Rapid cycling bipolar disorder in adults: Treatment of mania and hypomania

AUTHOR: Ralph Kupka, MD, PhD
SECTION EDITOR: Paul Keck, MD
DEPUTY EDITOR: David Solomon, MD

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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 bipolar patients who were unresponsive to lithium [3]. However, it is now clear that any pharmacotherapy is often less beneficial for rapid cycling patients than non-rapid cycling patients, and that lithium may be as effective as other drugs for rapid cycling [4,5].

This topic reviews the treatment of mania and hypomania in rapid cycling patients. The treatment of major depression 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 major depression".)
- (See "Rapid cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis".)
- (See "Bipolar disorder in adults: Assessment and 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 (DSM-5), 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 episodes, and nearly always experience major depressive and hypomanic episodes. Bipolar II disorder is marked by at least one hypomanic episode and at least one major depressive episode, but 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 in DSM-5 are as follows:

- At least four mood episodes in the previous 12 months.
- The episodes meet both the symptom and duration criteria for mania, hypomania, or major depression. 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 are counted as being on the same pole; thus, a switch in polarity involves one of these episodes and an episode of major depression.

In some patients, hypomanic/manic and depressive episodes alternate for relatively longer periods without an interval of remission (continuous cycling) [6].

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

Mania and hypomania differ in that manic episodes are more severe and have a greater impact on psychosocial functioning (table 1 and table 2) [2]. Nevertheless, for the purpose of treatment, they are considered to be similar and thus treated with the same medications [7-11].

Treatment of manic and hypomanic episodes in patients with rapid cycling bipolar disorder is comparable to the treatment of mania or hypomania in non-rapid cycling patients [7-11]. Mania always necessitates pharmacotherapy. However, the severity of a hypomanic episode may be so limited that watchful waiting is an acceptable alternative to acute pharmacotherapy, especially for patients who are functioning well and have good social support and a history of good adherence to monitoring; in these cases, maintenance pharmacotherapy is emphasized. In addition, we suggest that clinicians discontinue antidepressants in patients with mania or hypomania.

Remission of individual 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, and clinicians should attempt to prescribe medications for acute mood episodes that are suitable for maintenance treatment.

Response to pharmacotherapy appears to be poorer in rapid cycling bipolar disorder than non-rapid cycling bipolar disorder [6,12-14]. A meta-analysis of nine studies (primarily observational, 1424 bipolar patients) examined improvement of mood episodes and rates of recurrence in rapid cycling and non-rapid cycling patients, and found that an inferior response to medications was more probable in rapid cycling patients (risk ratio 1.4, 95% CI 1.3-1.6) [4]. Clinicians may find that it is not feasible for rapid cycling patients to fully remit from a mood episode or avoid recurrences [15], and that a more realistic goal is to improve functioning and reduce the frequency, intensity, and duration of mood episodes [4]. The difficulties posed by rapid cycling usually necessitate referral to a psychiatrist.

The mood episodes that occur during rapid cycling are demarcated by a period of euthymia for at least two months, or by a switch from an episode of one polarity to an episode of the other polarity (eg, major depression to mania) without intervening euthymia [8]. Rapid cycling that is characterized by continuous switching between poles may respond more poorly to treatment than rapid cycling that includes intermittent periods of euthymia [16,17].

Poor adherence to pharmacotherapy occurs in 20 to 40 percent of rapid cycling bipolar patients [18-20], and appears to be more common in rapid cycling than non-rapid cycling patients [21]. Nonadherence in bipolar disorder is often managed with psychoeducation, but this has not been studied in rapid cycling patients. Adherence to treatment and use of psychoeducation in

bipolar disorder are discussed separately. (See "Bipolar disorder in adults: Choosing maintenance treatment".)

Monitoring the patient — Rapid cycling bipolar patients should be monitored for therapeutic and adverse medication effects, with particular attention to suicidal ideation and psychosis. The frequency of monitoring is determined by the patient's clinical status. Hospitalized patients are monitored daily. Outpatients are commonly seen on a weekly basis until they have responded (ie, the patient's safety has stabilized and the number, intensity, and frequency of psychotic and mood symptoms has improved substantially). Following response, patients can be seen every two to four weeks until they remit. Although some clinicians suggest that patients or caregivers record daily symptoms in a mood diary to help judge the effectiveness of treatment [22], this is not standard practice.

For rapid cycling bipolar patients who remit and remain stable, monitoring can be tapered, with progressively longer intervals between assessments. As an example, a patient who is seen every two weeks at the time of remission can be seen every two weeks for one to three more visits, then every month for one to three visits, and then every two months for one to three visits. Continuously stable patients can ultimately be seen every three to six months. More frequent visits should be scheduled for patients who develop symptoms or side effects.

Duration of treatment trial — For rapid cycling bipolar patients, we suggest that clinicians try to prescribe a particular treatment regimen for at least two to four months before determining whether it effectively improves acute symptoms and reduces the frequency, intensity, and duration of recurrent mood episodes [14,23].

SEVERE EPISODES

Severe mania is characterized by one or more of the following:

- Suicidal ideation or behavior.
- Homicidal ideation or behavior.
- Aggressive behavior.
- Psychotic features (ie, delusions or hallucinations).
- Poor judgement that places the patient or others at imminent risk of being harmed (eg, disinhibited or impulsive behavior at work or at home). Severe mania may lead to job loss and the break-up of relationships.

Severely ill patients generally require hospitalization [7-9].

For rapid cycling bipolar patients with severe mania, we usually use a medication combination, which is consistent with the recommendation of treatment practice guidelines [7-10] and many authorities [6,23]. Selecting a medication combination for treatment of severe mania is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Initial treatment'.)

For rapid cycling bipolar patients with severe mania that does not respond to one medication combination, we suggest additional medication combination trials. Treatment of resistant patients is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Treatment-resistant patients'.)

For rapid cycling bipolar patients with severe maniac episodes that do not respond to four to six medication combinations, we suggest electroconvulsive therapy (ECT). Treatment of refractory patients is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Treatment-refractory patients'.)

MILD TO MODERATE EPISODES

Mild to moderate illness is marked by the absence of suicidal or homicidal ideation or behavior, aggressiveness, psychotic features, and poor judgement that places the patient or others at imminent risk of being harmed. Nevertheless, the instability of mood and functioning in mild to moderate rapid cycling bipolar disorder is distressing to patients and caregivers. Monotherapy is commonly used for initial treatment of rapid cycling patients with hypomania or mild to moderate mania.

First line medications — For rapid cycling patients with hypomanic or mild to moderate manic episodes, we suggest risperidone, aripiprazole, or olanzapine monotherapy, based upon results from randomized trials for subgroups of rapid cycling patients [24-26], as well as results for bipolar patients in general [27]. We generally prefer risperidone and aripiprazole because they cause less weight gain [28]. Reasonable alternatives to risperidone, aripiprazole, or olanzapine include lithium, valproate, quetiapine, haloperidol, or carbamazepine, in order of preference. The doses, side effects, and pharmacology of these drugs are discussed separately:

- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Medication doses and side effects'.)
- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

- (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects".)
- (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects".)

For rapid cycling bipolar patients who do not respond to treatment with one first-line medication, or do not tolerate the drug, we suggest tapering and discontinuing the failed medication over one to two weeks at the same time that another first-line medication is started and titrated up. (Response is defined as stabilization of the patient's safety and substantial improvement in the number, intensity, and frequency of psychotic and mood symptoms). The failed medication is generally tapered by the same amount for each dose decrease. As an example, risperidone 4 mg per day is decreased by 1 to 2 mg per day, every one to two days.

For rapid cycling patients with hypomania or mild to moderate mania, evidence for the efficacy of risperidone, aripiprazole, olanzapine, lithium, valproate, quetiapine, and carbamazepine includes the following studies:

- **Risperidone** – A three-week randomized trial compared risperidone (mean dose 4 mg per day) with olanzapine (mean dose 15 mg per day) in patients with a manic or mixed (major depression concurrent with mania) episode [26]. In the subgroup with rapid cycling (n = 149), symptoms improved by approximately 60 percent 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 non-rapid cycling patients.

- **Aripiprazole** – Two randomized trials, each lasting three weeks, compared aripiprazole (15 or 30 mg per day) with placebo in patients with a manic or mixed episode [29,30]. A pooled analysis found that in the subgroup with rapid cycling (n = 103), remission occurred in significantly more patients who received aripiprazole than placebo (48 versus 22 percent) [24]. This was consistent with the finding that aripiprazole was superior in the total sample.

- **Olanzapine** – Two randomized trials (three and four weeks in duration) compared olanzapine (5 to 20 mg per day) with placebo in patients with a manic or mixed episode [31,32]. A pooled analysis found that in the subgroup with rapid cycling (n = 90), response (improvement from baseline on the mania rating scale ≥ 50 percent) occurred in significantly more patients treated with olanzapine than placebo (75 versus 46 percent) [25]; this was consistent with the finding that olanzapine was superior in the total sample [31,32].

- **Lithium**

- A 20-month randomized trial compared lithium (mean serum concentration 0.9 mmol/L) with divalproex (mean serum concentration 77 mcg/mL) in 60 rapid cycling bipolar patients, who were initially stabilized for four weeks with open-label lithium plus divalproex [18]. Relapse was comparable in patients who received lithium or valproate monotherapy (56 versus 50 percent), as was discontinuation due to adverse side effects (16 versus 4 percent).

- A review of eight studies (primarily open label) found that in 273 rapid cycling bipolar patients who were treated with lithium for a mean of 50 months, the course of illness improved in 48 percent [4].

- 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 [33]. 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.

- **Valproate (divalproex)** – A 47-week randomized trial compared divalproex (mean serum concentration 70 mcg/mL) with olanzapine (5 to 20 mg per day) in patients with a manic or mixed episode [34]. In the subgroup with rapid cycling (n = 144), improvement from baseline with each drug was comparable. This was consistent with the finding in the total sample that remission was comparable for divalproex and olanzapine [35].

- **Quetiapine**

  - A prospective observational study of 16 rapid cycling bipolar patients who were treated with quetiapine (target dose 150 to 200 mg per day, maximum 800 mg per day) for up to one year found that manic symptoms improved by at least 50 percent in eight of the patients [36].

  - A prospective observational study of 5 rapid cycling bipolar patients who were treated with adjunctive quetiapine (mean dose 720 mg per day) for a mean of four months found that the mean mania rating scale score decreased from baseline by approximately 60 percent [37].

- **Carbamazepine** – A review of 3 studies (primarily open label) found that in 133 rapid cycling bipolar patients who were treated with carbamazepine for a mean of 17 months, the course of illness improved in 45 percent [4]. In addition, carbamazepine and lithium were comparably effective in studies that directly compared the two treatments.

Resistant patients — Based upon clinical experience, rapid cycling patients with hypomania or mild to moderate mania often do not respond to treatment with two to three sequential monotherapy trials with first-line medications. For these resistant patients, we suggest combining lithium or valproate with a second-generation antipsychotic (except clozapine), based upon meta-analyses of randomized trials that studied the general treatment of manic and mixed (major depression concurrent with mania) episodes [38-40]. Generally, every medication that has not clearly improved the course of illness over approximately three cycles of manic/hypomanic plus depressive episodes should be tapered and stopped to prevent the accumulation of multiple ineffective medications. The efficacy of medication combinations is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Initial treatment'.)

We generally use a medication combination consisting of:

- Lithium plus risperidone, aripiprazole, or olanzapine; or
- Valproate plus risperidone, aripiprazole, or olanzapine

However, there is no high quality evidence of superior efficacy for any specific combination in treating rapid cycling patients with hypomania or mild to moderate mania. Reasonable alternatives to risperidone, aripiprazole, and olanzapine include haloperidol or another first-generation antipsychotic, quetiapine, and ziprasidone. Selecting a combination is guided by past response to medications, the past response of family members with bipolar disorder to medications, specific symptoms, side effect profiles, potential drug-drug interactions, comorbid general medical conditions, patient preference, and cost. Specific medication interactions that can occur may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

For resistant rapid cycling bipolar patients receiving lithium or valproate monotherapy for hypomanic or mild to moderate manic episodes, we add risperidone, aripiprazole, or olanzapine to their regimen. For resistant patients receiving risperidone, aripiprazole, or olanzapine monotherapy, we add lithium or valproate to their regimen. The dose and side effects of lithium, valproate, risperidone, aripiprazole, and olanzapine are discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Medication doses and side effects'.)

Resistant rapid cycling bipolar patients who do not respond to or tolerate one medication combination should be treated with a second medication combination. Generally, lithium is switched to valproate or vice versa. As an example, for patients who do not respond to lithium plus risperidone, aripiprazole, or olanzapine, we suggest tapering and discontinuing lithium at

the same time that valproate is started and titrated up. Lithium is generally tapered over one to two weeks by the same amount for each dose decrease (eg, lithium 1500 mg per day is decreased by 300 to 600 mg per day, every one to two days).

Conversely, for resistant rapid cycling patients who do not respond to valproate plus risperidone, aripiprazole, or olanzapine, we suggest tapering and discontinuing valproate at the same time that lithium is started and titrated up. Valproate is generally tapered over one to two weeks by the same amount for each dose decrease (eg, valproate 2000 mg per day is decreased by 250 to 500 mg per day, every one to two days).

Although the antipsychotic (risperidone, aripiprazole, or olanzapine) is generally continued at the same dose when lithium is switched to valproate or vice versa, it is also reasonable to switch the antipsychotic after lithium has been switched to valproate (or vice versa). The failed antipsychotic is generally tapered over one to two weeks by the same amount for each dose decrease (eg, risperidone 4 mg per day is decreased by 1 to 2 mg per day, every one to two days), and at the same time, the new antipsychotic is started and titrated up.

Refractory patients — Based upon clinical experience, rapid cycling bipolar patients with hypomania or mild to moderate mania generally respond to sequential pharmacotherapy trials. For refractory patients who do not respond to four to eight medication combinations involving lithium or valproate plus a second- or first-generation antipsychotic (not including clozapine), we suggest, in order of preference, using clozapine as monotherapy or add-on therapy, administering electroconvulsive therapy, or adding high-dose levothyroxine (T4).

- **Clozapine** – Clozapine as monotherapy or augmentation is an alternative to levothyroxine for refractory rapid cycling bipolar patients with hypomania or mild to moderate mania [41]. We generally use clozapine as monotherapy if the existing medication regimen has provided little to no benefit or is poorly tolerated; clozapine is titrated up as the failed drugs are tapered and discontinued concurrently over one to two weeks. The failed drugs are usually decreased by the same amount for each dose decrease. The dose, side effects, and pharmacology of clozapine are discussed separately. (See "Schizophrenia in adults: Guidelines for prescribing clozapine".)

  For rapid cycling patients with refractory hypomanic or mild to moderate manic episodes, we generally use clozapine as augmentation if the existing medications have provided modest to moderate benefit and is well tolerated, and maintain the existing drugs at the same doses. However, if clozapine is added to a regimen that includes another second-generation antipsychotic, the failed antipsychotic is generally tapered over one to two weeks by the same amount for each dose decrease (eg, aripiprazole 30 mg per day is

decreased by 5 to 10 mg per day, every one to two days), and at the same time, clozapine is started and titrated up.

Evidence for the efficacy of clozapine in treating refractory rapid cycling bipolar patients with hypomania or mild to moderate mania includes the following:

- A one-year, open-label, randomized study compared clozapine plus treatment as usual with treatment as usual in patients with treatment resistant bipolar disorder [42]; in the subgroup with rapid cycling (n = 15) who received adjunctive clozapine (mean dose 238 mg per day), more than 80 percent showed at least some improvement [43]. This was consistent with the finding that clozapine was beneficial in the total sample [42].

- A prospective observational study of 7 patients treated for 13 weeks with clozapine monotherapy (350 to 800 mg per day) found that mean scores on the mania rating scale decreased by more than 60 percent [44].

- 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 [45]. Outcomes during the year before clozapine treatment were compared with the year after clozapine was started. Clozapine was associated with fewer manic episodes, depressive episodes, hospitalizations, and suicide attempts.

- **Electroconvulsive therapy** – Electroconvulsive therapy (ECT) appears to be effective for mania that occurs in the context of rapid cycling, based upon randomized trials that found ECT was efficacious for the general treatment of mania, as well as observational studies of ECT for rapid cycling patients [46]. In addition, ECT induced mania is rare, and there are no reports of ECT induced rapid cycling. The efficacy of ECT for the general treatment of mania is discussed separately. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Mania'.)

- **Levothyroxine (T4)** – For refractory rapid cycling bipolar patients with hypomanic or mild to moderate manic episodes, we suggest high dose, supraphysiologic levothyroxine (T4) added to ongoing pharmacotherapy, based upon limited evidence [47-50]. Prior to using T4, patients should be screened for contraindications such as hyperthyroidism, cardiac conditions, pregnancy and breastfeeding, osteoporosis in postmenopausal women, and dementia.

  The goal of treatment with supraphysiologic T4 doses is to increase serum free T4 concentrations by approximately 50 percent of baseline concentrations; the dose of T4 should result in free T4 concentrations that exceed upper reference values for normal and

a low thyroid-stimulating hormone (TSH) (<0.01 mU/L). In rapid cycling patients with a normal baseline TSH concentration, T4 is started at 50 mcg per day, as a single morning dose approximately 30 minutes before breakfast. The dose is increased by increments of 50 mcg per day every week, depending upon response and tolerability, until the target values for free T4 and TSH are achieved. The maximum dose is 400 mcg per day. In patients with subclinical or overt hypothyroidism, the dose should be started at 25 mcg per day and increased by 25 mcg per day every week, until the target values for free T4 and TSH are achieved. Monitoring of patients should include signs of hyperthyroidism. (See "Overview of the clinical manifestations of hyperthyroidism in adults".)

Limited evidence for the efficacy of adjunctive, high dose levothyroxine includes the following:

- One trial enrolled euthyroid patients (n = 23) with rapid cycling who had not responded to a course of lithium plus other medications (eg, antidepressants, benzodiazepines, and/or valproate), and randomly assigned them to add-on levothyroxine or placebo; patients were followed for at least four months [51]. The dose of levothyroxine was titrated up until the free T4 index was between 4.5 and 7.5 mcg/dL or until TSH suppression was achieved (<0.1 mcIU/mL). Improvement was superior with adjunctive levothyroxine than placebo, such that the total duration of euthymia was greater with levothyroxine, and the duration of mixed states was less with levothyroxine. Adverse effects with levothyroxine included mild tremor, hot flashes, and diaphoresis.

- Additional evidence for the efficacy of levothyroxine includes open-label treatment of 27 rapid cycling bipolar patients (described in single-case reports and three case series) [52]. Levothyroxine was dosed between 50 to 500 mcg daily and given for 1 to 108 months. At least mild to moderate improvement occurred in 81 percent of the patients, and levothyroxine was usually well tolerated. In addition, there was generally no relationship between baseline thyroid status and response [53].

MAINTENANCE TREATMENT

For rapid cycling bipolar patients with hypomania or mania that responds to acute pharmacotherapy, we recommend maintenance treatment and typically use the same regimen that achieved response. Evidence for the efficacy of maintenance treatment includes the following trials [54]:

- A 52-week, randomized maintenance trial compared risperidone long-acting injectable (25 to 50 mg intramuscularly every two weeks) plus treatment as usual with placebo plus treatment as usual in 139 rapid cycling bipolar patients (who initially remitted with risperidone injectable plus treatment as usual) [13,55]. Relapse of a mood episode occurred in significantly fewer patients who received adjunctive risperidone than placebo (22 versus 48 percent). In addition, discontinuation due to adverse events was comparable for risperidone and placebo (4 and 2 percent of patients).

- A 100-week, randomized maintenance trial compared aripiprazole (15 or 30 mg per day) with placebo in bipolar patients who were initially stabilized for at least six weeks with open-label aripiprazole [56]. In the subgroup with rapid cycling (n = 28), time to relapse was significantly longer with aripiprazole than placebo [57]; this was consistent with the finding that aripiprazole was superior in the total sample [56].

- A 48-week, randomized maintenance trial compared olanzapine (5 to 20 mg per day) with placebo in bipolar patients who were initially stabilized for two weeks with open-label olanzapine [58]. In the subgroup with rapid cycling (n = 179), time to recurrence of a mood episode was significantly longer with olanzapine than placebo. This was consistent with the finding that olanzapine was superior in the total sample.

- A 104-week, randomized maintenance trial compared quetiapine (mean dose 546 mg per day), lithium (median serum concentration 0.63 mEq/L), and placebo in bipolar patients who were initially stabilized for four weeks with open-label quetiapine [59]. In the subgroup with rapid cycling (n = 163), time to recurrence of a mood episode was significantly longer with quetiapine than placebo. Although the difference between lithium and placebo in rapid cycling patients was not significant, neither was the difference between quetiapine and lithium. Both quetiapine and lithium were superior to placebo in the total sample.

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, written by David J. Miklowitz, PhD (published by The Guilford Press, 2002); 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 (available 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 (available 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'.)

- Whereas rapid cycling mania always necessitates pharmacotherapy, hypomanic episodes may be so mild that acute pharmacotherapy is not necessary. In addition, antidepressants are discontinued in patients with hypomania or mania. 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 severe mania, we suggest initial treatment with a medication combination rather than monotherapy (**Grade 2B**). (See 'Severe episodes' above and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Initial treatment'.)

- For resistant rapid cycling bipolar patients with severe mania that does not respond to one medication combination, we suggest additional medication combination trials rather than electroconvulsive therapy (ECT) (**Grade 2B**). (See 'Severe episodes' above and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Treatment-resistant patients'.)

- For treatment refractory patients with severe mania that does not respond to four to six medication combinations, we suggest ECT rather than additional trials of medication

combinations (**Grade 2C**). (See 'Severe episodes' above and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Treatment-refractory patients'.)

- For rapid cycling bipolar patients with hypomanic or mild to moderate manic episodes, we suggest initial treatment with risperidone, aripiprazole, or olanzapine monotherapy, rather than other medications (**Grade 2B**). We prefer risperidone and aripiprazole because they cause less weight gain. Reasonable alternatives to risperidone, aripiprazole, or olanzapine include lithium, valproate, quetiapine, or carbamazepine (see 'First line medications' above).

- For resistant rapid cycling bipolar patients with hypomania or mild to moderate mania that does not respond to treatment with two to three sequential monotherapy trials, we suggest combining lithium or valproate with risperidone, aripiprazole, or olanzapine rather than additional monotherapy trials (**Grade 2C**). However, reasonable alternatives include lithium or valproate plus haloperidol, quetiapine, or ziprasidone. (See 'Resistant patients' above.)

- Rapid cycling bipolar patients with hypomanic or mild to moderate manic episodes may not respond to treatment with four to eight medication combinations. Treatment options for these refractory patients include, in order of preference, clozapine as monotherapy or augmentation, electroconvulsive therapy, or adding high-dose levothyroxine. (See 'Refractory patients' above.)

- For rapid cycling bipolar patients with hypomania or mania that responds to acute pharmacotherapy, we recommend maintenance treatment rather than no treatment (**Grade 1A**). We typically use the same regimen that achieved response. (See 'Maintenance treatment' above.)

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