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What drugs are best for bipolar depression?

Evidence-based answer

Antidepressants and lamotrigine are effective. Atypical antipsychotics, lithium, and anticonvulsants also may help.

Antidepressants, including tricyclics and selective serotonin reuptake inhibitors (SSRIs), are useful adjuncts in short-term treatment of bipolar depression and have low rates of inducing mania (strength of recommendation [SOR]: **A**, 1 systematic review and randomized controlled trials [RCTs]). Lamotrigine is beneficial for both acute treatment of bipolar depression and prevention of recurrent episodes (SOR: **A**, 1 systematic review and 1 RCT).

Some atypical antipsychotics alone (SOR: **B**, 2 RCTs) or in combination with antidepressants (SOR: **B**, 1 multicenter RCT) effectively treat acute bipolar depression. Lithium and anticonvulsants such as valproate also may be useful (SOR: **B**, limited number of studies with small sample sizes).

Clinical commentary

Many options, but patience is key

Many treatments for bipolar depression are reasonably effective, but the literature has little to say about which to choose. For milder depression, starting a (or adding a second) mood stabilizer, especially lamotrigine, or using empirically validated psychotherapy (cognitive-behavioral or interpersonal) seems a good first step. More marked depression may merit treatment with an antidepressant (or olanzapine or quetiapine), but the patient should take a mood stabilizer concurrently to reduce the risk of switching to mania.

Patients with a history of severe mania, rapid cycling, or antidepressant-induced switch may be understandably wary of antidepressant treatment. Because of the risks of suicide, mania, or mixed mood states in bipolar patients, prudent care must include prompt psychiatric referral if necessary. Most treatments work slowly, so patience on the part of physician, patient, and family is important.

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FAST TRACK

For mild depression, a mood stabilizer, especially lamotrigine, is a good first step

Evidence summary

Depression is the most common phase of bipolar disorder. Until recently, no specific pharmacotherapies approved by the United States Food and Drug Administration have been available to treat this form of depression.

Antidepressants and lamotrigine produce results

A systematic review of 4 RCTs (662 patients) found that antidepressants—fluoxetine, paroxetine, imipramine, tranylcypromine, and selegiline (l-deprenyl)—significantly increased treatment

response for bipolar type I or II disease at 4 to 10 weeks. About 75% of patients received a concurrent mood stabilizer or an atypical antipsychotic (relative risk [RR]=1.86; 95% confidence interval [CI], 1.49-2.30; number needed to treat=4.2; 95% CI, 3.2-6.4).[1] Although a few head-to-head comparisons suggested that some SSRIs and monoamine oxidase inhibitors are more effective first-line agents than tricyclics, the differences were not significant.[1]

One systematic review identified a single RCT of 195 adults with type I bipolar disorder who were experiencing a major depressive episode.[2] Lamotrigine (200 mg/day) significantly improved patient scores on the Montgomery-Asberg Depression Rating Scale (MADRS; *P*<.05) and increased the response to treatment (measured by mean change in scores on the Clinical Global Impression Scale; *P*<.05). Response rates were 51% (200 mg/day), 41% (50 mg/day), and 26% (placebo; *P*<.05).

Olanzapine works best with an antidepressant

In a double-blind, 8-week RCT involving 84 international sites, 833 adults with bipolar I depression (MADRS score of ≥20) received olanzapine, an olanzapine-fluoxetine combination (OFC), or placebo.[3] Although the trial had a low completion rate (38.5%) and no fluoxetine monotherapy arm, the olanzapine and OFC groups showed improvement in depressive symptoms (defined as ≥50% improvement in the MADRS total score). The olanzapine response rate was 39% (*P*<.02; odds ratio [OR]=1.46; 95% CI, 1.07-2.00); the OFC response rate was 56.1% (*P*<.001; OR=2.92; 95% CI, 1.23-3.26). The OFC group showed statistically greater improvement than the olanzapine group.

A secondary analysis assessed health-related quality of life based on the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) and Quality of Life in Depression Scale (QLDS).[4] OFC-

treated patients showed greater improvements in general health perception, social functioning, vitality, and a number of other depression markers compared with both the olanzapine monotherapy and placebo groups. However, the SF-36 and QLDS were administered in only 7 of 13 participating countries, possibly skewing results because of variations between countries in sociocultural factors and quality-of-life issues that may also affect mental health.

Quetiapine alone also helps

Two 8-week, double-blind RCTs assessed the efficacy of quetiapine in treating bipolar I or II depression. The first studied 542 outpatients with acute bipolar depression, randomly assigned to quetiapine, 300 mg/day; quetiapine, 600 mg/day; or placebo. Mean changes in MADRS total scores were the primary outcome measures.[5] Quetiapine showed dose-dependent improvement in MADRS total scores after the first week ($P<.001$), with a moderate clinical effect size of 0.67 at 300 mg/day and a large effect size of 0.81 at 600 mg/day.

In the second RCT, 509 patients were randomized to double-blind treatment with quetiapine (300 or 600 mg/day) or placebo and assessed weekly with the MADRS and Hamilton Depression Rating Scale (HDRS).[6] Improvements in mean HDRS scores were greater with both quetiapine doses than with placebo ($P<.001$). Clinical effect sizes were moderate at week 8 (0.61 at 300 mg/day and 0.54 at 600 mg/day), although dose titration effects were not established.

FAST TRACK

The APA recommends lithium or lamotrigine as first-line treatment for acute bipolar depression

Antidepressants don't enhance the effect of lithium or valproate

A recent RCT demonstrated no improvement in bipolar depression using paroxetine or bupropion in conjunction with mood stabilizers (primarily lithium or valproate) compared with mood stabilizers alone. However, the trial also showed no difference in treatment-emergent mania between groups.[7]

Recommendations

The American Psychiatric Association (APA) recommends lithium or lamotrigine as first-line treatment for acute bipolar depression. Antidepressant monotherapy is not recommended.[8] Interpersonal therapy, cognitive behavior therapy, and psychosocial interventions may be useful additions.

Depressive episodes with psychotic features require adjunctive treatment with an antipsychotic or electroconvulsive therapy, especially in the presence of life-threatening inanition or suicidality.

The APA supports maintenance therapy using lithium and valproate, with lamotrigine, carbamazepine, or oxcarbazepine as alternatives. If effective, the medication generally should be continued. ■

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