Rapid Cycling in Bipolar Disorder: Diagnostic Issues and Treatment Options

August 01, 2006 | Bipolar Disorder[1], Major Depressive Disorder[2], Mania[3] By Mario Maj, MD, PhD[4]

A discussion of the many difficulties in treating patients with the rapid-cycling subtype of bipolar disorder, along with a history of the condition and the author’s treatment approach.

Rapid cycling is included in DSM-IV as a course specifier for bipolar disorder (BP) I and II. However, its conceptualization remains controversial, and research concerning its treatment is still at an early stage. This article provides a synthesis of currently available evidence.

DEFINITION OF RAPID CYCLING

DSM-IV defines rapid cycling as the occurrence of at least 4 major depressive, manic, hypomanic, or mixed episodes during the previous year in a patient with a diagnosis of BP I or BP II. These episodes must be demarcated either by a partial or full remission of at least 2 months' duration or by a switch to an episode of opposite polarity. Duration criteria for episodes are not waived, which means that each major depressive episode must last at least 2 weeks, each manic or mixed episode must last at least 1 week, and each hypomanic episode must last at least 4 days.

This definition has been criticized even by the leaders of the DSM-IV task force, who stated, “In practice, some patients are encountered who have a large number of episodes, each of which has a brief duration of only a few days. Although such patients would not be diagnosed as having BP with rapid cycling in the conservative world of DSM-IV, they may present with similar course, management, and treatment response problems. The clinician may want to override this strict interpretation and consider such patients as rapid cycling.”

Actually, on the basis of the DSM-IV definition, a patient with BP who has had several direct transitions from one polarity of mood to the other during the previous year, but in whom most periods of abnormal mood have not fulfilled the duration criteria for an affective episode (Figure, patient A), may not be classified as a rapid cycler, whereas a patient with BP who has had a prolonged depressive recurrence with 3 partial remissions (Figure, patient B) during the previous year may be classified as a rapid cycler (since a bipolar course during the previous year is not required).

The fact is, however, that most clinicians and researchers would regard the first patient, and not the second, as a rapid cycler. Indeed, in several empiric studies on rapid cycling, duration criteria for affective episodes have been waived[2-4]; in some studies a circular course, ie, the direct transition from mania to depression or vice versa, has been required[4]; and in others, a continuous circular course, ie, the direct transition from mania to depression to mania, or from depression to mania to depression, has been a prerequisite.[3]

These differences in the definition of rapid cycling have important clinical implications. In a study published several years ago, my colleagues and I tested the reliability and validity of 4 alternative definitions of rapid cycling[5]:

The first requires at least 4 major depressive, manic, or hypomanic episodes, as defined by Research Diagnostic Criteria (RDC), during the previous year, demarcated by a euthymic period of at least 8 weeks or by a switch to an episode of opposite polarity.

The second is similar to the first but includes all major depressive, manic, or hypomanic episodes meeting RDC severity criteria and lasting at least 1 day.

The third is similar to the second but with the added requirement of at least 1 direct transition from mania or hypomania to major depression or vice versa during the previous year.

The fourth is similar to the second but with the added requirement of a total duration of fully symptomatic affective illness during the previous year of at least 8 weeks.

The highest interrater reliability (Cohen κ = 0.93) was obtained for the first definition (consistent with DSM-IV criteria). The Cohen κ values for the other 3 definitions were, respectively, 0.73, 0.75, and 0.80. Patients consistently identified as rapid cyclers by both assessing psychiatrists numbered
31 (14.8% of the entire sample of 210 bipolar patients recruited for the study) using the first definition, 57 (27.1%) using the second definition, 33 (15.7%) using the third definition, and 40 (19.0%) using the fourth definition.

Compared with non–rapid-cycling bipolar patients, there was a significantly higher proportion of women among the patients fulfilling the last 3 definitions for rapid cycling; and patients meeting the second and third definitions had a significantly higher frequency of the BP II pattern. Each group of rapid cyclers had a significantly lower proportion of patients with a favorable outcome with lithium prophylaxis compared with non–rapid cyclers, but the least significant difference was observed for patients fulfilling the first definition ($P < .02$ for this group, $P < .0001$ for the other 3 groups). During the followup period, a stability of the rapid cycling pattern was observed in 58.1% of patients fulfilling the first definition, and in 62.5%, 76.6%, and 45.2%, respectively, of those meeting the last 3 definitions. A summary of these results is given in Table 1.

Table 1
Summary of the results of a study comparing 4 alternative definitions of rapid cycling

<table>
<thead>
<tr>
<th>Definition</th>
<th>Interrater reliability</th>
<th>More women compared with NRC</th>
<th>More BP II compared with NRC</th>
<th>Worse lithium response than NRC</th>
<th>Stability of rapid cycling pattern (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent with DSM-IV</td>
<td>0.93</td>
<td>No</td>
<td>No</td>
<td>Yes ($P &lt; .02$)</td>
<td>58.1</td>
</tr>
<tr>
<td>Waiving duration criteria for affective episodes</td>
<td>0.73</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes ($P &lt; .0001$)</td>
<td>62.5</td>
</tr>
<tr>
<td>Waiving duration criteria and requiring pole switching during previous year</td>
<td>0.75</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes ($P &lt; .0001$)</td>
<td>76.6</td>
</tr>
<tr>
<td>Waiving duration criteria and requiring at least 8 weeks of fully symptomatic affective illness during previous year</td>
<td>0.80</td>
<td>Yes</td>
<td>No</td>
<td>Yes ($P &lt; .0001$)</td>
<td>45.2</td>
</tr>
</tbody>
</table>

NRC, non–rapid cyclers; BP, bipolar disorder.

These findings are in line with those reported in 5 other large studies of rapid cycling summarized in Table 2.\(^2\)\(^-\)\(^4\)\(^6\)\(^7\) In fact, a significantly higher proportion of patients with BP II among rapid cyclers was found in 2 of the 3 studies that waived duration criteria for affective episodes,\(^2\)\(^3\) whereas the third study\(^4\) did not report any data in this respect. The studies that did not waive duration criteria did not find a greater proportion of patients with BP II among rapid cyclers.\(^6\)\(^7\) On the other hand, the 2 studies in which circularity of course was a prerequisite found rapid cycling to be a relatively stable pattern on follow-up,\(^3\)\(^4\) whereas the 3 studies that did not require circularity of course found rapid cycling to be a very unstable pattern.\(^2\)\(^6\)\(^7\)

The difference is particularly striking if we compare the studies by Wehr and colleagues\(^4\) and Coryell and colleagues.\(^2\) The former study (waiving duration criteria for affective episodes and requiring circularity of course) found that 41% of patients continued to be rapid cyclers through an average follow-up duration of about 5 years, whereas the latter (waiving duration criteria but not requiring circularity of course) found that only 2.6% of patients remained rapid cyclers through a follow-up period of 4 years.

These results suggest that the DSM-IV definition of rapid cycling, although very reliable, may not be
sufficiently inclusive (ie, it may exclude patients with very short episodes of very high frequency, who are typical in terms of external validators and are currently regarded as rapid cyclers by many researchers and clinicians). Moreover, the addition of the requirement of pole switching (ie, at least 1 direct transition from 1 polarity of mood to the other) during the previous year may increase the prognostic and therapeutic implications of the diagnosis of rapid cycling.

**TREATMENT OF RAPID CYCLING**

**Lithium**

A statement that is commonly made in the literature on bipolar disorder is that rapid cyclers are refractory to lithium prophylaxis. This notion dates back to the classic paper by Dunner and Fieve in which the concept of rapid cycling was introduced. These investigators reported a failure of lithium prophylaxis in 82% of rapid cyclers and 41% of non–rapid-cycling bipolar patients, a statistically significant difference ($P < .05$). However, their comparison was actually flawed. In fact, failure of lithium prophylaxis was defined as the occurrence of at least 1 new episode during an observation period of at least 6 months, not considering that rapid cyclers are by definition more likely than non–rapid cyclers to have a new episode during any observation period, whether or not they are treated.

Dunner and Fieve certainly realized the tautology intrinsic in their observation, since 3 years later they published a study of 29 rapid cyclers treated with lithium for at least 1 year, in which they correctly compared the lithium-treatment period with a period of the same duration preceding the start of treatment, and found that the percentage of time spent in euthymia was significantly increased and the percentage of time spent in mania and depression was significantly reduced during the treatment period. Their conclusion was that lithium does have an impact on rapid cycling. The 1974 paper by Dunner and Fieve is always quoted in publications concerning treatment of rapid cyclers, whereas the 1977 paper is almost never mentioned. Dunner, commonly quoted as the investigator who first demonstrated that rapid cyclers are refractory to treatment with lithium, actually stated that, “lithium alone should be the first pharmacological treatment of rapid cycling.” In that same article, Dunner points out that it may take a long time before the mood-stabilizing effect of lithium becomes apparent in rapid cyclers. This observation calls our attention to a potential bias of those studies in which an experimental drug is added to the mood stabilizer that the patient is already receiving (often lithium), a protocol that has become very fashionable. The improvement that is sometimes observed in these studies, and ascribed to the drug that has been added, may actually be caused by the delayed effect of lithium.

Most studies that add an experimental drug to the mood stabilizer do not actually explore the prophylactic effect of the experimental drug (ie, its capacity to prevent new episodes) but rather its acute antimanic and antidepressant effect. This acute antimanic and antidepressant effect of the experimental drug is often compared in rapid cyclers versus non–rapid cyclers. This comparison, however, may be biased by the fact that the natural course of affective episodes is different in the 2 groups of patients. The average duration of both manic and depressive episodes may be shorter in rapid cyclers than in non–rapid cyclers, so that the likelihood of a spontaneous remission during the treatment period may be higher in rapid cyclers.

**Lamotrigine**

The only drug for which a statistically significant superiority over placebo has been reported in the prevention of recurrences of rapid-cycling patients with bipolar disorder is lamotrigine. In a double-blind study of 182 rapid cyclers who received lamotrigine or placebo for 6 months, 41% of the patients in the lamotrigine group were stable without relapse for 6 months compared with 26% of those in the placebo group ($P = .03$); however, the difference was significant with BP II but not BP I.

In a meta-analysis based on 16 reports involving 1856 patients with BP, it was found that rapid cycling was associated with lower effectiveness of all treatments evaluated. No evidence of superiority of any treatment was found. In a double-blind parallel-group trial of 254 subjects who were rapid cyclers, no significant difference was found between lithium and valproate regarding the rate of relapse into any mood episode and the time to relapse.

In a double-blind crossover study, Denicoff and colleagues randomly assigned a sample of patients with BP, including a subsample of rapid cyclers, to 1 year of treatment with lithium, 1 year with carbamazepine, and 1 year with the combination. A marked or moderate improvement on the
Clinical Global Impression Scale was found in 28% of the rapid cyclers during the year of treatment with lithium, in 19% of them during the year of treatment with carbamazepine, and in 56.3% of them during the year of treatment with the combination, a statistically significant difference ($P < .05$).

**Combination therapy**

These last results support the clinical impression that the combination of at least 2 mood stabilizers is needed for most rapid cyclers. According to Dunner, “if the patient does not respond to lithium monotherapy, we suggest adding a second mood stabilizer, either carbamazepine or valproate. Our general approach is to add either carbamazepine or valproate (with no particular preference for either) to lithium rather than switching, because we have found better results clinically by adding rather than switching.”

Further double-blind studies comparing the various available mood stabilizers (and atypical antipsychotics) and their combinations in patients fulfilling the different definitions of rapid cycling are clearly warranted.

Table 2

Summary of the results of 5 large studies of rapid cycling

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration criteria waived</th>
<th>Circular course required</th>
<th>More women compared with NRC</th>
<th>More BP II compared with NRC</th>
<th>Stability of rapid cycling pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koukopoulos³</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wehr⁴</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>Coryell²</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Bauer⁶</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Maj⁷</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

NRC, non–rapid cyclers; BP, bipolar disorder.

**Drugs Mentioned in This Article**

Carbamazepine (Carbatrol, Tegretol, others)
Lamotrigine (Lamictal)
Lithium (Eskalith)
Valproate/Valproic acid (Depakote, others)

**Disclosures:**

Dr Maj is professor of psychiatry and chairman of the department of psychiatry of the University of Naples SUN. He is president-elect of the World Psychiatric Association. He was president of the European Psychiatric Association (2003-2004) and of the Italian Psychiatric Association (2000-2002). He reports that he has no conflicts of interest concerning the subject matter of this article.

**References:**

7. Maj M, Magliano L, Pirozzi R, et al. Validity of rapid cycling as a course specifier for bipolar...

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