Bipolar major depression in adults: Efficacy and adverse effects of antidepressants

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INTRODUCTION

The use of antidepressants for acute and maintenance treatment of bipolar depression is controversial because of concerns that these drugs are not effective and may harm patients by causing switches from depression to mania as well as rapid cycling [1-3]. Nevertheless, antidepressants (table 1) are the most commonly prescribed drugs for bipolar depression. Studies of bipolar patients in the United States (n = 7760) [4] and Europe (n = 2231) [5] found that an antidepressant had been prescribed for 50 and 81 percent; this may be due in part to the limited efficacy and tolerability of other treatments [6].

This topic reviews the efficacy of antidepressants for patients with bipolar major depression and the risk of switching polarity. Separate topics discuss antidepressants and the risk of rapid cycling, choosing treatment for adults with bipolar major depression, the general principles of treating bipolar major depression in adults, the efficacy and adverse effects of second-generation antipsychotics for bipolar major depression in adults, investigational approaches to treating bipolar major depression in adults, choosing pharmacotherapy for adults with acute mania and hypomania, choosing maintenance treatment for adults, and choosing pharmacotherapy for pediatric bipolar major depression:

- (See "Rapid cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Antidepressants'.)
- (See "Bipolar major depression in adults: Choosing treatment".)

- (See "Bipolar major depression in adults: General principles of treatment".)
- (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics".)
- (See "Bipolar major depression in adults: Investigational and nonstandard approaches to treatment".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Bipolar disorder in adults: Choosing maintenance treatment".)
- (See "Pediatric bipolar major depression: Choosing treatment".)

DEFINITIONS

Bipolar disorder — Bipolar disorder is a mood disorder that is characterized by episodes of mania (table 2), hypomania (table 3), and major depression (table 4) [7]. 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'.)

Antimanic drug — We use the term antimanic drug to refer to medications that can reduce acute symptoms of mania/hypomania, without causing a switch to the opposite polarity. Examples include lithium, antiepileptics such as carbamazepine and valproate, and second-generation antipsychotics such as aripiprazole, cariprazine, lurasidone, olanzapine, quetiapine, and risperidone.

ROLE OF ANTIDEPRESSANTS

Although the efficacy and safety of antidepressants for bipolar depression remains controversial [8,9], there is a limited role for these drugs as adjuncts to antimanic treatments for treating patients with acute episodes of bipolar major depression [10-18]. The choice of a specific treatment regimen for acute treatment of bipolar major depression is discussed separately. (See "Bipolar major depression in adults: Choosing treatment".)

Acute bipolar depression — Antidepressants appear to be effective for some patients with acute bipolar major depression, and it is thus reasonable to use adjunctive antidepressants for

patients who initially present with bipolar depression or who have responded favorably to these drugs in the past without treatment-emergent affective switching or mood cycle acceleration [13,14]. This approach is consistent with multiple practice guidelines [12,15,17-23].

By contrast, we suggest that clinicians generally avoid using antidepressants in patients with bipolar major depression who:

- Were previously treated with antidepressants and experienced poor outcomes such as treatment-emergent switching to mania/hypomania, rapid cycling, or acute suicidal ideation and behavior [12,17,24-30].
- Have concurrent manic symptoms (ie, mixed features), as well as patients with active substance use disorders, which can increase the risk of mood destabilization.
- Recently recovered from a manic or hypomanic episode (eg, within the past two to three months). However, there are no established criteria for using antidepressants after recovery from mania or hypomania, and adjunctive antidepressants may be started sooner in patients whose mania/hypomania is well controlled, whose depression is severe and not responding to antimanic drugs, and who have a prior history of responding well to antidepressants plus antimanic drugs.

The efficacy of antidepressants for acute bipolar major depression, and the risk of antidepressant induced mania or hypomania, rapid cycling, and suicidality are discussed elsewhere. (See 'Efficacy' below and 'Risk of switching to mania' below and "Rapid cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Antidepressants' and 'Risk of suicidality' below.)

Patients with bipolar depression who are treated with adjunctive antidepressants should be educated about the signs of treatment-emergent affective switching to mania, hypomania, or mixed features, and about the risk of mood cycle acceleration; patients should also be monitored for these potential complications. These recommendations are especially important for patients who have never received antidepressants but also apply to patients who were successfully treated with antidepressants in the past.

Using antimanic drugs to prevent switching — For patients with bipolar major depression who are treated with an antidepressant, we recommend that clinicians concurrently prescribe an antimanic drug such as lithium, valproate, carbamazepine, or a second-generation antipsychotic such as quetiapine, lurasidone, or olanzapine. A review of randomized trials concluded that when antidepressants are prescribed, the concurrent use of antimanic drugs

reduces the risk of switching to mania [3]. In addition, avoiding antidepressant monotherapy is consistent with multiple practice guidelines [12,15,18,23].

Lithium, lamotrigine, valproate, or carbamazepine — Prescribing lithium, lamotrigine, valproate, or carbamazepine in conjunction with antidepressants can reduce the likelihood of switching from depression to mania [12,17,18]. Evidence for the efficacy of this approach includes the following studies [31]:

- A pooled analysis of 15 randomized trials (n = 2691 patients with bipolar or unipolar depression) found that switching polarity was nearly twice as likely during treatment with imipramine, compared with imipramine plus lithium (51 versus 28 percent) [32]. The risk of switching with tricyclics is discussed further elsewhere in this topic. (See 'Antidepressant class and specific drugs' below.)

- A 26-week randomized trial compared an antidepressant (paroxetine or bupropion) with placebo in 366 patients with bipolar depression; the large majority of patients received lithium, valproate, and/or carbamazepine (the remaining patients received a second-generation antipsychotic). Switching to mania was comparable for adjunctive antidepressants and placebo (10 and 11 percent) [33].

- A national registry study identified bipolar patients who received an antidepressant plus lithium, lamotrigine, or valproate (n >1600), or received antidepressant monotherapy (n >1100) [34]. Patients had not received antidepressants in the year prior to onset of antidepressant treatment, and for each patient, the risk of mania during antidepressant treatment was compared with the risk during the previous year (in the absence of antidepressants). Thus, each patient served as his or her own control. During the first three months of antidepressant therapy, the risk of mania was not elevated in patients treated with concurrent antimanic drugs. However, patients who received antidepressant monotherapy had an increased risk of mania, compared with the previous year when they were not treated with antidepressants (hazard ratio 2.8, 95% CI 1.1-7.2).

For patients with bipolar depression who are treated with lithium, we suggest a target serum concentration between 0.8 to 1.2 mEq/L (0.8 to 1.2 mmol/L); if difficulty with tolerability occurs, we suggest a minimum target serum concentration of 0.6 mEq/L (0.6 mmol/L). In a randomized trial that included treatment with lithium monotherapy (n = 49) and lithium plus sertraline (n = 48), patients with a mean serum lithium concentration of 0.6 mEq/L (0.6 mmol/L) did not switch to mania/hypomania [35]. By contrast, patients who switched to mania/hypomania had a lower mean serum level of 0.4 mEq/L (0.4 mmol/L).

Second-generation antipsychotics — For patients with bipolar major depression who are treated with fluoxetine, concomitant olanzapine can reduce the risk of switching to mania/hypomania:

- An eight-week randomized trial compared olanzapine plus fluoxetine with placebo in 423 patients with bipolar I depression and found that treatment-emergent mania was comparable for patients who received the combination and patients who received placebo (7 and 6 percent) [36].

- A study enrolled patients with bipolar I depression (n = 114) who initially responded to acute phase therapy with olanzapine plus fluoxetine and randomly assigned them to 12 weeks of open-label olanzapine plus fluoxetine or olanzapine monotherapy [37]. Treatment-emergent mania during maintenance therapy was comparable for patients who received olanzapine plus fluoxetine or olanzapine monotherapy (2 and 0 percent).

It is not known if olanzapine reduces the risk of switching from other antidepressants or if other second-generation antipsychotics reduce the risk of antidepressant-induced switching.

Avoiding antidepressant monotherapy — We suggest that clinicians avoid antidepressant monotherapy in patients with acute or remitted bipolar I or bipolar II major depression [17,38,39]. This approach is consistent with multiple practice guidelines [12,15,18,23]. Combining an antimanic drug with an antidepressant appears to decrease the rate of switching polarity. (See 'Using antimanic drugs to prevent switching' above.)

Some randomized trials suggest that antidepressant monotherapy may be effective and safe for some patients with bipolar disorder [35,40-45], especially bipolar II disorder. However, many of the trials were small, brief in duration, and lacked a placebo control group [35,40-42,45]. As an example:

- A meta-analysis of two randomized trials, which lasted 12 and 16 weeks, compared antidepressants (sertraline or venlafaxine) with lithium in patients with bipolar II depression (total n = 223) [46]. Response (eg, reduction of baseline symptoms ≥50 percent) and treatment-emergent switches to mania in the two groups were comparable, but discontinuation of treatment due to side effects was greater with lithium. However, the absence of a placebo control makes it difficult to interpret the results regarding response, and lithium is often not an effective antidepressant agent in shorter-term treatment. In addition, these relatively short trials did not determine switch rates of longer-term treatment.

- In a relatively large randomized trial that lasted eight weeks and included 239 patients with acute bipolar I or II depression, response was comparable for patients who received either paroxetine monotherapy or placebo (55 and 53 percent) [47].

Maintenance treatment — For bipolar major depression that remits with an antidepressant plus an antimanic drug, it is unclear how long antidepressants should be continued. Generally, we continue antidepressants for approximately two to four months after remission of the depressive syndrome [15]. However, we attempt to avoid continuation/maintenance treatment with antidepressants in patients with a current course of rapid cycling, a history of antidepressant-associated switch from depression to mania/hypomania or increases in mood cycle frequency, or a history of frequent and/or severe manic episodes, including episodes complicated by psychotic features or suicidal ideation [17,48].

Nevertheless, bipolar patients who repeatedly suffer depressive symptoms in the absence of antidepressants may benefit from longer treatment [12,17,49]. In randomized trials that studied antidepressants as maintenance therapy in bipolar disorder, the duration of treatment ranged from 4 to 36 months [49].

The efficacy of antidepressants for maintenance treatment of bipolar disorder, and the risk of antidepressant induced mania or hypomania, are discussed elsewhere in this topic. (See 'Maintenance treatment' below and 'During maintenance treatment' below.)

Monitoring — If adjunctive antidepressants are used to treat bipolar major depression, mood symptoms should be assessed for increases in mood cycling, including more frequent depressive symptoms or episodes. The following self-report mood symptom rating scales may help in monitoring patients, but it is not known whether these instruments improve outcomes for patients with bipolar disorder:

- Mood Disorder Questionnaire – This 15-item instrument (table 5) is the most widely used measure that screens for episodes of mania and hypomania [50-53]. However, there is little information about using the Mood Disorder Questionnaire to monitor the efficacy of treatment in bipolar patients and provide measurement based care.

- Patient Health Questionnaire – Nine Item (PHQ-9) – This instrument (table 6) has good psychometric properties and is the standard among scales for monitoring symptoms of depression in patients who are receiving treatment for unipolar major depression [54]. Using the PHQ-9 to provide measurement based care is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)", section on 'Patient Health Questionnaire - Nine Item'.)

Tapering and discontinuing antidepressants — Antidepressants should generally be tapered slowly (eg, over two to four weeks) to avoid discontinuation syndrome symptoms and limit the risk of depressive relapses [55]. However, if treatment-emergent symptoms of mania/hypomania occur during antidepressant treatment, the antidepressant should be abruptly stopped and antimanic treatments should be optimized [12]. The discontinuation syndrome and antimanic drugs are discussed separately. (See "Discontinuing antidepressant medications in adults" and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)

EFFICACY

Overview — Most patients with bipolar disorder who were treated with antidepressants in randomized trials had bipolar I disorder rather than bipolar II disorder [56]. As an example, a review of 11 antidepressant trials found that the number of patients with bipolar I major depression was 1842, whereas the number with bipolar II major depression was only 227 [57].

Most antidepressants have not been adequately studied in patients with bipolar major depression, and it is not known whether antidepressants vary in their efficacy. Relatively few head–to-head comparisons of different antidepressants have been conducted in bipolar disorder.

In patients with bipolar major depression, adjunctive antidepressants may seemingly provide a benefit when none exists. Bipolar disorder is a cyclical condition, and patients are likely to cycle out of mood episodes spontaneously. Thus, patients may emerge from a depressive episode after the addition of an antidepressant due to the course of illness, rather than the antidepressant. In addition, antidepressants may induce rapid cycling in some patients, which can result in a rapid resolution of the depressive episode, often followed by mania, hypomania, or mixed features. These aspects of bipolar disorder may give the illusion of a therapeutic effect.

The use of antidepressants in patients with rapid cycling is discussed separately. (See "Rapid cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Antidepressants' and "Rapid cycling bipolar disorder in adults: Treatment of major depression", section on 'Use of antidepressants'.)

Acute treatment — For patients with acute bipolar I or bipolar II major depression, short-term (eg, 6 to 12 weeks) augmentation of antimanic drugs with antidepressants appears to provide a

small to moderate clinical benefit. The best established antimanic/antidepressant drug combination for treatment of bipolar major depression is olanzapine plus fluoxetine.

Evidence supporting augmentation of antimanic drugs with antidepressants includes meta-analyses of randomized trials with different antidepressants, which collectively provided a small to moderate clinical benefit:

- A meta-analysis of four randomized trials lasting five to eight weeks compared antidepressants (deprenyl, fluoxetine, imipramine, or tranylcypromine) with placebo in 662 patients; more than 70 percent received concomitant olanzapine or lithium [58]. After adjusting for the moderate to large heterogeneity across studies, the analysis found that response (reduction of baseline symptoms ≥50 percent) was more than twice as likely to occur with antidepressants than placebo (relative risk 2.3, 95% CI 1.3-4.0).

- A subsequent meta-analysis of 10 trials lasting 6 to 12 weeks compared antidepressants (bupropion, fluoxetine, imipramine, paroxetine, or phenelzine) with placebo in 1432 patients; most of the trials included an antimanic drug [59]. Response was more likely to occur with antidepressants than placebo (relative risk 1.4, 95% CI 1.1-1.8), and the pooled response rate was greater for antidepressants than placebo (45 versus 33 percent of patients). However, the trials were described as heterogeneous with respect to patient characteristics, duration, and additional treatments allowed.

- A third meta-analysis of six trials lasting 6 to 26 weeks compared antidepressants (agomelatine, bupropion, citalopram, fluoxetine, or paroxetine) with placebo in 1383 patients, all of whom were treated with an antimanic drug [56]. The analysis found that improvement of depressive symptoms was statistically greater with adjunctive antidepressants than placebo, but the clinical effect was small.

However, other trials indicate that for patients with acute bipolar I or bipolar II major depression, augmentation of antimanic drugs with antidepressants is not beneficial:

- A meta-analysis of five trials, lasting 6 to 26 weeks, compared antidepressants (bupropion, fluoxetine, imipramine, or paroxetine) with placebo in 906 patients; approximately 90 percent were treated with an antimanic drug [57]. The analysis found that the rate of response in patients treated with adjunctive antidepressants or placebo was comparable (relative risk 1.18, 95% CI 0.99-1.40); heterogeneity across studies was moderate to large.

- A meta-analysis of 16 open-label or double-blind trials, lasting 6 to 26 weeks, compared antidepressants plus antimanic drugs with antimanic drugs alone in nearly 2300 patients with bipolar depression [60]. The antidepressants included agomelatine, bupropion,

citalopram, fluoxetine, mirtazapine, paroxetine, sertraline, and tranylcypromine. The antimanic drugs included carbamazepine, lamotrigine, lithium, olanzapine, quetiapine, risperidone, and valproate. Response in the group that received adjunctive antidepressants and the group that did not was comparable; heterogeneity across studies was moderate.

- Subsequent to each meta-analysis described in this section, a six-week randomized trial compared citalopram (mean dose 27 mg/day) with placebo in 119 patients who were treated with antimanic drugs [61]. Response with adjunctive citalopram and placebo was comparable (48 and 46 percent).

The risk of switching from depression to mania or hypomania during acute treatment with antidepressants is discussed elsewhere in this topic. (See 'During acute treatment' below.)

Olanzapine plus fluoxetine — The best established antimanic/antidepressant drug combination for treatment of bipolar major depression is olanzapine plus fluoxetine [62]. This specific combination has been more widely studied than any other antimanic/antidepressant drug combination and has demonstrated efficacy in high quality randomized trials:

- An eight-week trial randomly assigned 788 patients to one of three treatments: olanzapine/fluoxetine (mean modal dose 7/39 mg per day), olanzapine monotherapy (mean modal dose 10 mg per day), or placebo [36]. The primary findings were as follows:
  - Remission occurred in more patients who received olanzapine/fluoxetine than olanzapine monotherapy or placebo (49 versus 33 and 25 percent). In addition, switching to mania was similar for the three groups (approximately 6 percent of patients in each group).
  - Discontinuation of treatment due to adverse events occurred in fewer patients who received olanzapine/fluoxetine than olanzapine monotherapy (2 versus 9 percent) and was comparable for olanzapine/fluoxetine and placebo (2 and 5 percent). Nevertheless:
    - Several side effects occurred more often with olanzapine/fluoxetine than olanzapine monotherapy, including diarrhea, extrapyramidal symptoms, nausea, orthostatic hypotension, and increased systolic blood pressure.
    - Several side effects also occurred more often with olanzapine/fluoxetine than placebo. As an example, clinically significant weight gain, defined as an increase from baseline ≥7 percent, occurred in more patients who received olanzapine/fluoxetine than placebo (20 versus 0 percent).

- A seven-week trial compared olanzapine/fluoxetine (mean modal dose 11/38 mg per day) with lamotrigine monotherapy (mean modal dose 106 mg per day) in 410 patients with bipolar I major depression [63]. Improvement of depressive symptoms and functioning was greater with olanzapine/fluoxetine than lamotrigine, and the incidence of suicidal behavior was less with olanzapine/fluoxetine. In addition, switching to mania was similar for olanzapine/fluoxetine and lamotrigine (4 and 5 percent of patients), as was discontinuation of treatment due to adverse events (8 and 7 percent). Nevertheless, several side effects occurred more often with olanzapine/fluoxetine than lamotrigine, including increased appetite, dry mouth, somnolence, and tremor. Mean weight gain was greater with olanzapine/fluoxetine than lamotrigine (3.1 versus -0.3 kg), as were increases in hemoglobin A1c, low-density lipoprotein cholesterol, prolactin, and triglycerides.

  The trial continued for another 18 weeks, such that patients were treated for a total of 25 weeks [64]. Improvement of depression over 25 weeks was greater with olanzapine/fluoxetine than lamotrigine, and treatment-emergent mania was comparable (5 and 7 percent of patients). Discontinuation of treatment due to adverse events with olanzapine/fluoxetine and lamotrigine occurred in 18 and 13 percent. Multiple adverse effects occurred more often with olanzapine/fluoxetine than lamotrigine, including increased appetite, dry mouth, somnolence, and tremor, as well as increases in metabolic parameters. Clinically significant weight gain occurred in more patients who received olanzapine/fluoxetine than lamotrigine (34 versus 2 percent of patients).

Predictors of response — For treatment of acute bipolar major depression with an antidepressant plus an antimanic drug, response may be better if the antimanic drug is a second-generation antipsychotic (eg, olanzapine), rather than a non-antipsychotic such as lithium, valproate, carbamazepine, or lamotrigine. As an example, a meta-analysis of six randomized trials compared antidepressants with placebo in 1383 patients, all of whom were treated with an antimanic drug [56]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients treated with an antidepressant plus an antipsychotic, compared with placebo plus an antipsychotic (odds ratio 1.9, 95% CI 1.2-3.0). By contrast, response was similar in patients treated with either an antidepressant plus a non-antipsychotic, or placebo plus a non-antipsychotic (odds ratio 1.0, 95% CI 0.7-1.3).

Bipolar II depression — Based upon randomized trials, improvement of acute depressive symptoms with antidepressants is commensurate in bipolar II depression and bipolar I depression [47,65]. As an example, a 26-week randomized trial found that response (reduction of baseline symptoms ≥50 percent) to antidepressants plus antimanic drugs (eg, lithium or valproate) was comparable in patients with bipolar II depression (n = 54) and patients with

bipolar I depression (n = 118) (20 and 25 percent) [33]. However, antidepressant-induced switching to mania may occur less often in patients with bipolar II depression than bipolar I depression. (See 'Bipolar I and bipolar II disorder' below.)

Maintenance treatment — For patients with acute bipolar depression who are treated with an antimanic drug plus an antidepressant and then recover, longer-term maintenance treatment with adjunctive antidepressants does not appear to prevent relapse of any mood episode (depressive plus manic/hypomanic). However, adjunctive antidepressants may reduce the specific risk of depressive relapses:

- One study enrolled 177 patients with an acute episode of bipolar I major depression who were successfully treated with an antimanic drug (eg, lithium) plus an antidepressant, and randomly assigned them to continue the antidepressant for 52 or 8 weeks [66]. The primary results included the following:
  - There was no statistically significant difference in relapse with any mood episode (depressive plus manic/hypomanic) between the two groups (hazard ratio 0.7, 95% CI 0.4-1.1)
  - Relapse of manic or hypomanic episodes was also comparable (hazard ratio 2.3, 95% CI 0.9-6.1)
  - However, fewer depressive episodes occurred in the group that received 52 weeks of adjunctive antidepressant treatment, compared with 8 weeks (hazard ratio 0.4, 95% CI 0.3-0.8)
- A meta-analysis of seven trials compared antidepressants plus antimanic drugs (eg, lithium) with placebo plus antimanic drugs as maintenance therapy in 532 patients with bipolar I or bipolar II disorder; pharmacotherapy was administered for a minimum of four months [49]. Relapse was less likely to occur in patients who received adjunctive antidepressants than placebo (relative risk 0.70, 95% CI 0.50-0.97).

Although randomized trials in patients with bipolar disorder indicate that maintenance treatment with antidepressant monotherapy is comparable to antimanic drug monotherapy in preventing new episodes of major depression, the risk of manic/hypomanic recurrences is greater with antidepressant monotherapy [49]. Thus, antidepressant monotherapy is typically avoided in bipolar disorder due to concerns about treatment-emergent mania. (See 'Avoiding antidepressant monotherapy' above and 'During maintenance treatment' below.)

RISK OF SWITCHING TO MANIA

Treatment of bipolar major depression with antidepressants remains controversial because of concerns that these drugs cause patients to switch polarity directly from depression to mania/hypomania or within a short time after the depressive episode has remitted (eg, two to three months [67]) [1,2,17]. However, switching often occurs in bipolar disorder in the absence of antidepressant treatment [2,25], and the evidence indicates that antidepressants may not increase switching during acute or maintenance treatment. As an example, a pooled analysis of randomized trials and observational studies (7915 bipolar patients) found that the risk of mania/hypomania was comparable for patients who were exposed to antidepressants and patients who were not (15 and 14 percent); heterogeneity was not reported [68].

Although the evidence suggests that antidepressants collectively (as a drug class) do not induce switching polarity, the risk of treatment-emergent mania may nevertheless exist for specific antidepressants; patients who are treated with antidepressant monotherapy; and patient subgroups, including certain genotypes [12,69].

If manic or hypomanic symptoms emerge during antidepressant treatment, antidepressants should be abruptly stopped and antimanic treatments should be optimized [12]. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)

During acute treatment — Acute (eg, 4 to 26 weeks) treatment of bipolar major depression with adjunctive antidepressants does not appear to increase the risk of switching to mania/hypomania [15,19,70], with the exception of tricyclics [58]. Across multiple randomized trials, the proportion of patients who switched polarity during treatment with antidepressants was approximately 4 to 8 percent, similar to the rate seen in patients treated with placebo:

- A meta-analysis of five randomized trials compared antidepressants (deprenyl, fluoxetine, imipramine, paroxetine, or tranylcypromine) with placebo in 779 patients with bipolar depression; approximately 75 percent received concomitant olanzapine or lithium [58]. Switch rates for the two groups were similar (relative risk 1.0, 95% CI 0.5-2.1), and a pooled analysis found that switch rates for antidepressants and for placebo were 4 and 5 percent.

- A subsequent meta-analysis of six randomized trials compared antidepressants (bupropion, fluoxetine, imipramine, or paroxetine) with placebo in 1026 patients with bipolar major depression; most patients received concomitant treatment with another drug such as lithium, valproate, or a second-generation antipsychotic [57]. Switch rates were similar (relative risk 1.0, 95% CI 0.6-1.5), and a pooled analysis found that switch rates for antidepressants and for placebo were 8 and 7 percent.

- A third meta-analysis of six trials lasting 6 to 26 weeks compared newer antidepressants (agomelatine, bupropion, citalopram, fluoxetine, or paroxetine) with placebo in 1338 patients, all of whom were treated with an antimanic drug [56]. Treatment-emergent mania/hypomania was similar for the two groups (odds ratio 0.9, 95% CI 0.6-1.5), and a pooled analysis found that switch rates for adjunctive antidepressants and placebo were identical (6 percent).

In addition, a subsequent, 16-week randomized trial in patients with bipolar II major depression (n = 97) compared lithium plus sertraline with lithium monotherapy and found that switching to mania/hypomania was comparable in the two groups (13 and 19 percent) [35].

However, randomized trials typically exclude sicker bipolar patients, including those with rapid cycling, psychiatric comorbidity (eg, substance use disorder), comorbid general medical disorders, and suicidal ideation and behavior. Thus, these trials may not generalize to many patients; as an example, comorbidity in bipolar disorder appears to be the rule rather than the exception [71,72]. In addition, randomized trials may provide closer monitoring than occurs in routine clinical care, permitting study investigators to discontinue antidepressants prior to onset of full blown manic/hypomanic episodes.

During maintenance treatment — It is not clear whether maintenance treatment with antidepressants plus antimanic drugs in patients with bipolar disorder causes treatment-emergent mania. Long-term treatment (eg, ≥4 months) studies have found inconsistent results:

- A meta-analysis of five randomized trials (n = 509) compared antidepressants plus antimanic drugs (eg, lithium) with placebo plus antimanic drugs; pharmacotherapy was administered for a minimum of four months [49]. The risk of new manic/hypomanic episodes for the two groups was comparable (relative risk 1.3, 95% CI 0.8-2.1). Subgroup analyses suggested that the risk of mania and hypomania was greater with older antidepressants such as tricyclics, than with newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs).

- A meta-analysis of two randomized trials (n = 463) compared newer antidepressants (agomelatine or citalopram) plus antimanic drugs (eg, lithium or valproate) with placebo plus antimanic drugs; pharmacotherapy was administered for 12 months [56]. The risk of new manic/hypomanic episodes was greater with adjunctive antidepressants than placebo (odds ratio 1.77, 95% CI 1.02-3.09).

Continuation and maintenance treatment with antidepressant monotherapy can cause new episodes of mania and hypomania. A meta-analysis of four randomized trials (n = 172 bipolar patients) lasting at least four months compared antidepressant monotherapy with antimanic

drug monotherapy [49]. The risk of new manic/hypomanic episodes was greater in patients who received antidepressant monotherapy (relative risk 2.4, 95% CI 1.4-3.9).

Pharmacologic risk factors — The risk of switching in patients with bipolar depression who are treated with antidepressants may vary according to the antidepressant class or specific drug that is used [12]. In addition, prescribing antidepressants in conjunction with antimanic drugs (eg, lithium, valproate, or second-generation antipsychotics) may mitigate the risk of switching to mania/hypomania. (See 'Using antimanic drugs to prevent switching' above.)

Although case reports describe mania/hypomania following abrupt withdrawal of antidepressants, tapered discontinuation, or a decrease in dose [73], it is not known whether onset of mania/hypomania in these cases was due to withdrawal of antidepressants or the natural course of illness.

Antidepressant class and specific drugs — It is not established whether the risk of treatment-emergent mania/hypomania varies among specific antidepressants because most drugs have not been compared in head-to-head trials. However, randomized trials suggest that switching polarity during treatment of acute bipolar depression occurs less often with bupropion and more often with tricyclics or venlafaxine [3,12]:

- **Bupropion** – A meta-analysis of two trials, in 240 patients who were treated with antimanic drugs, found that switching occurred less often with bupropion than desipramine, sertraline, or venlafaxine (relative risk 0.3, 95% CI 0.1-0.9) [57].

- **Citalopram** – A one-year randomized trial compared citalopram (mean dose 27 mg/day) with placebo in 119 patients who were treated with antimanic drugs [61]. The rate of switching to mania or hypomania with adjunctive citalopram or placebo was comparable (5 and 10 percent).

- **Tricyclics –** A meta-analysis of six trials (370 patients) found that switching occurred in more patients who received tricyclics (clomipramine, desipramine, or imipramine) than other antidepressants (bupropion, fluoxetine, fluvoxamine, moclobemide, paroxetine, or tranylcypromine) (relative risk 2.9, 95% CI 1.3-6.7) [58].

  In addition, a pooled analysis (415 patients) found that switching occurred in more patients who received tricyclics than SSRIs or placebo (11 versus 4 and 4 percent) [74].

- **Venlafaxine** – Two trials found that among patients who received venlafaxine plus antimanic drugs (combined n = 95), switching occurred in 15 percent [75,76]. In one of the

trials, switching to mania or hypomania occurred more often with venlafaxine than bupropion or sertraline, especially among patients with a history of rapid cycling [75].

Clinical risk factors

Bipolar I and bipolar II disorder — Switching from bipolar major depression to mania/hypomania during treatment with an antidepressant may be more likely to occur in patients with bipolar I disorder than bipolar II disorder [12,70]:

- In a meta-analysis of seven randomized trials and six prospective observational studies that compared antidepressant-induced mood elevation in bipolar I patients (n = 462) with bipolar II patients (n = 315), the risk of switching was greater in patients with bipolar I disorder (relative risk 2, 95% CI 1-3) [77].
- A subsequent observational study also found that the bipolar I subtype was associated with switching [78].

In addition, a 16-week trial randomly assigned patients with bipolar II major depression (n = 142) to one of three treatments: lithium plus placebo, sertraline plus placebo, or lithium plus sertraline [35]. Switching to hypomania was comparable with lithium alone, sertraline alone, and lithium plus sertraline (19, 20, and 13 percent of patients); none of the patients switched to mania.

Other — Switching to mania during treatment with antidepressants has been associated with early age of onset of bipolar disorder, female sex, history of suicide attempts, symptoms of mania/hypomania concurrent with depression, and comorbid substance abuse and anxiety disorders [24-29]. However, these factors are not consistently associated with switching across multiple studies, and are likely to have little predictive power for any specific patient [30].

RISK OF RAPID CYCLING

The possible risks of using antidepressants in bipolar depressed patients include increased mood cycle frequency and/or the development of rapid cycling, which is discussed separately. (See "Rapid cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Antidepressants'.)

RISK OF SUICIDALITY

For patients with bipolar depression, it is not clear if antidepressants cause new onset suicidal ideation and behavior. A review of prospective and retrospective observational studies found contradictory results [12]. Suicide deaths in particular are rare and thus difficult to examine in properly designed studies.

The risk of suicidal ideation and behavior in patients with unipolar major depression is discussed separately. (See "Effect of antidepressants on suicide risk in adults".)

SUMMARY

- **Role of antidepressants** – There is a limited role for antidepressants (table 1) as adjuncts to antimanic drugs for treating patients with acute bipolar major depression. For bipolar major depression that remits with an antidepressant plus an antimanic drug, we generally continue antidepressants for approximately two to four months after remission of the depressive syndrome. However, we attempt to avoid maintenance treatment with antidepressants in patients with a current course of rapid cycling, a history of antidepressant-associated switch from depression to mania/hypomania or increases in mood cycle frequency, or a history of frequent and/or severe manic episodes. (See 'Role of antidepressants' above.)

  Clinicians should always prescribe an antidepressant in conjunction with an antimanic drug such as lithium, valproate, carbamazepine, or a second-generation antipsychotic and avoid antidepressant monotherapy. (See 'Using antimanic drugs to prevent switching' above and 'Avoiding antidepressant monotherapy' above.)

- **Efficacy of antidepressants** – For patients with acute bipolar I or bipolar II major depression, short term (eg, 6 to 12 weeks) augmentation of antimanic drugs with antidepressants may be beneficial. The best established antimanic/antidepressant drug combination is olanzapine plus fluoxetine. (See 'Acute treatment' above.)

  For patients with acute bipolar depression who are treated with an antidepressant plus an antimanic drug and then recover, maintenance treatment with adjunctive antidepressants may possibly reduce the risk of depressive relapses in some patients. (See 'Maintenance treatment' above.)

- **Risk of switching to mania** – Switching polarity often occurs in bipolar disorder in the absence of antidepressant treatment, and the evidence indicates that acute treatment with adjunctive antidepressants may not increase switching from bipolar major depression to mania/hypomania. Nevertheless, the risk of treatment-emergent mania may exist for

patient subgroups (eg, bipolar I disorder) and patients who are treated with antidepressant monotherapy. It is not clear if maintenance treatment with adjunctive antidepressants increases the risk of switching. (See 'Risk of switching to mania' above and 'Clinical risk factors' above.)

Although it is not established whether the risk of switching varies according to specific antidepressants, the risk of mania/hypomania may be greater with tricyclics and serotonin-norepinephrine reuptake inhibitors than other drugs such as selective serotonin reuptake inhibitors (SSRIs). Across different acute randomized trials, the switch rate for venlafaxine was 15 percent, for tricyclics was 11 percent, and for SSRIs, bupropion, or placebo was 3 to 5 percent. (See 'Antidepressant class and specific drugs' above.)

If manic or hypomanic symptoms emerge during antidepressant treatment, antidepressants should be abruptly stopped and antimanic treatments should be optimized. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)

- **Risk of rapid cycling** – The possible risks of using antidepressants in bipolar depressed patients include increased mood cycle frequency and/or the development of rapid cycling. (See "Rapid cycling bipolar disorder: Epidemiology, pathogenesis, clinical features, and diagnosis", section on 'Antidepressants'.)

- **Suicidal ideation and behavior** – It is not clear whether antidepressants are associated with new onset suicidal ideation and behavior. (See 'Risk of suicidality' above.)

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