again psychotic, with frank manic symptoms. He was grandiose, euphoric, and talkative and showed flight of ideas. His urine tested positive for cocaine. On this occasion, treatment with an antipsychotic and benzodiazepines for 7 days failed to resolve the manic symptoms. A diagnosis of bipolar disorder was made.

At discharge, Mr. C was placed on a depot antipsychotic and an anticonvulsant mood stabilizer. Since then, he has been readmitted 3 times, in both manic and depressive states. He has been consistently noncompliant with his mood-stabilizing medication and continues to test positive for drugs.

Management issues. At this point, Mr. C is an extraordinarily difficult patient to manage because of his persistent noncompliance and his constant substance use. While it seems clear now that the correct diagnosis is bipolar disorder, the patient spent at least 10 years being treated with depot neuroleptic medication on the assumption that he had schizophrenia, even though he continued to have breakthrough manic episodes throughout. In retrospect, it is apparent that neuroleptic medication was inadequate to manage Mr. C's symptoms, although it is possible that the use of depot neuroleptics reduced the number of hospitalizations he needed over the 10-year period. On the basis of his history, it seems likely that, left to his own devices, Mr. C would wind up completely unmedicated, except for those occasions when he was hospitalized. In cases of extreme noncompliance like this, it is sometimes better to settle for a suboptimal treatment regimen on the grounds that some treatment is better than no treatment at all.

Treatment options. The best course of treatment for Mr. C at this point would include both pharmacologic and psychosocial interventions. The preferred pharmacologic management would include the following:

1. discontinue antipsychotic medication,
2. initiate therapy with a benzodiazepine and a mood stabilizer, and
3. reschedule dosing of mood-stabilizing medication to limit noncompliance.

Discussion. Mr. C most likely has bipolar disorder, not schizophrenia, so he may be able to respond to a mood stabilizer without maintenance antipsychotic therapy. However, if noncompliance remains an issue despite clinical intervention, depot antipsychotics should be reconsidered. The combination of a benzodiazepine (e.g., clonazepam, lorazepam) and a mood stabilizer (e.g., topiramate, valproate) is suitable for bipolar disorder, although compliance may depend on the extent to which Mr. C experiences side effects. Adjusting dosing regimens—giving the entire daily dose at bedtime, for instance—can sometimes be helpful in this regard.

Benzodiazepines must be used with caution in substance-using patients because of their potential for abuse. Careful monitoring of prescriptions is necessary, and clinicians should avoid those benzodiazepines known to have high potential for abuse, such as alprazolam and diazepam.

Additional concerns. In Mr. C's case, aggressive psychosocial management is essential. Possible interventions include

1. psychotherapy focused on coping skills,
2. family therapy geared to identifying enabling behaviors on the part of Mr. C's family,
3. aggressive treatment of the substance use disorder, including withholding disability payments unless urine tests negative for drugs, and
4. placement in a long-term residential treatment program for mentally ill chemical abusers.

PSYCHIATRY'S MOST CHALLENGING PATIENTS

The clinical management of difficult patients is a given for every clinician's practice. As the 2 patients just described clearly demonstrate, the combination of well-established bipolar disorder and substance use in a noncompliant patient may well be the most challenging task any clinician will ever face in practice. First, diagnostic confusion is common, and symptom overlap between bipolar disorder and substance use disorder all too frequently leads to misdiagnosis. In addition, it is rarely possible to decide with any certainty which came first,

substance use or bipolar disorder. It is entirely possible, as Sonne and Brady⁶ have pointed out, that bipolar disorder makes individuals more vulnerable to the development of a substance use disorder. At the same time, it is equally possible that patients self-medicate their bipolar disorder with drugs and/or alcohol. Cocaine users, for instance, may try to treat their depression by eliciting hypomania, whereas alcohol or sedative use may represent an attempt to control racing thoughts or treat insomnia.

Fortunately, more therapeutic agents are becoming available to treat complex cases like the 3 outlined in this article. In addition to traditional agents like lithium, which is most effective in classic mania,⁶ several relatively new anticonvulsants with more favorable side effect profiles (such as topiramate, lamotrigine, and gabapentin⁶) are available for use in the treatment of bipolar disorder. At the same time, mood stabilization may improve the clinical course of substance-using patients. These increased therapeutic options for managing complex cases, particularly the dual diagnosis of bipolar disorder and substance use disorder, go a long way toward achieving our ultimate goal of safe and effective therapy for our most demanding patients.

Drug names: alprazolam (Xanax and others), carbamazepine (Tegretol and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), diazepam (Valium and others), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal), topiramate (Topamax).

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