Antipsychotic Drug Therapy in Bipolar Depression and Maintenance Therapy

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Related to: Chapter 72: Bipolar Disorder

Since publication of the seventh edition of *Pharmacotherapy: A Pathophysiologic Approach*, research on the role of antipsychotics in bipolar disorder, particularly in bipolar depression and maintenance therapy for bipolar relapse prevention, has advanced. This update summarizes these findings.

Acute Bipolar Depression

Research on the natural history of bipolar disorder, including bipolar disorder, type I, indicates that individuals suffering from bipolar disorder spend more time in depressive episodes than in manic or mixed episodes, discussed in Chapter 72. Despite this evidence, no drugs usually classified as mood stabilizers are FDA approved for acute bipolar depression, although data support the efficacy of lithium. Quetiapine is approved as monotherapy for acute bipolar depression, as noted in Chapter 72.

More recently, olanzapine in combination with fluoxetine (OFC) was approved by the FDA for acute bipolar depression. The primary pivotal trial was an 8-week study that showed a superiority of olanzapine monotherapy over

placebo, but OFC was superior to both placebo and olanzapine monotherapy on improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores, response rates, time to response, and remission rates. The mean modal dosage of in the OFC group was 7.4 mg per day for olanzapine and 39.3 mg per day for fluoxetine.[1]

Aripiprazole was studied in non-psychotic acute bipolar I depression with a methodology similar to the quetiapine pivotal trials. Two randomized controlled studies assigned patients to placebo or aripiprazole 10 mg daily with dosing flexible from 5 to 30 mg per day. The primary outcome measure was change in MADRS ratings from baseline to endpoint at week 8, using a last observation carried forward analysis. Although differences were noted at earlier time points, there was no significant difference between aripiprazole and placebo at endpoint.[2]

To summarize the indications for antipsychotic therapy in acute bipolar depression, quetiapine is approved as monotherapy, and olanzapine is approved when combined with fluoxetine. Aripiprazole did not separate from placebo in the primary efficacy outcome and is not FDA approved for this indication. The diversity of data and outcomes indicates that response to antipsychotic drug therapy in bipolar depression is not a therapeutic class effect and that individual agents require careful study.

Maintenance Therapy of Bipolar Disorder

As noted in Chapter 72, olanzapine, either as monotherapy or adjunctive to mood stabilizing drugs, is FDA approved for maintenance treatment of bipolar

disorder. More recently, aripiprazole has been approved for maintenance treatment on the basis of a randomized controlled trial of aripiprazole 15 to 30 mg daily versus placebo for up to 100 weeks after initial stabilization on open-label aripiprazole. The primary outcome measure was time to relapse to any mood episode. Aripiprazole was superior to placebo on time to relapse into mania, but no difference from placebo was noted on time to relapse into depression.[3] However, currently approved prescribing information indicates that there are no systematic data to support use of aripiprazole beyond six weeks. Periodic re-evaluation of patients receiving longer-term treatment is recommended.

Quetiapine is now FDA approved for maintenance therapy of bipolar disorder when given in combination with lithium or divalproex. What is unusual about the design of the supporting study is that the index mood episode prior to stabilization could be either mania or depression. Following stabilization on open-label quetiapine at 400 to 800 per day in combination with lithium or divalproex, patients were randomized in a double-blind manner to either continued quetiapine plus a mood-stabilizing drug or to mood-stabilizing drug monotherapy for up to 104 weeks. The primary outcome measure was time to recurrence of any mood episode event. Combined quetiapine and mood-stabilizing therapy was superior to mood-stabilizing monotherapy on the primary outcome, as well as on time to recurrence of mania and depression, analyzed separately.[4] Adverse events were consistent with the known profile of quetiapine. Although the average weight gain in the quetiapine group was mild at 0.5 kg, the percentage of patients with clinically significant weight gain was

23% in the open-label phase followed by an additional 9% in the randomization phase, compared to 3% of placebo subjects. Serum insulin and triglyceride values were also greater on quetiapine than placebo.

To summarize antipsychotic drug therapy in maintenance treatment of bipolar disorder, olanzapine is approved as monotherapy or adjunctive with mood-stabilizing drugs. Aripiprazole showed efficacy for preventing manic relapse but not depressive relapse. Prescribing information for aripiprazole indicates no systematic data to support its use beyond six weeks and recommends periodic re-evaluation, which is good clinical practice for all patients. Quetiapine is approved for maintenance therapy in combination with lithium or divalproex. Efficacy was demonstrated for both mania and depression relapse prevention. Metabolic side effects of quetiapine included weight gain and elevations in serum insulin and triglycerides relative to placebo.

References

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