Acute bipolar mania and hypomania in adults: General principles of pharmacotherapy

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INTRODUCTION

Bipolar disorder is marked by episodes of mania (table 1) and hypomania (table 2), and nearly always includes episodes of major depression (table 3) [1]. Despite clinical differences between manic and hypomanic episodes, they are treated with the same medications [2-9].

This topic reviews the general principles of administering pharmacotherapy for acute mania and hypomania in adults. Choosing a specific pharmacotherapy regimen for acute mania and hypomania is discussed separately, as is choosing a regimen for bipolar depression and maintenance treatment. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Bipolar major depression in adults: Choosing treatment" and "Bipolar disorder in adults: Choosing maintenance treatment".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [1]. The subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes, and nearly always experience hypomanic and major depressive 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'.)

Despite clinical differences among manic and hypomanic episodes (eg, hypomania is less severe than mania), they are treated with the same medications [2-9].

GENERAL TREATMENT PRINCIPLES

Nature of the evidence — Evidence for the efficacy of treating mood elevated syndromes with medications is primarily based upon randomized trials with bipolar I manic patients; most trials included some patients with mixed features (ie, mania accompanied by symptoms of depression) [10,11]. Even though bipolar II disorder is more prevalent than bipolar I disorder, relatively little research has focused specifically on treating hypomania [12,13]. Many randomized trials either exclude patients with bipolar II disorder or combine them with bipolar I patients in the analyses.

Similar approach for mania and hypomania — Despite clinical differences between manic and hypomanic episodes (eg, hypomania is less severe than mania), they are treated with the same medications [2-9].

Assessment and monitoring — Treatment of mood elevated syndromes (ie, manic and hypomanic episodes) begins with an initial psychiatric history and mental status examination that emphasizes symptoms of the mood episode, particularly risk of suicide, aggressiveness, and violence to others, as well as signs of catatonia and psychosis [5,8,9,14]. Clinicians should also assess patients for comorbid disorders (eg, substance use disorders) that require treatment. The evaluation includes a general medical history, physical examination, and focused laboratory studies to establish whether the mood syndrome is due to the direct physiologic effects of a general medical condition, and to rule out any contraindications to treatment (eg, renal impairment and use of lithium, or hepatic disease and use of valproate). Additional information about the assessment for bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Assessment'.)

Patients who suffer mania or hypomania during maintenance pharmacotherapy should be assessed for adherence to treatment [9]. Managing poor adherence is discussed separately. (See "Bipolar disorder in adults: Managing poor adherence to maintenance pharmacotherapy".)

In addition, clinicians should assess patients for use of substances that may cause or exacerbate a mood elevated syndrome. (See 'Destabilizing drugs' below.)

Once treatment commences, clinicians can monitor outcomes by administering a standardized rating scale such as the Young Mania Rating Scale [15] or the Mania Rating Scale derived from the Schedule for Affective Disorders and Schizophrenia, Change Version [16]. Although these 11-item instruments are routinely used for systematically measuring outcome in research settings, this is not standard clinical practice. In addition, these scales were developed in 1978 and thus may not fully reflect our current nosology, which views increased goal-directed activity or energy as a core symptom of mania [1,17,18].

Level of care — The treatment setting for manic or hypomanic patients depends upon the severity of symptoms, comorbid psychopathology (eg, substance use disorder), level of psychosocial functioning, and available support:

- **Inpatient** – Hospitalization may be required for managing the patient's safety and symptoms such as suicidal ideation with a specific plan and intent, delusions or hallucinations, catatonia, and poor judgment that poses an imminent risk to the patient and others.

- **Partial hospital** – Moderately ill patients can often be treated in a partial hospital (day) program, including patients with suicidality that does not pose an imminent risk (eg, patients with fleeting thoughts of killing oneself, vague or nonexistent plans, and no intent).

- **Outpatient** – Outpatient care may be suitable for less acutely ill patients (eg, patients with thoughts that family members would be better off if the patient was dead, with no plan or intent to commit suicide).

For outpatient treatment of bipolar disorder, specialized mood disorder clinics may be preferable to general (standard) psychiatric clinics early in the course of illness. An open-label, two-year, randomized trial compared a mood disorder clinic with standard care in 158 bipolar patients who were discharged from their first, second, or third inpatient admission [19]. The mood disorder clinic was staffed by a cross-disciplinary team who administered pharmacotherapy and group psychoeducation; standard care consisted of pharmacotherapy provided at a local community health center or at a psychiatrist's office. Readmission to the hospital occurred in fewer patients who received specialized care than standard care (36 versus 55 percent). In addition, the median duration of the readmission was nearly two times shorter for patients who had received specialized care rather than standard care (12 versus 22 days).

The frequency of assessment generally ranges from daily to monthly, depending upon the severity of persistent symptoms. Hospitalized patients are monitored daily, and patients with

active suicidal ideation, a specific plan, and intent to kill themselves may require constant observation.

Among patients who are hospitalized for mania, outpatient follow-up should occur within at least 30 days of discharge. A retrospective study of administrative health care data found that among nearly 11,000 patients who were hospitalized for mania and then discharged, readmission was 30 percent less likely in patients who received outpatient care within 30 days, compared with patients who did not (attributable odds ratio 0.7, 95% CI 0.6-0.9) [20].

Goals — The initial goal of treating acute mania and hypomania is rapid response, which is defined as stabilization of the patient's safety and substantial improvement in the number, intensity, and frequency of mood (and psychotic) symptoms [9]. Many randomized trials of antimanic medications determine efficacy on the basis of response that is operationalized as a reduction of baseline symptoms ≥50 percent [21,22]. These studies assess outcomes with a standardized rating scale. (See 'Assessment and monitoring' above.)

The ultimate goal of treating acute mania and hypomania is remission, which is defined as resolution of the mood symptoms or improvement to the point that only one or two symptoms of mild intensity persist [9,22]. If patients present with psychotic features (delusions or hallucinations), resolution of the psychosis is required for remission. Patients with subsyndromal symptoms of mania are at increased risk of relapse [2].

Drug classes — Based upon randomized trials, drug classes commonly used to treat acute mania or hypomania include:

- Lithium
- Anticonvulsants
- Antipsychotics
- Benzodiazepines

The mainstays of treatment are lithium, anticonvulsants, and antipsychotics used in combination pharmacotherapy (eg, lithium plus an antipsychotic) or as monotherapy, depending upon the severity of symptoms. Benzodiazepines are primarily used as adjunctive treatment for insomnia, agitation, or anxiety. The general treatment of insomnia, agitation, and anxiety are discussed separately. (See "Overview of the treatment of insomnia in adults" and "Assessment and emergency management of the acutely agitated or violent adult" and "Generalized anxiety disorder in adults: Management".)

Duration of an adequate trial — Although it is not established how long clinicians should wait to assess the benefit of a medication regimen, it is reasonable to allow up to two weeks for a

treatment trial [2,5,8]. However, clinical urgency when treating hospitalized patients may necessitate shorter trials lasting one week or even less.

Most randomized trials last three weeks, and the superior efficacy of active drugs compared with placebo generally begins to manifest within one week [5,21,23]:

- In a randomized trial that compared olanzapine with risperidone in patients with pure mania or mania with mixed features, improvement at week 1 was evaluated as a predictor of either remission or response (reduction of baseline symptoms ≥50 percent) at week 3 [24]. Among 234 patients with improvement ≥25 percent at week 1, 52 percent remitted and 71 percent responded at week 3. Conversely, of the 40 patients with <25 percent improvement at week 1, 5 percent remitted and 25 percent responded at week 3.

- A meta-analysis of 12 randomized trials compared lithium, valproate, or carbamazepine plus an antipsychotic with lithium, valproate, or carbamazepine monotherapy in a total of 3164 patients with acute manic or mixed episodes [23]. At week 3, improvement of mania was greater with combination therapy than monotherapy, and the advantage of combination therapy first manifested at week 1.

Predictors of response — Among patients with mania, clinical factors that consistently predict a good response to pharmacotherapy have not been identified. As an example, several studies suggest that mixed features are associated with a poorer response [12,25-28], whereas other studies indicate that response to medications is comparable for patients with pure mania and mania with mixed features [29,30].

Relapse during maintenance phase — Patients who suffer mania or hypomania during maintenance pharmacotherapy are initially treated by optimizing existing medication doses [6,7,9]. This includes ensuring serum concentrations are in the therapeutic range for medications such as lithium or valproate, as well as increasing the dose to achieve a higher serum level within the therapeutic range, provided that side effects do not intervene. For medications that do not have an established therapeutic serum concentration, such as second-generation antipsychotics, the dose can be increased within the target dose range.

Patients who discontinue successful maintenance treatment and then suffer a relapse are often restarted on the same medication. Although concerns have been raised that the same medication is less effective after treatment is interrupted, a meta-analysis of three prospective observational studies (n = 212 patients with bipolar disorder) suggested that this was not the case.

Destabilizing drugs — Patients should reduce or eliminate their use of substances that may cause or exacerbate a mood elevated syndrome, such as alcohol, caffeine, and nicotine [9]. In addition, antidepressants should be abruptly discontinued [8].

Indications for referral — Although some primary care clinicians have the requisite training and experience to manage bipolar disorder, many patients are referred to psychiatrists and other mental health clinicians if these specialists are available. Common indications for referral include:

- Suicidal ideation and behavior
- Psychotic features (eg, auditory hallucinations commanding patients to kill themselves)
- Fluctuating symptoms
- Impulsive and dangerous behavior
- Functional impairment
- Comorbid psychopathology (eg, anxiety disorders and substance use disorders)
- Multiple (eg, two to four) failed medication trials
- Administration of adjunctive psychotherapy
- Recurrence of mood episodes

Primary care clinicians who refer patients to specialists are encouraged to remain involved in management. General internists and other clinicians can help educate patients and families about pharmacotherapy and reinforce the need for adherence, and typically collaborate in evaluating patients prior to treatment and monitoring vital signs, weight, height, and waist size during treatment.

CHOOSING TREATMENT

Choosing a specific treatment regimen for acute mania and hypomania in adults is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)

TREATING SPECIFIC SUBGROUPS

Rapid cycling patients — Pharmacotherapy for mania and hypomania that occur in the context of rapid cycling is discussed separately. (See "Rapid cycling bipolar disorder in adults: Treatment of mania and hypomania".)

Pregnant patients — Pharmacotherapy for antenatal mania and hypomania is discussed separately. (See "Bipolar disorder in pregnant women: Screening, diagnosis, and choosing

treatment for mania and hypomania".)

Postpartum patients — Pharmacotherapy for postnatal mania and hypomania is discussed separately. (See "Bipolar disorder in postpartum women: Treatment".)

Geriatric patients — Pharmacotherapy for late-life mania and hypomania is discussed separately. (See "Geriatric bipolar disorder: Treatment of mania and major depression", section on 'Mania and hypomania'.)

Pediatric patients — Pharmacotherapy for pediatric mania and hypomania is discussed separately. (See "Pediatric bipolar disorder: Overview of choosing treatment".)

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)")

The National Institute of Mental Health also has educational material explaining the symptoms, course of illness, and treatment 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 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) and An Unquiet Mind: A Memoir of Moods and Madness, written by Kay Jamison PhD (published by Random House, 1995).

The Depression and Bipolar Support Alliance (available at the website or 800-826-3632) is a national organization whose mission is to educate patients and family 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 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 providing education, support, and advocacy for patients with any mental illness. Bipolar disorder is one of their priorities.

SUMMARY

- Bipolar disorder is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3). (See 'Definition of bipolar disorder' above.)
- Choosing a medication regimen for patients with acute bipolar mania and hypomania depends in part upon the severity of the syndrome. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- Despite clinical differences between manic and hypomanic episodes, they are treated with the same medications. (See 'Similar approach for mania and hypomania' above.)
- The initial goal of treating acute mania and hypomania is rapid response, which is defined as stabilization of the patient’s safety and substantial improvement in symptoms. The ultimate goal is remission. (See 'Goals' above.)
- Treatment of mood elevated syndromes begins with an initial psychiatric history and mental status examination, as well as a general medical history, physical examination, and

focused laboratory studies. Once treatment commences, clinicians can monitor outcomes by administering a standardized rating scale, but this is not standard clinical practice. (See 'Assessment and monitoring' above.)

- Although it is not established how long clinicians should wait to assess the benefit of a medication regimen, it is reasonable to allow up to two weeks for a treatment trial. However, clinical urgency when treating hospitalized patients may necessitate shorter trials lasting one week or even less.
- Among patients with mania, clinical factors that consistently predict a good response to pharmacotherapy have not been identified. (See 'Predictors of response' above.)
- Mania or hypomania that occurs during maintenance pharmacotherapy is initially treated by optimizing existing medication doses. Patients who discontinue successful maintenance treatment and then suffer a relapse are often restarted on the same medication. (See 'Relapse during maintenance phase' above.)
- Patients should reduce or eliminate their use of substances that may cause or exacerbate a mood elevated syndrome. (See 'Destabilizing drugs' above.)
- Although some primary care clinicians can manage bipolar disorder, many patients are referred to psychiatrists and other mental health clinicians if these specialists are available. (See 'Indications for referral' above.)

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