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**Bipolar Disorders Expert Column Series**

## **Rapid-Cycling Bipolar Disorder: Emerging Treatments and Enduring Controversies**

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### **Introduction**

Rapid cycling is a descriptive term referring to the presence of 4 or more discrete affective episodes in a 1-year period. For patients, it may bring frequent hospitalizations and severe life disruptions. For their physicians, rapid cycling often means frustrating attempts to manage a phase of bipolar illness that can render traditional pharmacotherapies ineffective. However, in recent years, investigators have begun to better understand the clinical importance of this condition, and key questions about its nature and management have come into focus. The result is that clinicians can now have a clearer understanding of the phenomenology of rapid cycling and greater confidence in their ability to treat it.

### **The Phenomenology of Rapid Cycling**

High-frequency recurrence of mood episodes has been noted in the medical literature for at least 100 years.<sup>[1]</sup> The term *rapid cycling* was coined in 1974, when Dunner and Fieve<sup>[2]</sup> described a group of lithium-unresponsive manic-depressive patients who were noted to have at least 4 episodes of mania and/or depression per year. This general definition was later validated and then incorporated into the *DSM-IV*, which includes rapid cycling as a course specifier for bipolar disorder.<sup>[3]</sup> In *DSM-IV*, rapid cycling is defined by at least 4 mood episodes (mania, hypomania, depression, or mixed) that occur during the year prior to diagnosis. Each episode must be followed by return to euthymia for at least 2 months, or by a switch in mood polarity. Estimates of the point-prevalence of rapid cycling among bipolar patients are 10% to 20% among clinical samples.<sup>[3]</sup> "Looser" definitions involving monthly (ultrarapid) or weekly-daily (ultra-ultra-rapid) cycling have been described by both clinicians and investigators, although the diagnostic validity of such constructs remains controversial.

Rapid cycling clearly appears more frequently in females and seems to be associated with hypothyroidism and bipolar II disorder.<sup>[1,4]</sup> (Bipolar II disorder includes hypomanic and depressive episodes in the absence of mania, while bipolar I disorder is characterized by manic episodes.) Other features purported to differentiate rapid-cycling from non-rapid-cycling patients include earlier onset of illness, longer duration of illness, stronger family history of mood disorders, greater exposure to antidepressants,<sup>[1,4]</sup> and poorer global functioning.<sup>[4]</sup>

One of the key unresolved questions about rapid cycling is whether it should be considered a transient phenomenon, a distinct and persistent bipolar subtype, or an evolutionary outgrowth of repeated episodes of illness. Studies of the natural history of rapid cycling provide conflicting evidence. In a longitudinal study from Coryell and colleagues<sup>[5]</sup> of 39 rapid-cycling patients followed for 5 years, only 1 remained in a rapid-cycling state for the entire time. By contrast,

Koukopoulos and colleagues<sup>[6]</sup> naturalistic study of 109 rapid-cycling clinic patients showed that over half still met criteria for rapid cycling at the end of a follow-up period that ranged from 2 to 36 years.

## Do Antidepressants Cause Rapid Cycling?

A particularly contentious issue regarding rapid cycling is whether it is induced by antidepressant medication.<sup>[7]</sup> Perhaps the most convincing data to support this view were provided by a study from Wehr and colleagues<sup>[8]</sup> of 51 patients with rapid cycling. For a subgroup of patients whose rapid cycling appeared related to antidepressant use, the investigators employed repeated on-off trials of tricyclic antidepressants to demonstrate that about 20% of the total sample had rapid cycling clearly associated with antidepressant use. Lending further support to the link between antidepressants and rapid cycling are observations that rapid mood switching has become more prevalent since antidepressant medication has come into widespread use.<sup>[9]</sup>

However, some experts argue that the risk of antidepressant mood destabilization may have been overestimated, and that depression itself, rather than antidepressant drugs, may be responsible for periods of rapid cycling. In a 1992 prospective study from Coryell and colleagues,<sup>[5]</sup> there was no association between antidepressant use and rapid cycling when the investigators statistically controlled for the presence of a major depressive episode.

Although questions remain about the role of antidepressants in inducing rapid-cycling bipolar disorder, US guidelines, including the American Psychiatric Association (APA) practice guidelines for the treatment of bipolar disorder,<sup>[10]</sup> reflect the opinion that antidepressants do pose a risk for manic switching and mood destabilization -- and are therefore relatively contraindicated in patients with rapid cycling. However, because depression appears to represent a driving force behind rapid cycling,<sup>[11]</sup> there exists a tremendous need to identify therapeutic agents with antidepressant efficacy that do not destabilize mood or induce further cycle acceleration.

## Treatment Options for Rapid Cycling

**Mood stabilizers.** These are the cornerstone of treatment for all types of bipolar disorder, and the current APA practice guidelines recommend lithium, valproate, or lamotrigine as first-line agents for patients who meet criteria for rapid cycling. The inclusion of lithium may be surprising, since a significant percentage of rapid-cycling patients have been noted to be lithium-unresponsive.<sup>[2]</sup> However, a recent meta-analysis of treatment studies suggests that lithium may be no less effective than other mood stabilizers.<sup>[12]</sup> The survey of 16 studies comprising 905 rapid-cycling patients treated with carbamazepine, lamotrigine, lithium, topiramate, or valproate demonstrated no superiority for any particular treatment. More recently, a 20-month trial of rapid-cycling patients randomized to receive lithium or valproate demonstrated equivalent efficacy for both agents.<sup>[13]</sup>

Lamotrigine has demonstrated effectiveness for acute bipolar depression and was recently studied as maintenance treatment in rapid-cycling patients. A double-blind, placebo-controlled trial by Calabrese and colleagues<sup>[14]</sup> involving 182 patients demonstrated that 46% of rapid-cycling bipolar II patients receiving lamotrigine were stable for 6 months without relapse, compared with 18% of those receiving placebo. For rapid-cycling bipolar I patients, however, the difference between the placebo and lamotrigine arms was not significant, apparently due to a high placebo response. No controlled data exist to support the value of any other anticonvulsants in the treatment of rapid cycling.

**Atypical antipsychotics.** These agents have begun to receive growing attention for treating varied subtypes of bipolar illness beyond acute mania, including rapid cycling. Efficacy data are at present strongest for olanzapine. These data include a secondary analysis of a 3-week placebo-controlled trial of olanzapine as acute treatment of bipolar I disorder, which demonstrated clinical improvement in 58% of rapid-cycling patients taking olanzapine vs 28% of those on placebo.<sup>[15]</sup> The combination of olanzapine and fluoxetine has also been studied. An 8-week, placebo-controlled trial in which depressed bipolar I patients were randomized to receive olanzapine monotherapy, olanzapine/fluoxetine combination, or placebo demonstrated that depressed rapid cyclers randomized to olanzapine/fluoxetine, but not to olanzapine, monotherapy had significant improvement in depressive symptoms compared with placebo.<sup>[16]</sup>

Among studies of quetiapine, the strongest evidence of efficacy in rapid cycling was demonstrated by the so-called BOLDER trial, an 8-week, double-blind, placebo-controlled trial that randomized depressed bipolar patients to placebo or quetiapine. A subgroup analysis<sup>[17]</sup> of 108 rapid-cycling patients showed significant improvement in depressive symptoms among the quetiapine-treated patients, with minimal changes in mania ratings.

Other atypical antidepressants, including ziprasidone, aripiprazole, and risperidone, have demonstrated effectiveness in treating acute mania but lack data for use in patients with rapid cycling. However, in a clozapine add-on trial involving 15 patients with rapid cycling, more than 80% showed some improvement over a 12-month study period, although it was not as robust as that seen in non-rapid-cycling patients.<sup>[18]</sup>

**Other treatments.** Electroconvulsive therapy is often used in refractory mood disorders, and limited evidence suggests its efficacy in rapid cycling as well.<sup>[19]</sup> Suprametabolic doses of thyroid hormone are advocated by some authors even in the absence of biochemical hypothyroidism, although data to support this intervention are not extensive. The anticonvulsant calcium channel blocker nimodipine also has received attention based on preliminary observations.<sup>[20]</sup> Omega-3 fatty acids have gained growing interest for the treatment of bipolar disorder, although an 8-week placebo-controlled study failed to demonstrate efficacy in rapid cycling.<sup>[21]</sup> Finally, although somatic therapies remain a cornerstone of treatment for bipolar illness, adjunctive cognitive-behavioral therapy and interpersonal/social rhythm therapies have demonstrated value, particularly with regard to normalizing sleep hygiene patterns and minimizing the impact of interpersonal and environmental stressors that can destabilize mood.<sup>[22]</sup>

## Tips for Managing Rapid Cycling

The limited evidence from systematic studies of rapid-cycling bipolar disorder leaves much to the clinician's judgment. However, general guidelines include the following:

- First, rule out medical etiologies, including endocrinopathies (eg, hypothyroidism), neurologic disorders with psychiatric manifestations (eg, multiple sclerosis and pseudobulbar palsy), and psychoactive substances of abuse (eg, cocaine and steroids).
- Consider lithium, valproate, and/or lamotrigine as a first-line treatment. Lithium or valproate may be better choices for acutely manic patients, and lamotrigine may be more appropriate for the acutely depressed. Atypical antipsychotics, notably olanzapine or quetiapine, also have demonstrated evidence-based efficacy in rapid cycling.
- Antidepressant monotherapies should seldom, if ever, be used in rapid cycling, and the discontinuation of antidepressants alone may help to ameliorate rapid cycling. If antidepressants are used, patients should be monitored carefully for signs of affective switching.
- Consider electroconvulsive therapy in treatment-refractory or severely ill patients.

- Educate all patients about their illness and the importance of lifestyle manipulations to avoid relapse. These include maintaining a regular sleep/wake cycle, managing stress, adhering to medication regimens, and avoiding alcohol and recreational drug use.

## Conclusion

Although it has been 30 years since the term *rapid cycling* was coined, the condition is still something of a mystery. It remains an open question as to whether rapid cycling is a transient or enduring phenomenon, and whether certain pharmacotherapies demonstrate compelling advantages over others. Rapid cycling may represent a negative prognostic factor more than a marker for specific treatment outcomes. Compounds that do not destabilize mood, particularly those with at least a moderate or large effect size for the treatment of depressive symptoms, may represent the most compelling and evidence-based interventions for this condition.

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