Treatment of Rapid-Cycling Bipolar Disorder

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Rapid-cycling bipolar disorder is associated with poorer treatment response, poorer long-term prognosis, and probable higher suicide risk than bipolar disorder without rapid cycling. Patients with rapid cycling tend to experience more depressive than manic episodes, and the depressive episodes tend to be more refractory in nature compared with those in patients without rapid cycling. Results from studies of rapid cycling show that antidepressant use is most likely associated with the onset or worsening of rapid cycling. Controversy also exists as to whether rapid cycling is a transitory phenomenon in the course of bipolar illness or a more chronic condition better characterized as a subtype of the illness. Results from the first 500 patients with bipolar I or bipolar II disorder enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study found an association between rapid cycling and depression and younger age at illness onset. Treatment involves a 3-part pathway to manage rapid cycling that includes reducing or stopping any possible cycle-promoting agents, adding or optimizing mood stabilizers, and using experimental or putative treatments for persistent rapid cycling after more traditional treatments have failed. Effective treatments for some patients with rapid-cycling bipolar disorder currently include lithium, divalproex, lamotrigine, carbamazepine, atypical antipsychotics, and psychosocial therapy.

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While the first observations of rapid cycling were noted by Emil Kraepelin in 1913, the expression itself was first coined by Dunner and Fieve in 1974,[1] in their study examining predictors of lithium prophylaxis failure. Of the 55 bipolar patients enrolled in the study, 27 (49%) failed lithium prophylaxis over the observation period of 6 to 66 months. Nine (82%) of 11 patients who had 4 or more episodes in a year—a group designated as rapid cyclers—failed lithium, compared with 18 (41%) of 44 patients who did not have rapid cycling. Moreover, most of the rapid-cycling group continued to be ill after 2 or more years of lithium treatment. Thus, Dunner and Fieve's study[1] provided the first evidence that an increased rate of mood episodes might be related to higher relapse rates and decreased efficacy of lithium.

PHENOMENOLOGY OF RAPID CYCLING

Definition

Rapid cycling is currently designated as a course specifier and not a subtype of the illness,[2] implying that all bipolar patients are potentially at risk for rapid cycling during the course of their illness. According to the Fourth Edition of the *Diagnostic and Statistical Manual of Mental Disorders*,[2] patients must have at least 4 mood episodes per year to meet criteria for rapid cycling. Mood episodes are demarcated either by a minimum of 8 weeks of euthymia or by a switch to a mood episode of opposite polarity.[2]

Prevalence

Studies during the past 30 years have found widely variable prevalence rates for rapid cycling, ranging from 14% to 56% (Table 1)[3] in unselected bipolar populations. These rates may be somewhat inflated, as they are typically derived from tertiary or specialty treatment centers where patients sought treatment and therefore may not necessarily reflect rates found in general bipolar populations. In the recent Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, 20% of the patients were diagnosed with rapid cycling at study entry.[11]

Course of Illness

Controversy exists as to whether rapid cycling is a transitory phenomenon in the course of bipolar illness or whether it is a persistent state that might be better defined as a subtype of the illness. Coryell et al.[6] found that after 1 year of prospective observation, approximately 19% of patients were diagnosed with rapid cycling. Of the 39 patients who completed all 5 years of follow-up, only 1 (2.6%) had continued rapid cycling, suggesting that the course of rapid cycling was short-lived and transitory. In

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Table 1. Variance in the Prevalence of Rapid Cycling Across Different Studies[a]

Study (publication date)	Total N	Percentage With Rapid Cycling
Dunner and Fieve (1974)[1]	12	20
Cowdry et al (1983)[4]	24	56
Joffe et al (1988)[5]	17	40
Coryell et al (1992)[6]	45	19
Maj et al (1994)[7]	37	14
Maj et al (1999)[8]	31	15
Baldessarini et al (2000)[9]	56	16
Coryell et al (2003)[10]	89	26
Schneck et al (2004)[11]	91	20

[a]Data from Kupka et al.[3]

contrast, Koukopoulos et al.[12] found rapid cycling to have a more persistent course. In their study examining 109 patients with a new diagnosis of rapid cycling, a total of 59 patients (54%) had a persistent rapid-cycling course over the follow-up period of 2 to 36 years.[12] Of these 59 patients, 44 had an unchanged rapid-cycling course, and 15 had rapid cycling with attenuated episodes. Cycle pattern appeared to be the most significant distinguishing characteristic between rapid- and non–rapid-cycling patients: persistent rapid cycling was associated with a course of illness that began with depression followed by mania rather than mania followed by depression.

The Role of Depression

Although the term *rapid cycling* connotes equal time spent between depression and mania, rapid cycling has more recently been considered a disease primarily of depression. Patients with rapid cycling more often present in the depressed phase of the illness[13] and have been found to have substantial depressive morbidity and higher risk for suicide compared with patients without rapid cycling.[10] In addition, the depression associated with rapid cycling may be more severe than that of patients without rapid-cycling bipolar disorder[11,14] and more difficult to treat.[13] Among the first 500 patients enrolled in the STEP-BD study, patients with rapid cycling had higher Montgomery-Asberg Depression Rating Scale (MADRS) scores than patients without rapid cycling.[11] Mean MADRS scores were 19.3 in patients with rapid cycling and 12.8 in patients without rapid cycling. In addition, significantly fewer patients with rapid cycling presented with the clinical status of "recovered" at study entry, a designation given to patients who had attained at least 8 continuous weeks of euthymia. Only 10 patients with a recent history of rapid cycling presented as recovered, compared to 147 patients without recent rapid cycling. The small number of patients with rapid cycling who recovered emphasizes the severity of illness in these patients and underscores the need to find treatments that are effective in this often refractory group.

Risk Factors

Few reliable characteristics appear to predict which patients may be most at risk of developing rapid cycling. In a review of clinical studies, Kupka et al.[3] found that the 2 most consistently observed risk factors were bipolar II subtype and female gender. However, gender appears to be a moderate risk factor and has not been observed in all studies. In addition, more recent findings[11] suggest that early age at illness onset may be associated with future cycling risk. While older studies of rapid cycling found either an older or similar age at illness onset[8] compared with non–rapid-cycling cohorts,[4,6] more recent findings by Coryell et al.[10] and the STEP-BD[11] found younger age at illness onset associated with rapid cycling. Coryell et al.[10] found that patients with rapid cycling had a mean age of 21.6 years at first episode, compared with patients without rapid cycling, whose mean age at onset was 24.4 years. In STEP-BD,[11] patients with rapid cycling experienced onset of their manic and depressive symptoms approximately 4 years earlier than non–rapid-cycling patients. The authors of both reports speculated that younger age at illness onset may lead to a liability or vulnerability to future rapid cycling.

ANTIDEPRESSANTS AND RAPID CYCLING

The etiology of rapid cycling is poorly understood.[15] The most common lines of investigation have examined hypothyroidism, gonadal/steroid effects, brain injury, and psychotropic drug effects. Studies of thyroid hypofunction[16] and gonadal and steroid effects[17] have yielded either equivocal or negative results. Studies of antidepressants[14,18] have often found an association with the onset or worsening of rapid cycling, although this association has not been found across all studies.

Bauer et al.[19] conducted a study that compared the rates and characteristics of spontaneous rapid cycling and antidepressant-associated rapid cycling. The study found that of 120 patients with rapid cycling, 98 (81.7%) also experienced spontaneous rapid cycling, and, of these patients, 92 (95.8%) also reported rapid cycling that was either induced or exacerbated by antidepressant use. Both groups had higher rates of female patients with rapid cycling compared with male patients with rapid cycling, experienced similar retrospective and prospective episodes, and had a comparable number of full and truncated episodes.

In contrast, Coryell et al.,[6,10] in 2 prospective studies, found no association between antidepressants and the development of rapid cycling, after controlling for the presence of major depression. The authors suggested that the presence of depression prompted treatment with antidepressants, which implies a false causal relationship between antidepressant use and the development of rapid cycling, and that depression itself may have been the cause of subsequent cycling.

STEP-BD TREATMENT STRATEGIES

Due to the paucity of well-designed, controlled studies in homogeneous cohorts of patients with rapid cycling, no clear consensus exists as to what constitutes optimal treatment of rapid cycling.[20] The rapid-cycling care pathway in STEP-BD used a methodical, 3-stage pathway for the treatment of rapid cycling.[21] In the first year of prospective analysis, the percentage of rapid-cycling patients dramatically decreased, from approximately 32% at study entry to only 4% at the end of 1 year.

Treatment of Rapid Cycling

Fortunately, an increasing number of recent studies have begun either examining exclusive cohorts of rapid-cycling patients or including large numbers of rapid-cycling patients in their design with the intention of conducting later subanalyses. Recent studies of several atypical antipsychotics, lamotrigine, divalproex, and lithium have focused specifically on the treatment of rapid-cycling cohorts, recognizing the need to find more effective treatments in this often treatment-refractory group.

Treatment of rapid cycling in STEP-BD begins with a determination that a patient is actively cycling and not solely depressed, after which the patient enters the 3-part pathway for rapid cycling. First, patients must minimize or eliminate any potential cycle-promoting agents, such as antidepressants, stimulants, caffeine, sympathomimetics, or steroids. Rather than abrupt discontinuation of antidepressant use, the STEP-BD rapid-cycling algorithm favors gradual tapering of antidepressants by 20% to 30% per month. Clinicians must be alert for uncovering less obvious cycle-promoting agents, particularly psychosocial activities that interfere with sleep-wake cycles, such as shift work or travel across time zones.[22] Other identifiable secondary causes of cycling, including underlying medical conditions and comorbid substance abuse problems, should be identified and treated.

The second treatment step involves adding or optimizing mood stabilizers, particularly those agents that have been proven in maintenance treatment such as lithium, lamotrigine, olanzapine, aripiprazole, or divalproex.[23] The outcome of interventions should be evaluated over approximately 4 months or 3 cycle lengths by using a systematic mood-charting method. If cycling persists at the end of that time, then an additional anticycling agent should be considered. Combinations would most likely involve 2 traditional mood-stabilizing agents or the addition of an atypical antipsychotic or dopamine-blocking agent to a standard mood agent. Medications with the most robust data should be used first before moving to more experimental treatments.[23] Psychotherapy may also be a helpful adjunct. Interventions should again be carefully evaluated over at least 4 months or 3 cycle lengths, especially since a relatively rapid improvement in mood state may lead to the false impression of recovery when it is, in fact, a mood cycle.

Third, if cycling still persists, then more experimental or putative treatments for rapid cycling should be considered (see below). Clinicians must balance the acute needs of the patient, particularly when he or she is depressed, with long-term stability (i.e., most likely avoiding the use of antidepressants and further destabilizing the course of the illness).

Triggers of Affective Instability

Common triggers of affective instability include comorbid medical conditions, substance abuse, and psychosocial stressors. Common medical triggers include hypothyroidism, conditions that disrupt or interrupt sleep patterns (e.g., untreated sleep apnea), the use of or withdrawal from substances, and medications such as steroids, hormones, and muscle relaxants. Psychosocial triggers such as conflict with others, grief, success (e.g., job promotion), shift work, travel across time zones, or loss of support systems may contribute to affective instability.

STRATEGIES FOR THE TREATMENT OF RAPID CYCLING

Many different treatment strategies have been used to treat rapid cycling, ranging from use of standard mood agents, such as lithium, divalproex, and carbamazepine (either alone or in combination), to treatment with atypical antipsychotics, including clozapine. Because of the often refractory nature of rapid cycling, more experimental treatments have been employed, including topiramate, gabapentin, electroconvulsive therapy, omega-3 fatty acids, nimodipine, choline, high-dose levothyroxine, light therapy, and melatonin. However, only a few medications have prospective, controlled data, and those will be the focus here.

Lithium

Despite the fact that nonresponse to lithium was part of the original description of rapid cycling, lithium can reduce the severity and duration of subsequent episodes in rapid cycling.[1,13] Lithium's primary effect appears to be more robust on mania and hypomania than depression, and its efficacy in depression may be increased if antidepressants are avoided or stopped. Kukopulos et al.[14] found that lithium response increased from 16% to 78% after antidepressants were discontinued. Dunner et al.,[24] in a study of 29 patients with rapid-cycling bipolar disorder, examined the effect of lithium treatment over 1 year. Patients treated with lithium experienced an increase in the amount of time spent euthymic and a decrease in the amount of time spent manic or depressed. The authors noted that although the frequency of mood episodes did not necessarily change, the severity of the episodes was reduced.

Divalproex

Data from 6 open studies[25–30] suggest that patients shown to be unresponsive to lithium have a better response to divalproex. Many studies have suggested that, like lithium, divalproex has a moderate-to-marked effect in treating the manic phase of rapid cycling but a poor-to-moderate effect against depression. In a recent, randomized, double-blind, parallel-group study, Calabrese et al.[31] compared lithium and divalproex in the treatment of an exclusive rapid-cycling cohort. All subjects were initially given both lithium and divalproex until their condition stabilized. Of the initial 254 patients, only 60 achieved stability and were randomly assigned to lithium or divalproex monotherapy for 20 months. The majority of those who failed to reach stability relapsed into depression, rather than mania. Of those patients who continued on monotherapy, 56% percent of the lithium patients relapsed and 50% of the divalproex patients relapsed in the 20-month follow-up period. Median survival times to an intervention for a mood episode showed a numerical advantage for divalproex (45 weeks) compared with lithium (18 weeks), but the difference did not achieve statistical significance. Lithium and divalproex were able to achieve persistent bimodal response in only 24% of patients, and the trial failed to show a difference between lithium and divalproex monotherapy over 20 months.

Lamotrigine

In a placebo-controlled, double-blind, 26-week trial, Calabrese et al.[32] studied lamotrigine in bipolar I and II patients with rapid cycling. Of 324 patients who entered the preliminary phase of the study, 182 patients were randomly assigned to treatment with lamotrigine or placebo. No difference in time to additional pharmacotherapy (the primary outcome measure) was found between lamotrigine and placebo. Most patients who required additional pharmacotherapy were treated for depression. However, median survival times between the 2 groups did achieve statistical significance: 14 weeks for the lamotrigine group versus 8 weeks for the placebo group. In addition, when the 2 groups were stratified by bipolar I versus bipolar II status, lamotrigine appeared to provide a more robust effect for the bipolar II subtype. Median survival time for bipolar II patients treated with lamotrigine was 17 weeks compared with 7 weeks with placebo. In the bipolar I patients, however, no significant treatment differences were observed.

Carbamazepine

A total of 19 open studies and 4 controlled studies[33] of carbamazepine found evidence similar to the findings of lithium and divalproex research, suggesting a marked-to-moderate treatment effect in mania but a poor-to-moderate effect in the depressed phase. The largest study was performed by Denicoff et al.,[34] using a 3-year, cross-over comparison of carbamazepine, lithium, and the combination. The trial used a mixed cohort of patients, as 61% had a history of rapid cycling. Fifty-two patients were randomly assigned to receive either lithium or carbamazepine monotherapy in the first year of the study, then crossed over to the opposite drug in the second year, and then received a combination of the drugs in the third year. While only 7 (28%) of 25 patients responded to lithium treatment with moderate-or-marked improvement and 4 (19%) of 21 patients responded to carbamazepine treatment, 9 (56%) of 16 patients taking the combination had a marked-to-moderate improvement. Of the 9 patients who responded to combination therapy, 4 had not responded to either monotherapy.

Atypical Antipsychotics

Data from several mania and bipolar depression trials using atypical antipsychotics have shown efficacy in the treatment of rapid-cycling patients. The atypical antipsychotics are emerging as a promising pharmacologic option in the treatment of rapid cycling.

Olanzapine. Sanger et al.[35] conducted a subanalysis from a larger olanzapine mania trial. In this 3-week, placebo-controlled, randomized trial, 45 patients with rapid cycling were included in the mania trial. Olanzapine produced significantly greater improvement[7] compared with placebo in patients' mean Young Mania Rating Scale (YMRS) total score and Positive and Negative Syndrome Scale positive symptom subscore. Clinical response (defined as ≥ 50% reduction in YMRS score) was seen in 11 (58%) of the 19 olanzapine-treated rapid-cycling patients, compared with 7 (28%) of the 25 placebo-treated patients. While this difference did not achieve statistical significance, this study was the first to examine the efficacy of an atypical antipsychotic in an exclusively rapid-cycling group.

In a study of the olanzapine-fluoxetine combination (OFC) in the treatment of bipolar depression, Keck et al.[36] reported that patients receiving OFC had higher rates of improvement for depressive symptoms than patients given placebo or olanzapine monotherapy. The study analyzed a subset of 315 patients with a history of rapid cycling, and of these patients, 138 received placebo, 140 received olanzapine, and 37 received OFC. While patients had high remission rates with placebo (49.5%) and with olanzapine (54.1%), the patients given OFC had substantially higher remission rates (77.8%).

Aripiprazole. Keck et al.[37] conducted a randomized, double-blind trial in which patients with mania received either aripiprazole at 30 mg/day or placebo. Patients receiving aripiprazole had a significantly greater response compared with those taking placebo. Fifty-one (40%) of 127 patients in the group given aripiprazole experienced a reduction in their YMRS score greater than or equal to 50% improvement, compared with only 24 (19%) of 127

patients given placebo. A total of 61 patients with rapid cycling were included in the study (33 received aripiprazole, 28 placebo), but their responses were not reported separately. Jody et al.,[38] in a later analysis, examined pooled data from 3 aripiprazole mania trials (a total of 899 patients). The study examined subpopulations of bipolar disorder, including 103 patients with rapid cycling, half of whom received placebo. In patients with rapid cycling, aripiprazole led to more significant reductions in YMRS scores than placebo (–10.6 vs. –5.5). Efficacy of aripiprazole in patients with rapid cycling was found to be comparable to that in patients without rapid cycling.

Quetiapine. Recently, Calabrese et al.[39] conducted a randomized, double-blind, controlled trial of quetiapine in bipolar depression. Patients in the 8-week study were randomly assigned to 300 or 600 mg/day of quetiapine or to placebo. Included in the study were 108 patients with rapid cycling. Regardless of the presence of rapid cycling, patients taking either dose of quetiapine experienced significantly greater improvement in their mean MADRS scores compared with patients taking placebo.[40] Effect size for the entire group (rapid- and non–rapid-cycling patients) showed moderate-to-large effect: 0.81 for 600 mg/day of quetiapine and 0.67 for 300 mg/day of quetiapine, although the effect size for the rapid-cycling group was not reported separately. There were no differences between groups in treatment-emergent mania.

Clozapine. Suppes et al.[41] conducted the first controlled trial using clozapine as add-on therapy in a 1-year, randomized study of 38 treatment-refractory bipolar patients. Ratings on the Brief Psychiatric Rating Scale and the Clinical Global Improvement scale improved significantly overall, but data specific to the 21 rapid-cycling patients were not reported. However, a more recent trial[42] using clozapine as add-on therapy in a group of refractory cycling patients found that patients without rapid cycling experienced significantly greater improvement in symptoms compared with patients with rapid cycling over the course of 1 year.

Other atypical antipsychotics. Data on the efficacy of risperidone in rapid cycling[43,44] are limited to small, open-label studies, used as augmentation to existing mood stabilizers. To date, there are no published studies using ziprasidone in a rapid-cycling cohort.

Psychosocial Treatment

Although there are no specific psychosocial therapies for rapid cycling, several therapies designed specifically for bipolar disorder most likely are of benefit as an adjunct to medication. Two such therapies are family-focused treatment, developed by Miklowitz et al.,[45] and interpersonal social rhythm therapy, developed by Frank et al.[46] Psychosocial treatments improve adherence to medications, lower psychosocial stress, improve sleep-wake cycles, educate patients and their families about warning signs of illness and the importance of early interventions, and establish relapse prevention plans for both depression and mania.

Assessment of Treatment Response

Treatment response in patients with rapid cycling must be assessed over at least 4 months or 3 cycle lengths, as resolution of an acute episode is not necessarily evidence that a treatment intervention has worked. Over the first few months, evidence of decreased cycle frequency or intensity may be a sign of improvement. A single improvement does not necessarily mean success, just as a single recurrence does not necessarily mean failure. Mood charts are extremely helpful in tracking the course of illness and the progress of treatment over time.

CONCLUSION

Rapid cycling remains a difficult condition to treat. At this juncture, mania is more effectively treated than depression, and despite some evidence to the contrary, treatment with antidepressants is best avoided. Since no single drug currently treats both mania and depression, combination therapy is probably necessary, using proven therapies first and then moving to more putative agents later. The growing literature on the efficacy of the atypical antipsychotics in this disorder suggests they will be of great help in treating rapid cycling in the future. Prospective data from the STEP-BD program should shed more light on managing this difficult-to-treat aspect of bipolar illness.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Epitol, and others), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), levothyroxine, (Synthroid, Levo-T, and others), lithium (Eskalith, Lithobid, and others), nimodipine (Nimotop), olanzapine (Zyprexa), olanzapine/fluoxetine combination (Symbyax), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, aripiprazole, carbamazepine, choline, clozapine, divalproex, gabapentin, lamotrigine, levothyroxine, lithium, nimodipine, olanzapine, olanzapine/fluoxetine combination, quetiapine, risperidone, topiramate, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of rapid-cycling bipolar disorder.

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