Clincian Interview

Complexities of Bipolar Disorder

Interview with Charles B. Nemeroff, MD, PhD

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A senior clinical editor for Advanced Studies in Medicine (ASiM) interviewed Dr Nemeroff to discuss the complexities of bipolar disorder and important considerations in the differential diagnosis of unipolar depression and bipolar depression. Dr Nemeroff also stresses the importance of understanding the psychiatric and medical comorbidities that often occur in bipolar disorder.

ASiM: Bipolar disorder has generated a great deal of interest and it seems that such a complex illness has generated even more complex treatment approaches. Why do you think this is so?

Dr Nemeroff: Bipolar disorder is a complex disorder, more so than the other disorders that we treat. In bipolar disorder there are alterations in mood in both directions. Thus, unlike in depression, in which the goal is to ameliorate depression and attain euthymia, in bipolar disorder you are dealing with depression and mania, or in the mixed state, with rapid cycling. Consequently, there is always the issue of patients becoming too high, hypomanic or manic, or too low (ie, clinically depressed). As far as depression is concerned, certain treatments, particularly the older antidepressants, often actually push patients into mania. This is one of the reasons why this disease invariably requires multiple drug therapy. There are very few patients that respond to mood stabilizer monotherapy. The ideal outcome would be to modify their very wide mood swings, so that they are abbreviated in magnitude, leading to mood swings similar to that of normal individuals. This is really what a mood stabilizer should ideally do. There are patients treated with lithium monotherapy, although few in number, that actually do have this almost miraculous response and go from severe bipolar I disorder to being rendered euthymic (ie, their depressive episodes and their manic episodes disappear when they are treated).

Unfortunately, most patients do not respond to a single mood stabilizer. Therefore, they require rational polypharmacy, and there is very little literature to help support clinical practice here. There are certainly treatments that are effective in acute mania and there are treatments that are effective in treating bipolar depression, but considering the number of mood stabilizers available, particularly if you include atypical antipsychotics, there is not a lot of evidence-based medicine to help guide practice in this area. There are also a number of variants of this disorder. Bipolar II disorder clearly is different from bipolar I disorder, and treatment is often fundamentally different. With bipolar II, you don’t have to worry as much about patients switching into mania. In addition, there is a spectrum of bipolarity that goes from cyclothymia—characterized by greater than normal variability in mood, with patients experiencing hypomanic and mild depression for which there are virtually no data on treatment—to the other end of the spectrum, which is severe bipolar I disorder characterized by severe manic depressive episodes and several clinical presentations in between. We also know little regarding the response of subtypes of bipolar I disorder. We do know quite a bit about mixed bipolar disorder and rapid cycling responding...
differently than, for example, euphoric mania. Furthermore, bipolar depression by its very nature tends to be treatment refractory, which is a complex issue in the management of bipolar disorder.

ASiM: Because of the layers of complexity or the variation in presentation, do you think that clinicians understand the distinction between bipolar I and bipolar II?

*Dr. Nemeroff:* I think bipolar I disorder is less confusing than bipolar II disorder to most psychiatrists. I think we need to be clear about the fact that very few nonpsychiatrists are comfortable treating bipolar disorder, in part because mania is a frightening entity to treat. The distinction between bipolar I and bipolar II disorder is based largely on the magnitude of the manic severity because patients with bipolar I and II disorders have the same form of depressions. Bipolar II manias are never full manias; they are hypomanias. There is not a great deal of literature on the treatment of bipolar II disorder. There are only a few clinical trials. Sometimes bipolar I and II disorder patients are placed together in a trial, but in terms of separate trials for bipolar II disorder, there are relatively few. There is still controversy in the field regarding whether a switch from bipolar II to bipolar I disorder occurs after treatment with antidepressants or ingestion of drugs of abuse, such as stimulants. I personally don't think that you can convert someone with bipolar II disorder to bipolar I, but there are respected investigators who think this does occur.

ASiM: In comparing hypomania versus mania, would you treat them in the same fashion?

*Dr. Nemeroff:* A manic episode is a medical emergency. It is a clinical state in which patients most often need to be hospitalized and prevented from harming themselves or harming someone else. Hypomania is, in contrast, a clinical state that rarely is the presenting symptom. For example, patients who are hypomanic feel good. The people around them may be uncomfortable because they are excessive (eg, they may spend too much money). However, many hypomanic individuals are in positions, in business or in some other profession, in which the hypomania renders them extraordinarily productive and they actually do quite well at least for some time. Patients with bipolar II disorder never seek treatment to reduce their hypomania. Patients with bipolar II come to treatment only when they are depressed, and one of the first points they will make to you is, “don’t take my hypomania away, I just want you to treat my depression.”

ASiM: However, if you are seeing a patient with bipolar II and you are treating him for depression and he goes into a hypomanic phase, would you treat it the same way as someone with a full-blown mania (ie, would you treat it with similar pharmacologic approaches)?

*Dr. Nemeroff:* Again, there are little data on the treatment of hypomania. In theory, mood stabilizers, certain of the anticonvulsants, and some of the atypical antipsychotics appear to be effective in the treatment of hypomania. However, there are actually very little data to speak to this issue.

ASiM: Recently, the depressive phase has come more to the fore and it has been neglected somewhat in research and case reports. What change has made it more pronounced in the last couple of years?

*Dr. Nemeroff:* First, we are very good at treating acute mania. It is very unusual to see patients with mania who don’t respond to treatment, particularly when in an inpatient setting. With a combination of atypical antipsychotics, mood stabilizers, or benzodiazepines, one can effectively treat even the most severe manic episodes. It may take a few days to accomplish a significant reduction in symptoms, but it is usually attainable. Bipolar depression is the phase of the disorder during which most illness time is spent. If you plotted the percentage of time that patients with bipolar disorder I or II are ill, most patients are in the bipolar depression phase, not in the bipolar manic phase. This is particularly true of women when compared to men. In light of the high suicide rate (25% of patients with bipolar disorder will attempt suicide and mostly during episodes of bipolar depression), this phase of the illness is deservedly receiving a lot of attention. These episodes tend to be long and unrelenting. Many patients with bipolar depression do not respond to conventional antidepressant therapy. Some in the field consider it, by definition, a treatment-refractory depression. It is characterized by symptoms of atypical depression. Approximately 15% to 20% of patients with unipolar depression have atypical depression, which includes symptoms of hypersomnia, overwhelming fatigue, and so-called “lead limb paralysis.” This is the subtype of depression that patients with
bipolar disorder typically experience and, not infrequently, one episode can last 1 year or longer. These patients are at high risk for suicide.

**ASiM:** How can clinicians best differentiate between unipolar and bipolar depression and are there clear guidelines to help in the assessment?

**Dr Nemeroff:** Whenever a patient is diagnosed with unipolar depression, the clinician must ask if this is a patient who may be bipolar but hasn’t yet had his or her first manic episode. Two follow-up studies—one by Jules Angst, MD, many years ago in Zurich, Switzerland, and another more recent study by Joseph Goldberg, MD, at Cornell in New York City—showed that a very sizable percentage of patients who were first diagnosed with unipolar depression go on to have their diagnosis eventually changed to bipolar disorder because they experience a manic or hypomanic episode.

**ASiM:** Therefore, it should be foremost in your differential diagnosis?

**Dr Nemeroff:** Absolutely. The question is what would heighten your concern or your suspicion of bipolarity in someone who you see with a diagnosis of major depression? First and foremost is family history. If a patient has a first-degree blood relative with bipolar disorder, one should have a very high suspicion of bipolarity. Second is early age of onset. A substantial percentage of children and adolescents who have their first episode of depression early in life will, in fact, turn out to be bipolar. A much higher percentage of children with depression will end up having bipolar disorder than adults with their first episode of depression because bipolar depression typically has an earlier age of onset compared to unipolar depression.

**ASiM:** Are there guidelines available to help the clinician? I know there was a study group that came out last year regarding bipolar depression and looked at some of the literature.

**Dr Nemeroff:** The recent introduction of certain medications that appear to be particularly effective in bipolar depression has served as an impetus for more research in that area. In particular, lamotrigine has been introduced, which clearly is effective in the treatment of bipolar depression and probably represents an incremental advance in our ability to treat bipolar depression. This is a big step forward for the field, as is the emerging role of atypical antipsychotics in the treatment of mood disorders. I think we are going to see more and more data available on how to manage bipolar depression in the years to come.

**ASiM:** Do you think there is a role for antidepressants in managing bipolar disorders?

**Dr Nemeroff:** Absolutely. The American Psychiatric Association has guidelines for the treatment of bipolar depression and they indicate that lithium is a first-choice agent, which is quite reasonable because unlike many of the other so-called mood stabilizers, it clearly has inherent antimanic and antidepressant properties. Their second recommendation is lamotrigine, which clearly has been shown to be effective in treating bipolar depression, even though its FDA (Food and Drug Administration) approval is for the prevention of recurrence of manic and depressive episodes in bipolar disorder.

The 2 big advantages that we have are that there is a huge database on lithium and an emerging database on lamotrigine. However, for most patients with bipolar disorder, their depression is sufficiently severe that it may not respond to those 2 interventions alone or even to the combination of the two. This subgroup of patients will, in my clinical experience, often require antidepressants. There is considerable literature on the use of antidepressants in bipolar disorder, with the least desirable being tricyclic antidepressants (TCAs) because they have the poorest efficacy, the highest switch rate, and are lethal in overdose. Then there are the monoamine oxidase inhibitors (MAOIs), which have better efficacy than TCAs, but have unacceptably high switch rates into mania. Next would be the serotonin reuptake inhibitors, which have been shown as a class to have efficacy in bipolar depression with data available for fluoxetine and paroxetine. Similar to all antidepressants, they can cause switches into mania. Other antidepressants haven’t been studied (eg, mirtazapine, nefazodone, venlafaxine), and the clinical impression of them is that they are effective but, similar to venlafaxine, appear likely to switch patients into mania. Other antidepressants, such as bupropion, are thought to be somewhat intermediate in that they are less likely than tricyclics or MAOIs to cause switches into mania. However, there is not a rich database on their use in bipolar disorder in terms of controlled studies to come to any firm conclusions in this regard.
ASiM: During the past 2 years antipsychotics seem to have emerged in the long-term treatment of bipolar disorder and bipolar depression.

Dr Nemeroff: There is no question that atypical antipsychotics have been shown to be effective in the treatment of acute mania, and there is a sizeable percentage of patients that will require continued maintenance treatment with atypical antipsychotics to prevent additional manic episodes. Even in the era of typical antipsychotics, we knew that there were some patients who required an antipsychotic in addition to an antidepressant to treat their bipolar depression. Unfortunately, in those years the typical antipsychotic had a very unfavorable side-effect profile. The advent of atypical antipsychotic drugs with their more favorable side-effect profiles made it easier to maintain patients on long-term antipsychotic drug therapy. There are solid data indicating that the combination of fluoxetine and olanzapine is effective in the treatment of bipolar depression. Other atypical antipsychotics, including quetiapine and risperidone, have also been shown to be effective. Whether these drugs are effective as monotherapy for treating bipolar depression is still an open question.

ASiM: In terms of comorbidities, bipolar disorder seems to have several common comorbidities. Can you discuss the areas of comorbidity?

Dr Nemeroff: In terms of medical comorbidities, there is no question that patients with bipolar disorder are at increased risk for several common medical disorders, including heart disease, stroke, diabetes, perhaps even cancer, and they certainly have a shorter life expectancy, even if you factor out the elevated suicide risk. For that reason, we have to be particularly attentive to the medical consequences of any medications that we prescribe, particularly in the long term. In that regard, the emerging evidence that olanzapine, clozapine, and quetiapine (perhaps to a lesser extent) are associated with increased weight gain, metabolic syndrome, and diabetes is a very serious issue. Many psychiatric patients have no other physician but their psychiatrist, thus it is really of paramount importance that we are cognizant of this issue. I don't think this is a class effect because there is no compelling evidence that aripiprazole or ziprasidone exhibits any increased risk for the development of metabolic syndrome or type 2 diabetes in the schizophrenia or bipolar population. In terms of psychiatric comorbidity, many patients with bipolar disorder also fulfill diagnostic criteria for substance or alcohol abuse, anxiety disorders, and other psychiatric disorders. Comorbidity is more the rule than the exception, and it is obviously going to impact your choice of treatment.

ASiM: Which would you treat first?

Dr Nemeroff: In terms of substance abuse, it is obviously hard to treat somebody with bipolar disorder if they are actively abusing alcohol or substances. Substance abuse must be addressed from the beginning. However, it is virtually impossible to treat anything else when someone is acutely manic. A combination of pharmacotherapy and psychotherapy is usually optimal in treating individuals with complicated presentations, such as bipolar disorder. We know that psychotherapy markedly improves adherence to treatment recommendations and the sine qua non for success in treating bipolar disorder is patient compliance. The treatment regimen for a bipolar disorder can be quite complicated. If patients are taking 3 medications prescribed at different times of the day or in split doses, it can become challenging in the best of situations and a disaster in suboptimal conditions.

ASiM: A history of alcoholism seems to be a common theme in bipolar disorder or at least occurs frequently. Why do you think this is so?

Dr Nemeroff: Approximately 50% of patients with bipolar disorder have comorbid substance or alcohol abuse. Conventional wisdom has always suggested that this was an attempt to self-medicate. Therefore, alcohol, being a central nervous system depressant, was always thought to be an attempt on the patient's part to put the brakes on a manic episode. Whether this is, in fact, true or whether there are shared genetic risks so that simply by bad luck certain forms of bipolar disorder are associated with an increased genetic risk for alcoholism is another hypothesis that hasn't yet been adequately tested.

ASiM: The prevalence of bipolar disorder is listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition as being 0.4% to 1.6% and then higher in first-degree relatives. I think many people suggest this statistic is double or a great deal higher and that it is really not reported in the literature.

Dr Nemeroff: I think there are 2 separate issues here. On the one hand, I think it is a dangerous busi-
ness to talk about a broad definition of bipolar spectrum disorder in which there are very soft or virtually no definitions regarding the distinction between psychopathology and normal mood variation. We should also be very circumspect about the possibility that the pharmaceutical industry wishes to increase its market size. There are probably exuberant, somewhat hyperthymic individuals who are quite successful in what they do. They are very energized folks who really don't have bipolar disorder, and I wouldn't want to consider them—in any way, shape, or form—to be pathological and requiring treatment. The medications used to treat bipolar disorder are not without their adverse side effects, and one has to be very secure in the database before prescribing these medications in terms of the evidence that the entity you are treating is, in fact, responsive to the medication that you are prescribing.

I don't think having 1 or 2 symptoms of bipolar disorder is sufficient to reach the threshold for prescribing for these patients. However, one should not be rigid about the necessity to absolutely fulfill the exact number of diagnostic criteria before initiating treatment. This, of course, involves considerable judgment on the part of the practicing clinician. To give an analogy in unipolar depression, say you had a patient with 4 symptoms of major depression instead of 5, and suppose these symptoms were suicidality, severe psychomotor retardation, difficulty concentrating, and decreased appetite, but none of the other vegetative symptoms. You wouldn't say, “Oh, well, let's just not treat the person because they don't fulfill criteria.” In contrast, if a patient said that they were sad and had no other signs or symptoms of depression, you wouldn't treat them for major depression.