ELSEVIER

Bipolar Disorders in *DSM-IV*: Impact of Inclusion of Rapid Cycling as a Course Modifier

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In this paper, we review the process for inclusion of rapid cycling as a course modifier to bipolar disorders in DSM-IV. *This process involved definition of bipolar II disorder, delineating the duration of manic episode for bipolar I disorder, and clarification of the diagnosis of cyclothymic disorder and mixed mania.*
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The purpose of this paper is to discuss diagnostic changes for bipolar disorders in *DSM-IV* with particular reference to the inclusion of rapid cycling as a course modifier for bipolar disorders. With the *DSM* systems prior to *DSM-IV* (American Psychiatric Association 1994), particularly with *DSM III-R* (American Psychiatric Association 1987), there had been no delineation of bipolar II from bipolar I patients, and no specific duration for a manic episode was cited. The bipolar disorders listed in *DSM III-R* included bipolar disorder, cyclothymic disorder, and "bipolar disorder not otherwise specified." The latter included bipolar II as a specific subtype. "Rapid cycling" was not specified. "Bipolar disorder manic" and "bipolar disorder mixed" were included as forms of mania.

Because duration of a manic episode was not defined in *DSM III-R*, there was possible confusion in describing a group of patients who might experience frequent mood alterations using the diagnostic terms "mixed mania," "cyclothymic disorder," and "rapid cycling." Thus, one of the discussion points for the work group on mood disorders for *DSM-IV* was to clarify these three conditions. The methods available to the work group included reviews of the current literature, field trials, and multisite data reanalysis. For the issue of rapid cycling, a multisite data reanalysis was undertaken (Bauer et al. 1994). For bipolar II (recurrent depression with hypomania), a review of the literature was undertaken (Dunner 1993). The issue of mixed mania was essentially left unresolved because of the paucity of data regarding this condition. The definition of cyclothymic disorder resulted from the inclusion of duration criteria for manic episode and definition of duration and characteristics of hypomanic episode. These changes and clarifications were necessary for "rapid cycling" to be defined.

BIPOLAR II

The inclusion of bipolar II as a separate diagnostic bipolar subtype in *DSM-IV* was supported by a review of the literature of studies comparing bipolar I, bipolar II, and major depression (nonbipolar, unipolar) patients who were assessed regarding clinical course, family

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history, laboratory data, and treatment outcome (Dunner 1993). In summary, this review supported the clinical differentiation of these three subtypes of depression. Clinically, bipolar II patients had an intermediate age of onset as compared to bipolar II or unipolar patients. The gender ratio of bipolar II patients tended to favor women having this disorder as compared to bipolar I patients where the gender ratio was fairly equal. Rapid cycling was noted among bipolar I and bipolar II (but not unipolar) patients. Patients with seasonal affective disorder were more likely to be bipolar II than unipolar, and clinically depressed bipolar I patients evidenced psychomotor retardation; whereas, depressed bipolar I and unipolar patients were psychomotor agitated or psychomotor retarded. A history of suicide attempt was highest, as was death by suicide, among bipolar II as compared to bipolar I and unipolar depressed patients.

Family studies of affective disorders revealed interesting findings. A summation of three large-scale studies where relatives of bipolar I, bipolar II, and unipolar patients were interviewed to determine their diagnosis revealed an elevated morbid risk for mania (bipolar I disorder) in relatives of bipolar I patients and bipolar II patients, as compared to relatives of unipolar patients and an elevated morbid risk for bipolar II patients in relatives of bipolar II probands. These latter data suggested that bipolar II might "breed true." The family study data supported the notion that bipolar II was more similar to bipolar I than unipolar disorder but that bipolar II may be (on a familial basis) somewhat distinct from both bipolar I and unipolar disorder.

Biological and pharmacological data were also assessed. The major difficulty in assessing the review of the biological studies was the fact that no biological study consistently predicted discrimination of bipolar from unipolar patients, and many of the studies suffered from small sample size and lack of replication. Pharmacological studies did tend to support some differentiation of bipolar II from unipolar and bipolar I patients regarding antidepressant response to acute lithium administration and treatment outcome regarding administration of L-dopa.

Another factor that was considered regarding the diagnosis of bipolar II was stability of the disorder over time. Some bipolar I patients begin their disorder with a unipolar or bipolar II course of illness. A variety of studies suggested that the probability of this occurring was about 5 to 17% over up to 40 years of follow-up, with many of the studies supporting the lower rate of diagnostic conversion from bipolar II to bipolar I. Additionally, studies have demonstrated some difficulty in diagnosing hypomania, especially when using structured instruments rather than depending upon experienced clinical diagnosticians (Dunner and Tay 1993). This fact may have obscured some bipolar II patients who were otherwise classified as unipolar in these studies.

In summary, the data supported the inclusion of bipolar II as a separate mood disorder subtype. To effect the inclusion of bipolar II into *DSM-IV*, the elements of bipolar II needed to be defined. The depressed phase was defined as having one or more major depressive episodes (five or more affective symptoms persistently occurring over a 2-week or longer period with resulting psychosocial disability). The hypomanic phase was defined as including all of the symptoms of a manic episode but the syndrome not resulting in hospitalization, characterized by psychosocial disability or psychotic features. Additionally, the hypomanic episode needed to represent an unequivocal change in functioning that was uncharacteristic of the individual, and this change in functioning needed to be observable by others. Furthermore, the hypomanic episode could not be the result of substances or a general medical condition or treatment of a depressive episode (American Psychiatric Association 1994).

The duration of a hypomanic episode was arbitrarily set at 4 days or longer, and this arbitrary definition of duration was in accord with the criteria set forth in ICD-10, where a hypomanic episode was defined as 4 days or more. It should be noted that the previous definition of hypomanic episode for bipolar II employed by Dunner et al. (1976) include 3-day or longer periods of hypomania.

Having described and defined bipolar II, it became an easy task to define bipolar I as a disorder involving manic episodes characterized by psychosis, hospitalization, and severe psychosocial disability, and which were further defined to last at least 1 one week or require hospitalization. Thus, a bipolar I disorder involving both manic and depressive episodes would involve at least 1 week of a manic episode and at least 2 weeks of a depressive episode.

CYCLOTHYMIC DISORDER

Having defined the minimal duration criteria for a manic episode (1 week or hospitalization) and a hypomanic episode (4 days), and for the depressed phase of bipolar I and bipolar II disorder as 2 weeks or longer (i.e., a major depressive episode), the definition of cyclothymic disorder then became clarified. Cyclothymic patients would be characterized by a chronic (2 years or more) condition with hypomanic periods that were not long enough to meet criteria for a hypomanic episode (4 days), and depressive periods that did not meet criteria for major depressive episode; i.e., lasting less than 2 weeks. Additionally, similar to the pattern seen in dysthymic disorder, there should not be a 2-month symptom-free period, and the disorder could not be characterized as having major depressive episodes, manic episodes, or mixed episodes in the first 2 years of the

disorder. Patients who experienced hypomanic episodes and brief depressive periods or patents who experienced major depressive episodes and brief hypomanic periods would be classified as "bipolar disorder, not otherwise specified."

MIXED MANIA

The criteria for a mixed manic episode in *DSM III-R* and *DSM-IV* essentially involve a manic episode wherein symptoms of both a manic episode and a major depressive episode are present nearly every day during at least a 1-week period. Mixed mania requires the same psychosocial impairment as a manic episode and, thus, is defined as a severe disorder.

RAPID CYCLING

The definition of rapid cycling as a course modifier for bipolar I and bipolar II disorders was based on a multisite data reanalysis involving four sites (Bauer et al. 1994). Data regarding 120 rapid cycling and 119 nonrapid cycling bipolar disorder patients were reviewed. One main point at issue was the minimal number of episodes per year that would define the occurrence of rapid cycling. Rapid cycling occurs more frequently in women than men, and, thus, the change in gender ratio as a function of episode frequency was used as a validating criterion. This data reanalysis supported the notion of a minimum of four affective episodes per year to define rapid cycling. Interestingly, this is the same operational definition employed by Dunner and Fieve (1974) in their description of rapid cycling. In the Dunner and Fieve study, rapid cyclers were determined to be a group of patients who were less likely to respond to lithium carbonate maintenance therapy than other bipolar patients. The value of identifying this subgroup mostly lay in the ability of clinicians to differentiate this subtype from other bipolar subtypes and to develop more vigorous treatments. Other factors associated with rapid cycling over the years have included differences in gender ratio (more women than men), the possibility of an underlying thyroid abnormality, and the possibility of bipolar II patients being more likely to be rapid cyclers than bipolar I patients (Cho et al. 1978; Cowdry et al. 1983; Bauer et al. 1990; Bauer and Whybrow 1993). The work group for mood disorder for *DSM-IV* supported the inclusion of rapid cycling as a course modifier as applied to bipolar I and bipolar II disorder. By definition, the greatest number of episodes per year would be 40 for bipolar II patients. (Four-day hypomanic episodes and 2-week depressive episodes equal 18 days per cycle or 20 cycles per year.) Similarly, about 17 cycles per year would be the maximum number for bipolar patients.

In summary, the factors that differentiate cyclothymic disorder from rapid cycling and from mixed mania involve both duration of symptoms and severity of the presentation. Rapid cycling is defined as a disorder with frequent well-characterized manic, hypomanic, or depressive episodes. It is a persistent and outpatient-type disorder. Cyclothymic disorder tends to be a very stable disorder, again, mostly seen among outpatients and involving brief depressive and hypomanic periods. Mixed mania should be considered a severe disorder usually requiring hospitalization and much more like a manic episode in terms of its severity and symptoms but with an admixture of depressive symptoms.

RECENT STUDIES OF RAPID CYCLING AND THE ISSUE OF "TRUNCATED" CYCLING

Our group has recently completed a study assessing the effect of alcohol and substance abuse on the course of bipolar disorder (Feinman and Dunner 1996). In this study, we compared three groups of patients. The first group (n = 103) had primary bipolar disorder, and these patients had no significant history of alcohol or substance abuse. The second group of patients (n = 35) had primary bipolar disorder, and after the onset of their bipolar disorder, developed alcohol or substance abuse, and the third group (n = 50) had alcohol or substance abuse as their initial disorder and after stopping substance abuse, developed a bipolar disorder. Findings from this study suggested that the effects of substance abuse on the course of bipolar disorder were marked. Patients with substance abuse histories were more likely to have such complications as suicidal behavior and panic attacks than nonsubstance-abusing bipolar patients. Additionally, patients with substance abuse histories were more likely to have a cyclothymic type pattern to their illness than nonsubstance abusing patients. Patients who described hourly or daily mood alterations from high to low ("truncated cycling") were significantly more frequently found among individuals with substance abuse histories than nonsubstance abusing bipolar patients.

AREAS FOR FUTURE RESEARCH

One of the difficulties apparent in *DSM-IV* regards those patients who become manic or hypomanic in response to antidepressant pharmacotherapy. Technically, in *DSM-IV*, these hypomanic episodes should not be counted as true hypomanic episodes, but the patients should be classified as "major depressive disorder with (antidepressant-) induced hypomania." How-

ever, it is not likely that true unipolar patients can become bipolar with the application of antidepressant pharmacotherapy. For example, in the package inserts of most antidepressant medication, the rate of hypomania seen in placebo-treated or medication-treated unipolar depressed patients is on the order of 1 to 2% (Medical Economics Data Publication Co. 1996). This is well within the diagnostic error that might occur in including some bipolar II patients in a study of major depression subjects and clearly supports the notion that only a small percentage of depressed patients who are treated with antidepressants are likely to become bipolar. Further research and discussion of this topic might be of interest.

It also has been suggested that tricyclic antidepressants may have a greater role in inducing rapid cycling than the more modern antidepressant treatments, which, in general, show somewhat lower rates of medication-induced hypomanic episodes than are reported for tricyclic antidepressant treatment of depression (Kukopulos et al. 1980; Wehr et al. 1988). Unfortunately, the rate of hypomanic induction during antidepressant treatment is low, and thus it is unlikely that a large group of such patients could be collected to determine whether, for example, family histories of "switchers" might be more bipolar laden than "nonswitching" patients.

Rapid cycling seems to be a form of bipolar I and bipolar II disorder that occurs at times episodically in the course of the illness of these patients and may itself remit. Family studies of rapid cyclers show no increase in rapid cycling among relatives of rapid cycling versus nonrapid cycling bipolar patients (Nurnberger et al. 1988). These data suggest that genetic factors do not play a role in determining which bipolar patients might become a rapid cycler.

An underlying thyroid abnormality has been postulated to play a role in the etiology of rapid cycling, and, indeed, thyroid administration has been reported to be of benefit in the treatment of treatment-resistant rapid cycling patients (Bauer et al. 1990; Bauer and Whybrow 1990). Clarification of the role of thyroid dysfunction in the etiology of rapid cycling would seem to be an important area of research for the future.

Treatment of rapid cyclers with lithium carbonate is less successful than lithium maintenance treatment of nonrapid cyclers (Dunner and Fieve 1974). Positive treatment effects with anticonvulsants have been reported (Ballenger and Post 1980; Calabrese and Delucchi 1990). Further research is needed to determine the optimal treatment for this condition.

In summary, the inclusion of rapid cycling as a course modifier in *DSM-IV* enables clinicians to identify individuals who are less likely to be lithium-maintenance therapy responsive than other bipolar patients. Data from a multisite reanalysis supported the minimal frequency of episodes (four or more per year) necessary to define rapid cycling. Rapid cycling is rare among unipolar (major depressive disorder) patients and can be a course modifier for bipolar I and bipolar II patients. The process of including rapid cycling in *DSM-IV* also involved the inclusion and definition of bipolar II disorder, the definition of the duration of a manic episode, and clarification of the definition of cyclothymic disorder and mixed manic states.

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