Rapid cycling bipolar disorder in adults: Treatment of major depression

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INTRODUCTION

Bipolar disorder is characterized by mood episodes that are nearly always recurrent [1,2]. Patients who experience at least four episodes during a 12-month period are classified as “rapid cycling” [2].

The term was first used in 1974 to describe patients with bipolar disorder who were unresponsive to lithium [3]. However, it is now clear that any form of pharmacotherapy is typically less beneficial for rapid cycling bipolar disorder than non-rapid cycling bipolar disorder [4]. In addition, lithium is not less effective than other drugs in rapid cycling [5], and may perhaps be as effective in rapid-cycling and non-rapid cycling bipolar patients [6,7].

This topic reviews the treatment of major depression in rapid cycling patients. The treatment of mania and hypomania in rapid cycling patients, and the epidemiology, pathogenesis, clinical features, and diagnosis of rapid cycling in patients with bipolar disorder are discussed separately, as is the diagnosis and general treatment of bipolar disorder:

- (See "Rapid cycling bipolar disorder in adults: Treatment of mania and hypomania".)
- (See "Rapid cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis".)
- (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)

- (See "Bipolar major depression in adults: Choosing treatment".)
- (See "Bipolar disorder in adults: Choosing maintenance treatment".)

DEFINITION OF RAPID CYCLING BIPOLAR DISORDER

According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), bipolar disorder is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [2]. The major subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic, and nearly always experience major depressive and hypomanic episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes. Additional information about the clinical features and diagnosis of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

Rapid cycling specifies a particular course of illness that can occur in bipolar I disorder or bipolar II disorder, rather than a subtype of bipolar disorder [2]. The diagnostic criteria for rapid cycling are as follows:

- At least four mood episodes in the previous 12 months.
- The episodes meet both the symptom and duration criteria for a manic, hypomanic, or major depressive episode. Although the symptoms that occur as part of a rapid cycling pattern are no different from symptoms that occur as part of a non-rapid cycling pattern, rapid cycling episodes are typically of shorter duration.
- The episodes are demarcated by a period of partial or full remission for at least two months, or by a switch to an episode of opposite polarity. Manic and hypomanic episodes are counted as being on the same pole; thus, a switch in polarity involves one of these episodes and an episode of major depression.

Additional information about the clinical features and diagnosis of rapid cycling are discussed separately. (See "Rapid cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis".)

GENERAL PRINCIPLES

Remission of rapid cycling mood episodes often results from the natural course of illness, rather than treatment. Thus, the primary goal of treatment is to prevent further episodes, and clinicians should attempt to prescribe medications for acute mood episodes that are also suitable for maintenance treatment.

Clinicians may find that it is not feasible for rapid cycling patients to fully remit from a mood episode or avoid recurrences [8], and that a more realistic goal is to improve functioning and reduce the frequency, intensity, and duration of mood episodes [5]. The difficulties posed by rapid cycling usually necessitate referral to a psychiatrist.

Additional information about the general principles of treating rapid cycling bipolar disorder, including the frequency of monitoring patients and the duration of a treatment trial, are discussed separately. (See "Rapid cycling bipolar disorder in adults: Treatment of mania and hypomania", section on 'General principles'.)

Use of antidepressants — For acute episodes of major depression that occur in patients with rapid cycling bipolar disorder, antidepressants combined with an antimanic drug may be beneficial. As an example, a meta-analysis pooled four trials that randomly assigned patients (n = 101) to either an antidepressant or a comparator (eg, placebo); the antidepressants included citalopram, escitalopram, paroxetine, or venlafaxine [4]. Assessments before and after treatment with the antidepressant suggested that depressive symptoms improved, and the clinical effect was large. However, heterogeneity across studies was moderate. In addition, the duration of the trials was relatively short; thus, potential worsening of the overall rapid cycling course by antidepressants could not be evaluated. Nevertheless, the investigators performed a qualitative review that suggested switching to mania was relatively high with venlafaxine.

There is a broad consensus that antidepressants should generally not be used as maintenance treatment in patients with rapid cycling [9-11]. Evidence supporting this approach includes a study of bipolar patients who were successfully treated for major depression with an antidepressant plus carbamazepine, divalproex, lamotrigine, or lithium, and then randomly assigned to continue or discontinue the antidepressant [12]. The mean length of follow-up was 1.7 years. In the group that continued antidepressants, the mean number of depressive episodes was greater in rapid cycling patients (n = 7) than non-rapid cycling patients (n = 23; 1.3 versus 0.4 episodes/year). By contrast, in the group that discontinued antidepressants, the rate of subsequent depressive episodes was the same in rapid cycling (n = 9) and non-rapid cycling patients (n = 28; 0.8 episodes/year).

TREATMENT

In general, response to pharmacotherapy appears to be poorer in rapid cycling bipolar disorder than non-rapid cycling bipolar disorder [5,13-16].

Overview — Rapid cycling bipolar patients with major depression are typically treated with pharmacotherapy. However, patients refractory to multiple medication regimens may benefit from electroconvulsive therapy (ECT).

Although different drugs have been studied for treating acute episodes of rapid cycling bipolar disorder, multiple systematic reviews have concluded that the paucity of evidence from randomized trials precludes definitively determining the efficacy of specific medications [4,7]. In addition, the natural course of illness complicates interpretation of results from relatively short-term trials.

First line medication — We suggest quetiapine as first line treatment for rapid cycling bipolar major depression based upon its efficacy and tolerability in randomized trials [4,17-19]. In addition, other randomized trials have demonstrated that quetiapine is efficacious for the general treatment of bipolar major depression and also for maintenance treatment [20-24].

Quetiapine is usually started at 50 mg at bedtime and titrated up by increments of 50 to 100 mg per day to achieve a target dose of 300 mg per day within four to seven days, provided that side effects do not intervene [22]. (Doses of 600 mg per day have been studied for bipolar major depression, but provide no advantage over a dose of 300 mg per day.) The side effects (table 4) and pharmacology of quetiapine are discussed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Evidence for the efficacy of quetiapine in rapid cycling bipolar patients with major depression includes systematic reviews of multiple studies [4,7]. As an example:

- An eight-week randomized trial compared quetiapine (300 or 600 mg per day) with placebo for treating bipolar major depression [22]. In the subgroup with rapid cycling (n = 108), response (improvement from baseline on the depression rating scale ≥ 50 percent) occurred in significantly more patients who received quetiapine than placebo (66 versus 29 percent) [15,17]. This was consistent with the finding that each dose of quetiapine was superior to placebo in the total sample [22].

- An eight-week randomized trial compared quetiapine extended release (300 mg per day) with placebo for treating bipolar major depression [18]. In the subgroup with rapid cycling (n = 74), improvement was greater with quetiapine than placebo. This was consistent with the finding that quetiapine was superior in patients without rapid cycling (n = 196).

- A one-year, open-label, randomized study compared quetiapine (mean dose 465 mg per day) with valproate (mean dose 1340 mg per day) in 38 rapid cycling patients who were euthymic or primarily suffering from depressive symptoms at baseline [25]. Fewer days with moderate to severe depressive symptoms occurred in patients who received quetiapine than in patients who received valproate (12 versus 28 percent of days).

Resistant patients — Many rapid cycling bipolar patients with major depression do not respond to quetiapine [15,17]. For these resistant patients, we suggest sequential treatment with lamotrigine, lithium, and the combination of olanzapine and fluoxetine. To switch drugs, quetiapine is tapered and discontinued over one to two weeks at the same time that another medication is started and titrated up. We generally taper quetiapine by 50 to 200 mg per day, every one to two days.

The following drugs are listed in order of preference, based upon how often each drug has been studied and how well it worked. For resistant rapid cycling bipolar patients with major depression who do not respond to one second-line drug, or do not tolerate the drug, we suggest tapering and discontinuing the failed medication over two or more weeks at the same time that another second-line medication is started and titrated up. The failed medication is generally tapered by the same amount for each dose decrease. As an example, lamotrigine 200 mg per day is decreased by 50 mg per day, every two to three days.

- **Lamotrigine** – The initial dose of lamotrigine is 25 mg per day for weeks one and two. For weeks three and four, the dose is increased to 50 mg per day, taken in two divided doses (an extended release formulation is available for once a day dosing). The dose can then be titrated up by 25 to 50 mg per day, one week at a time for each increase. This slow titration reduces the risk of life-threatening skin rash, such as Stevens-Johnson syndrome. The target dose ranges from 50 to 300 mg per day [26]. The side effects and pharmacology of lamotrigine are discussed separately. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Lamotrigine'.)

  Evidence for the efficacy of lamotrigine in treating rapid cycling bipolar patients with major depression includes the following studies:

  - A 26-week randomized trial compared lamotrigine (mean dose 288 mg per day) with placebo in 177 rapid cycling bipolar patients who were clinically stable for two weeks [27]. Relapse occurred in significantly fewer patients who received lamotrigine than placebo (59 versus 74 percent). In addition, discontinuation of treatment due to adverse side effects was identical for lamotrigine and placebo (two percent of each group).

- A randomized, crossover trial compared lamotrigine (mean daily dose 274 mg per day) with placebo in 31 patients with treatment-resistant mood disorders (74 percent had rapid cycling bipolar disorder) [28]. In the total sample, response occurred in significantly more patients who received lamotrigine than placebo (52 versus 23 percent).

- A 16-week, open-label, randomized trial (outcome assessed by blinded raters) compared lamotrigine (median dose 250 mg per day) with lithium (median serum concentration 0.8 mmol/L) in patients with bipolar major depression [29]. In the subgroup with rapid cycling (n = 68), significant improvement from baseline occurred with each drug, with no significant difference between the two medications; this was consistent with the finding that improvement with each drug was comparable in the total sample.

- **Lithium** – The dose, side effects, and pharmacology of lithium, as well as the use of serum levels, are discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects".)

  Evidence for the benefit of lithium in treating depressed, rapid cycling patients includes the following studies:

  - As discussed above, a trial found that improvement of rapid cycling bipolar major depression was comparable for lithium and lamotrigine [29].

  - A pooled analysis of three observational studies found that in 172 rapid cycling bipolar patients who were treated with lithium, recurrent mood episodes did not occur in 34 percent [30]. In a separate pooled analysis of three observational studies with 90 rapid cycling patients who received lithium, the frequency, intensity, and duration of mood episodes decreased by 50 percent or more in 59 percent of patients.

  - A 12-week randomized trial compared lithium with venlafaxine for treatment of bipolar depression, and the group of patients assigned to lithium included patients who were rapid cyclers (n = 28) and patients who were non-rapid cyclers (n = 36) [31]. Response (reduction of baseline symptoms ≥50 percent) to lithium for rapid cyclers and non-rapid cyclers was comparable (39 and 31 percent of patients).

- **Olanzapine plus fluoxetine** – For patients who do not respond to sequential trials of quetiapine, lamotrigine, and lithium, we suggest olanzapine plus fluoxetine [15,32]. However, it is reasonable to use a different second-generation antipsychotic such as

lurasidone or quetiapine, and/or to use a different selective serotonin reuptake inhibitor such as citalopram, escitalopram, or sertraline.

The initial dose of olanzapine is generally 5 mg per day taken once daily, and the usual target dose range is 5 to 20 mg per day. Olanzapine is increased by 5 mg per day, every one to seven days, depending upon the intensity of specific symptoms, intervening side effects, and response to treatment. As an example, persistent insomnia should prompt a dose increase. The side effects and pharmacology of olanzapine are discussed separately. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

The initial dose of fluoxetine is usually 20 mg per day taken once daily, and the target dose range is generally 20 to 60 mg per day. For patients who do not respond to 20 mg per day within two to four weeks, the dose is increased by 10 to 20 mg per day, depending on how well the medication is tolerated. Patients who remain unresponsive to treatment should receive additional increases of 10 to 20 mg per day every two to four weeks as tolerated, to an effective dose within the target dose range. We generally taper and discontinue fluoxetine over one to two weeks soon after the depressive syndrome has resolved (eg, within two to three months). Longer treatment may be associated with poorer outcomes [12]. Fluoxetine is decreased by 10 mg per day, every one to two days. The side effects and pharmacology of fluoxetine are discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Evidence for the efficacy of olanzapine plus fluoxetine includes an eight-week randomized trial that compared olanzapine (mean dose 7 mg per day) plus fluoxetine (mean dose 40 mg per day) with placebo in patients with bipolar major depression [32]. In the subgroup with rapid cycling (n = 164), response (improvement from baseline on the depression rating scale ≥50 percent) occurred in more patients who received the combination than placebo (78 versus 39 percent) [15,32]. This was consistent with results in the total sample that found the combination was superior to placebo. In addition, discontinuation of treatment due to adverse side effects in the rapid cycling subgroup was comparable for patients who received the combination or placebo (5 and 3 percent), as was switching from major depression to mania or hypomania (10 versus 4 percent of patients) [15].

Some authorities avoid antidepressants in rapid cycling bipolar patients with major depression [33,34], because observational studies suggest that antidepressants may exacerbate rapid cycling [8]. However, other observational studies [30,35,36] and randomized trials [31] have failed to find this association. The possible role of antidepressants in the pathogenesis of rapid cycling is discussed separately. (See "Rapid

cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Antidepressants'.)

Refractory patients — Based upon several studies, rapid cycling bipolar patients with major depression frequently do not respond to pharmacotherapy [16,27,29,37-39]. For refractory patients whose depression does not respond to trials of quetiapine, lamotrigine, lithium, and the combination of olanzapine and fluoxetine, we suggest ECT.

- **Electroconvulsive therapy (ECT)** – ECT is generally safe and there are no absolute contraindications, even in patients whose general medical status is compromised [40]. However, safety concerns regarding ECT necessitate preprocedure medical consultation. Adverse effects include cardiopulmonary events, aspiration pneumonia, fractures, dental and tongue injuries, headache, nausea, and cognitive impairment. Medical consultation prior to ECT is discussed separately. (See "Medical evaluation for electroconvulsive therapy".)

  Electrode placement and other aspects of ECT technique for treating rapid cycling bipolar patients with major depression have not been standardized. Thus, ECT is typically administered with the same technique used for other indications and is generally given three times per week on alternating days. Most patients regardless of indication remit with 6 to 12 treatments, but some patients may require 20 or more. Additional information about ECT is discussed separately. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

  Evidence for the efficacy of ECT in treating rapid cycling bipolar patients with major depression includes studies that have found ECT is beneficial for the general population of patients with bipolar depression, who were not selected for rapid cycling. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Bipolar major depression'.)

  Other evidence includes the following studies [41-44]:

  - A prospective observational study followed 43 patients with rapid cycling bipolar disorder who received ECT; the mood episode resolved and there were no recurrences for at least one year in 26 percent, and temporary improvement occurred in the remaining patients [33].

  - In a retrospective study, 14 rapid cycling bipolar patients with major depression received ECT (mean number of treatments 23, mean duration of treatment 21 months) [44]. Rapid cycling resolved in every patient and the mean number of mood episodes

per year decreased from six to one. However, another retrospective study found that among 24 patients with rapid cycling bipolar disorder who were treated with ECT, none remitted [45].

- **Second-generation antipsychotic** – For rapid cycling bipolar patients with refractory major depression who decline or do not have access to ECT, a reasonable alternative is an adjunctive second-generation antipsychotic other than quetiapine, which we suggest as first-line treatment. (See 'First line medication' above.)

  Evidence that supports using a second generation antipsychotic for acute major depression in rapid cycling bipolar disorder includes a prospective observational study of 10 patients who were treated with adjunctive risperidone (2 to 6 mg per day) for at least six months; mean depression rating scale scores decreased significantly from baseline [46].

  However, second-generation antipsychotic monotherapy does not appear to be useful. An eight-week randomized trial compared olanzapine monotherapy with placebo in bipolar patients with major depression [32]; in the subgroup with rapid cycling (n = 261), response (improvement from baseline on the depression rating scale ≥50 percent) was comparable for olanzapine and placebo [15].

- **Levothyroxine (T4)** – For rapid cycling bipolar patients with refractory major depression who decline or do not have access to ECT, and do not respond to treatment with a second-generation antipsychotic, a reasonable alternative is adjunctive levothyroxine (T4), but not triiodothyronine (T3) [47,48]. Use of T4 for rapid cycling patients is discussed separately. (See "Rapid cycling bipolar disorder in adults: Treatment of mania and hypomania", section on 'Refractory patients'.)

- **Clozapine** – Although clozapine is primarily effective for the treatment of manic episodes in rapid as well as non-rapid cycling bipolar disorder, clozapine may also improve bipolar depression in rapid cycling. A retrospective study identified 13 patients with rapid cycling bipolar disorder who received clozapine (mean dose 180 mg/day, range 25 to 600 mg/day) as add-on therapy or monotherapy [49]. Outcomes during the year before clozapine treatment were compared with the year after clozapine was started. Clozapine was associated with fewer depressive episodes, manic episodes, hospitalizations, and suicide attempts.

ADJUNCTIVE PSYCHOTHERAPY

Augmenting pharmacotherapy with psychotherapy can help all patients with bipolar disorder, including those with rapid cycling bipolar major depression. We suggest psychoeducation (which teaches patients about the clinical features, treatment, and prognosis of rapid cycling bipolar disorder), based upon the demonstrated efficacy of adjunctive psychoeducation in a meta-analysis of six randomized trials for the general treatment of bipolar disorder [50]. Effective alternatives include cognitive-behavioral therapy (CBT), family therapy, and interpersonal social rhythm therapy. Adjunctive psychotherapy for treating bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Choosing adjunctive psychotherapy'.)

In a prospective observational study, 10 depressed or euthymic bipolar patients with rapid cycling were treated with 20 sessions of CBT that included psychoeducation, cognitive restructuring of depressive and manic thoughts (eg, “No one loves me” or “I can afford to buy everything”), and skills for managing mood shifts and comorbid psychiatric disorders [51]. Symptomatic improvement occurred in the six patients who completed the study.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bipolar disorder".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (See "Patient education: Bipolar disorder (The Basics)" and "Patient education: Coping with high drug prices (The Basics)".)

- Beyond the Basics topics (See "Patient education: Bipolar disorder (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)".)

These educational materials can be used as part of psychoeducational psychotherapy. (See "Bipolar disorder in adults: Psychoeducation and other adjunctive maintenance psychotherapies", section on 'Group psychoeducation'.)

The National Institute of Mental Health also has educational material explaining the symptoms, course of illness, and treatment of bipolar disorder in a booklet entitled "Bipolar Disorder," which is available online at the website or through a toll-free number, 866-615-6464. The web site also provides references, summaries of study results in language intended for the lay public, and information about clinical trials currently recruiting patients.

More comprehensive information is provided in many books written for patients and family members, including The Bipolar Disorder Survival Guide: What You and Your Family Need to Know, Third Edition, written by David J. Miklowitz, PhD (published by The Guilford Press, 2019); An Unquiet Mind: A Memoir of Moods and Madness, written by Kay Jamison, PhD (published by Random House, 1995); and Treatment of Bipolar Illness: A Casebook for Clinicians and Patients, by RM Post, MD, and GS Leverich, LCSW (published by Norton Press, 2008).

The Depression and Bipolar Support Alliance (accessible at the website or 800-826-3632) is a national organization that educates members about bipolar disorder and how to cope with it. Other functions include increasing public awareness of the illness and advocating for more research and services. The organization is administered and maintained by patients and family members, and has local chapters.

The National Alliance on Mental Illness (accessible at the website or 800-950-6264) is a similarly structured organization devoted to education, support, and advocacy for patients with any mental illness. Bipolar disorder is one of their priorities.

SUMMARY AND RECOMMENDATIONS

- Bipolar disorder is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3). (See 'Definition of rapid cycling bipolar disorder' above and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

- Rapid cycling bipolar disorder is diagnosed in patients with four or more mood episodes during the past 12 months. Although the symptoms that occur as part of a rapid cycling

pattern are no different from symptoms that occur as part of a non-rapid cycling pattern, rapid cycling episodes are typically of shorter duration. Separate episodes are demarcated from each other either by a switch from one pole to the other (eg, major depression to mania), or by full or partial remission for at least two months. (See 'Definition of rapid cycling bipolar disorder' above and "Rapid cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Diagnosis'.)

- Remission of rapid cycling mood episodes often occurs as a result of the course of illness, rather than treatment. Thus, the primary goal of treatment is to prevent further episodes. (See 'General principles' above.)

- For rapid cycling bipolar patients with major depression, we suggest initial treatment with quetiapine rather than other drugs (**Grade 2C**). (See 'First line medication' above.)

- For resistant rapid cycling bipolar patients with major depression that does not respond to quetiapine, we suggest sequential treatment with lamotrigine, lithium, and the combination of olanzapine and fluoxetine, rather than other medications (**Grade 2C**). (See 'Resistant patients' above.)

- For refractory rapid cycling bipolar patients with major depression that does not respond to trials of quetiapine, lamotrigine, lithium, and the combination of olanzapine and fluoxetine, we suggest electroconvulsive therapy (ECT) rather than additional pharmacotherapy trials (**Grade 2C**). (See 'Refractory patients' above.)

- For depressed rapid cycling bipolar patients, we suggest augmenting pharmacotherapy with psychotherapy rather than using pharmacotherapy alone (**Grade 2C**). We generally use psychoeducation; however, cognitive-behavioral therapy, family therapy, and interpersonal social rhythm therapy are reasonable alternatives. (See 'Adjunctive psychotherapy' above.)

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