

Treatment Guidelines for Bipolar Disorder

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The following is a brief review of new information that has become available over the past two years in the treatment of bipolar disorder (BD).

Acute Mania

Quetiapine XR (FDA approved for the treatment of acute mania) monotherapy has been shown to be more effective than placebo in treating acute mania with improvement starting at day 4. Aripiprazole adjunctive therapy was more effective than placebo adjunctive therapy in treating manic symptoms in BD manic patients with inadequate response to lithium or divalproex in a 6 week trial. Olanzapine plus carbamazepine was no more effective than placebo and carbamazepine in BD patients with manic or mixed episodes. In light of the fact that the combination was associated with significantly higher rates of lipid abnormalities and weight gain, the combination is not recommended.

Two new atypical antipsychotics have been assessed for their efficacy in acute mania. Paliperidone was tested in two 3-week, double-blind randomized controlled trials (RCTs) in patients with BD. In the Flexible-dose study, paliperidone (mean dose 9 mg/day) was more effective than placebo in improving manic symptoms as early as day 2. In the fixed-dose study, paliperidone 12 mg/day but not 3 mg/day or 6 mg/day was more effective than placebo in acute mania. Because of the lack of clinical experience with this agent, paliperidone monotherapy is recommended as a second-line option, based on the reported efficacy data and adverse event profile of this agent. Adjunctive flexible-dose paliperidone was not superior to adjunctive placebo in patients with BD manic or mixed episodes. Given that paliperidone monotherapy is effective and given that lithium or valproate does not affect the metabolism of paliperidone, the lack of efficacy of combination therapy is puzzling.

Asenapine, (approved by the FDA for the treatment of acute mania) may be a promising agent for the management of mania. Two similar 3-week, double-blind RCTs demonstrated that asenapine was significantly more effective than placebo. Furthermore, adjunctive asenapine was more effective than adjunctive placebo to lithium/divalproex in treating acute manic or mixed episodes.

Oxcarbazepine was not superior to placebo in a recent 7-week, RCT in 116 youths with BD I manic or mixed episode.

Acute Bipolar Depression

Lamotrigine was assessed in 5 double blind RCT's in treating acute bipolar depression. Although only one out of these 5 trials was positive, a meta-analysis of individual patient data from all five RCTs showed that response rates

were significantly greater in those treated with lamotrigine compared with those treated with placebo. Lamotrigine is not FDA approved for the treatment of acute bipolar depression.

Divalproex was assessed in three small RCTs for the treatment of BD I or II depression. All three RCTs and a recent meta-analysis suggests that divalproex has efficacy in treating acute bipolar depressive symptoms but this needs to be confirmed in a large double blind RCT. Divalproex is not FDA approved for the treatment of acute bipolar depression.

Quetiapine has been tested in 4 large RCTs and all four showed that quetiapine was more effective than placebo in treating acute bipolar depression. In EMBOLDEN I, quetiapine (300 or 600 mg/d) was significantly more effective than placebo on the primary efficacy measure of change in MADRS scores as well as response and remission rates but lithium was not. However, the mean serum lithium level in this study was only 0.6 meq/L, which may not have been therapeutic for alleviating depressive symptoms. Similarly, in EMBOLDEN II, both doses of quetiapine were significantly more effective than placebo but paroxetine was not. It is unclear if a higher dose of paroxetine (greater than 20 mg/day) would have been effective as patients in this study were treated with a fixed dose of 20 mg/day. Quetiapine XR is more effective than placebo in another RCT for bipolar depression (FDA approved for the treatment of acute bipolar depression). Aripiprazole failed to separate from placebo in two double-blind RCTs.

In the NIH funded STEP-BD study of acute bipolar depression, the rates of durable recovery were similar in lithium/divalproex plus an adjunctive antidepressant (bupropion or paroxetine) and lithium/divalproex plus placebo groups. Since patients for this trial were recruited primarily from tertiary care specialized mood disorders centers, the data may not be generalizable to all bipolar depressed patients. Given that antidepressants are widely used, in clinical practice to treat bipolar depression, further trials assessing their efficacy are required.

Modafinil, a drug used for treating narcolepsy, was found to be better than placebo in one study when given as an adjunct to patients with acute bipolar depression who had not responded to lithium/divalproex with or without concomitant antidepressants. Modafinil has a high potential for interactions with drugs from all classes, and can cause serious dermatological reactions particularly when used at higher doses.

Maintenance Treatment

Quetiapine alone or in combination (FDA approved for maintenance therapy as an adjunct to lithium or valproate) with lithium/divalproex was assessed in five RCTs for efficacy in maintenance treatment of BD. The two EMBOLDEN studies showed that the acute efficacy of quetiapine in bipolar

depression was maintained in continuation treatment for 26-52 weeks compared with placebo. The risk of recurrence of any mood event or a depression event was significantly lower with quetiapine than with placebo. Further, in the SPARKLE study, both quetiapine and lithium were significantly more effective than placebo in reducing the risk of manic and depressive episodes. Adjunctive quetiapine to lithium or divalproex was significantly more effective than adjunctive placebo to lithium or divalproex in the prevention of mood episodes over a 2 year study period

Risperidone long acting injection (LAI) (Approved by the FDA for maintenance therapy as monotherapy or as adjunctive therapy with lithium or valproate) maintenance therapy was superior to placebo therapy in preventing relapse of mood episode over a two year period in BD patients who had been stabilized on risperidone LAI for 6 months. The risperidone LAI adjunctive therapy was also more effective than placebo adjunctive therapy in frequently relapsing BD patients (requiring intervention for 4 or more episodes in the past year) who had been stabilized on risperidone LAI.

Adjunctive ziprasidone was more effective than adjunctive placebo to lithium/divalproex in BD I in preventing relapse of mood episodes in a 6 month RCT.

References

Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry* 2009;194:4-9

Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *J Clin Psychopharmacol* 2008;28:13-20

Suppes T, Liu S, Brecher M, Paulsson B et al: Maintenance treatment for patients with bipolar I disorder: Results from North American Study of quetiapine in combination with lithium or divalproex. *Am J Psychiatry*, 2009 Apr;166(4):476-88