CNS SPECTRUMS

A review of FDA-approved treatment options in bipolar depression

CME Information

Accreditation and credit designation statements

Target audience

This activity has been developed for prescribers specializing in psychiatry. There are no prerequisites. All other health care providers interested in psychopharmacology are welcome for advanced study, especially primary care physicians, nurse practitioners, psychologists, and pharmacists.

Statement of need

Bipolar disorder (BD) may be misdiagnosed in nearly 60% of cases, most often because patients present in the depressed state; this can lead to inappropriate or inadequate treatment.

Many clinicians do not recognize the importance of treatments aimed at preventing relapse or addressing depression in bipolar disorder, and only half of 2011 NEI Congress participants could correctly identify evidence-based/recommended treatment options for bipolar depression. Clinicians need education on the current best practice guidelines for treating bipolar depression, including recent advances in bipolar depression treatments and strategies for long-term care.

To help address these professional practice gaps and improve outcomes for patients with bipolar disorder, quality improvement efforts need to provide education regarding (1) differential assessment of various depressive presentations, and (2) evidence-base and recommendations for best practices in patient care for bipolar depression, including not just acute episodes but also long-term care.

Learning objectives

After completing this activity, participants should be better able to:

- Interpret efficacy and safety data for current and emerging therapies for bipolar depression

- Implement treatment strategies to enhance adherence and improve patient functioning during the long-term maintenance stage

Date of release/expiration

Sponsor

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A review of FDA-approved treatment options in bipolar depression

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Objectives/Introduction. Herein we review the evidence supporting Food and Drug Administration (FDA) approved and emerging treatments for bipolar depression.

Methods. A PubMed search of all English-language articles published up to July 2013 was conducted. The search terms were quetiapine, olanzapine-fluoxetine, olanzapine, lurasidone, ketamine, modafinil/armodafinil, and lamotrigine. The search was augmented with a manual review of relevant article reference lists, as well as posters presented at national and international meetings. Articles selected for review were based on the adequacy of sample size, the use of standardized diagnostic instruments, validated assessment measures, and overall manuscript quality.

Results. Olanzapine-fluoxetine combination (OFC), quetiapine, and lurasidone are FDA-approved for the acute treatment of bipolar depression. Lurasidone is the most recently approved agent for bipolar depression. Olanzapine-fluoxetine combination and quetiapine are approved as single modality therapies while lurasidone is approved as a monotherapy and as an adjunct to lithium or divalproex. The overall effect size of the 3 treatments in mitigating depressive symptoms is similar. Clinically significant weight gain and metabolic disruption as well as sedation are significant limitations of OFC and quetiapine. The minimal propensity for weight gain as well as the metabolic neutrality of lurasidone in the bipolar population is a clinically significant advantage. Evidence also supports lamotrigine with compelling evidence as an adjunct to lithium and in recurrence prevention paradigm; suggested evidence also exists for ketamine and modafinil/armodafinil; notwithstanding, these treatments remain investigational.

Conclusion. Relatively few agents are FDA-approved for bipolar depression. The selection and sequencing of agents in bipolar depression should give primacy to those agents that are FDA-approved. Further refinement of the selection process will need to pay careful attention to the relative hazards of weight gain and metabolic disruption in this highly susceptible population. Other agents with differential mechanisms (eg, ketamine) offer a promising alternative in bipolar depression.

Introduction

Results from prospective phenomenological studies have provided replicated evidence that depressive symptoms and episodes dominate the longitudinal course of bipolar I/II disorder.[1] The relevance of depressive symptoms is further instantiated by several clinically relevant observations: (1) they represent the index presentation in most individuals with bipolar disorder (BD); (2) they are highly associated with suicidal ideation, non-lethal self-injurious behavior, and completed suicide; (3) they are related to medical and psychiatric comorbidity; and (4) they are the principal mediators of psychosocial impairment in BD. A separate observation of clinical relevance is the over representation

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of "depression-prone phenotypes" in females with BD (eg, mixed states and rapid-cycling).

During the past 2 decades, substantial progress has been made in the pharmacological treatment of bipolar mania insofar as there is an expanded list of Food and Drug Administration (FDA)-approved treatment options. In contradistinction, there has been substantially fewer treatment options FDA-approved and/or proven effective in bipolar depression. Notwithstanding the paucity of efficacy data, 3 agents are now currently approved for the acute treatment of bipolar depression. The overarching aim of this review is to synthesize extant evidence supporting the efficacy of FDA-approved and emerging treatment options for bipolar depression.

Method

A PubMed search of all English-language articles published up to July 2013 was conducted. The search terms were quetiapine, olanzapine-fluoxetine, olanzapine, lurasidone, ketamine, modafinil armodafinil, and lamotrigine. The search was augmented with a manual review of relevant articles, reference lists, as well as posters presented at national and international meetings. Articles selected for review were based on the adequacy of sample size, the use of standardized diagnostic instruments, validated assessment measures, and overall manuscript quality.

Results

Olanzapine-fluoxetine

Olanzapine-fluoxetine combination (OFC) was approved for the treatment of bipolar I depression in 2003. The approval was based on replicated evidence of efficacy in adults (18 or older who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria for bipolar I disorder).[2]

The primary objective of the 8-week study was to compare the efficacy and safety of olanzapine monotherapy and placebo in the treatment of bipolar I depression. This was a single-protocol study divided into 2 identical 8-week studies. The OFC treatment arm was included concurrently for exploratory purposes. The pivotal registration trials were published as a combined paper wherein a total of 1072 patients were recruited from inpatient and outpatient services of 84 study sites in 13 countries.[2]

Eligible subjects were required to have a score of at least 20 on the Montgomery–Åsberg Depression Rating Scale (MADRS) at randomization. Subjects were also required to have had a history of at least 1 prior manic or mixed episode of sufficient severity to require treatment with a mood stabilizer or antipsychotic agent. Randomization was disproportionate for olanzapine (n = 370), placebo (n = 377), and OFC (n = 86) assignment (ie, 4:4:1, respectively). Olanzapine dosing was 5–20 mg while OFC was 6 and 25 mg, 6 and 50 mg, or 12 and 50 mg for olanzapine and fluoxetine, respectively. Patients were permitted adjunctive use of benzodiazepine (up to 2 mg of lorazepam equivalents per day) throughout screening and acute phases of the study. Anticholinergic therapy was permitted throughout the study for the treatment of extrapyramidal symptoms (ie, benztropine mesylate or biperiden ≤ 6 mg per day or trihexyphenidyl ≤12 mg per day).[2]

The patients taking OFC had the highest rate of study completion (ie, 64%) with higher rates of discontinuation with olanzapine (ie, 48.4%) and placebo (ie, 38.5%). Starting at week 1 and continuing throughout the study, both the olanzapine and OFC groups demonstrated significantly greater mean improvement in MADRS total scores than those receiving placebo. Starting at week 4 and continuing to week 8, the OFC group also demonstrated significantly greater mean total MADRS score when compared to olanzapine alone. The therapeutic effect size for OFC and olanzapine was 0.68 and 0.32, respectively. The response rate for the olanzapine group was 39.0% while for OFC it was 56.1%, both of which were significantly greater than placebo. The remission rate for olanzapine was 32.8% while for OFC it was 48.8%, again significantly higher than reported for placebo. The olanzapine-treated subjects demonstrated greater mean improvements on the Clinical Global Impressions Bipolar Version–Severity of Depression Scale (CGI-BP-S) than placebo, while OFC showed greater mean improvement than placebo and olanzapine.[2]

Treatment-emergent mania was defined as a Young Mania Rating Score (YMRS) of ≤15 at baseline and ≥15 at any time thereafter. There were no significant differences between groups in the rate of treatment-emergent mania (ie, 6.7%, 5.7%, and 6.4% for placebo, olanzapine, and OFC, respectively). The most commonly reported adverse events for OFC were somnolence, diarrhea, weight gain, dry mouth, and headache. The most commonly reported adverse events for olanzapine were somnolence, weight gain, increased appetite, headache, and dry mouth. Mean weight gain was higher in individuals receiving olanzapine (ie, olanzapine 2.59 ± 3.24 and OFC 2.79 ± 3.23 vs. placebo –0.47 ± 2.62). Both olanzapine and OFC groups exhibited significant change from baseline in total cholesterol.[2]

Olanzapine monotherapy is not FDA-approved for the acute treatment of bipolar I depression. However, olanzapine is approved for the acute treatment of bipolar depression in several other countries (eg, Japan).[2] The efficacy of olanzapine as a monotherapy

in bipolar depression is supported by the foregoing single-protocol studies.[3] Further evidence supporting olanzapine's efficacy in bipolar depression is from a separate study that primarily evaluated olanzapine (5–20 mg) compared to placebo in adults with bipolar I depression as part of a parallel-group study. Eligibility criteria were similar to the foregoing study that also included OFC. The olanzapine monotherapy study was, however, a 6-week randomized, double-blind, placebo-controlled trial. A total of 514 patients were randomly assigned to either olanzapine (n = 343) or placebo (n = 171).[3]

The baseline to endpoint decrease in least squares mean MADRS total score was significantly greater in the olanzapine group than in the placebo group after 6 weeks of double-blind treatment (–13.82 vs –11.67; P = 0.018), with an effect size of 0.22. Significantly higher rates of response and remission were noted in the olanzapine vs. placebo-treated subjects (ie, 52.5% vs 43.3%; 38.5% vs 29.2%, respectively). The olanzapine-treated subjects had significantly greater reduction in least-squares mean MADRS total scores in each visit other than week 1. The olanzapine-treated subjects also exhibited a greater baseline-to-endpoint improvement in CGI-BP depression, CGI-BP mania, and CGI-BP subscale scores. The adverse event profile (eg, clinically significant weight gain and significant change from baseline in fasting cholesterol, fasting triglycerides, and fasting glucose) was also noted.[3] A separate pooled analysis further supports the efficacy of olanzapine in bipolar depression.[4]

Quetiapine

Quetiapine was approved as monotherapy for the treatment of bipolar depressive episodes by the FDA in October 2006. The efficacy of quetiapine in acute bipolar depression is supported by results from 5 studies with quetiapine immediate release (IR) and 1 study with quetiapine extended release (XR). The design of all 6 clinical trials was similar insofar as the principal aim was to compare the efficacy of quetiapine monotherapy to placebo in adults with bipolar I/II depression (the registration trial that compared quetiapine XR to placebo was limited to depression in bipolar I disorder).

The subjects were outpatients 18–65 years of age; all subjects were required to have a Hamilton Depression Rating Scale (HAM-D) score of ≥20, HAM-D item 1 score ≥2, and YMRS ≤12 at the screening and randomization visits. The primary efficacy parameter was the MADRS in all studies. The dosing of quetiapine used was 300 mg or 600 mg per day (the quetiapine XR study aimed for quetiapine XR dosing of 400–800 mg from day 3 to day 22).[5] Concomitant psychiatric medications that were permitted were zolpidem tartrate (5–10 mg per day) and lorazepam (1–3 mg per day for severe anxiety) for the first 3 weeks but withheld for 8 hours before psychiatric assessments were conducted.[5–10]

The primary outcomes for each of the studies are presented in Table 1. The results of the first 2 trials [ie, BipOLar DEpRession I and II studies (BOLDER I and BOLDER II)] were summarized in a *post hoc* analysis of combined data.[7–9] In the combined analysis individuals with bipolar I depression receiving quetiapine 300 mg and 600 mg per day exhibited statistically significant improvement in symptoms of depression compared with those of placebo throughout the 8-week treatment period, beginning at week 1. The effect size for quetiapine was 0.78 for 300 mg and 0.80 for 600 mg. There was a similar reduction seen in 2 individuals in BOLDER I and II studies in patients with bipolar I disorder.[6] The rates of response (defined as a ≥50% decrease in MADRS total score from baseline) were higher in the quetiapine 600 mg group than placebo while remission rates (defined as a reduction in MADRS score to ≤12) were higher for both doses of quetiapine vs placebo. The efficacy of quetiapine was noted to be significantly higher in bipolar I depression vs bipolar II depression. The most commonly reported adverse events with quetiapine 600 mg were dry mouth, sedation, somnolence, dizziness, and fatigue. Significant advantage in efficacy was also noticed on CGI-BP-S and Clinical Global Impression of Change in Bipolar Depression Scale (CGI-BP-C) scores.[7]

The efficacy of quetiapine was further supported by 2 similarly designed studies [Efficacy of Monotherapy Seroquel in BipOLar DepressioN I and II (EMBLODEN I and II)]. Efficacy of Monotherapy Seroquel in BipOLar DepressioN I included lithium as an active control while EMBOLDEN II included paroxetine as an active control. The overall effect sizes in tolerability profiles for quetiapine in both studies were similar to what was reported in the original BOLDER registration trials.[8,9]

Lurasidone

Lurasidone was approved for the treatment of adults with bipolar I depression as a monotherapy or an adjunct to lithium or divalproex. The monotherapy study design was a double-blind, placebo-controlled, 6-week study, wherein eligible subjects were assigned to lurasidone 20–60 mg per day, lurasidone 80–120 mg per day, or placebo. All subjects started on 20 mg for the first 2 days then increased to 80 mg by day 7 and flexibly dosed thereafter. The double-blind phase was followed by 24 weeks open-label extension with lurasidone 20–120 mg per day. The monotherapy study enrolled subjects 18–75 with a *Diagnostic and Statistical Manual of*

TABLE 1. Studies Evaluating Treatment Options for Bipolar Depression

	Lurasidone			
Reference	Design	Measures	Results	Adverse effects
Poster presented at the American Psychiatric Association Meeting in Philadelphia, Pennsylvania. May 2012.[11]	**Subjects** - N = 500 - Age: 18–75 - Bipolar I depression - Major depressive episode (DSM-IV-TR) - With or without rapid cycling - Without psychotic features - ≥1 manic or mixed manic episode history - Recent depressive episode - MADRS ≥ 20 - YMRS ≤ 12 **Study** - 6-week, lurasidone monotherapy (20–60 mg/d, n = 71 or 80–120 mg/d, n = 66) or placebo (n = 78) - screening (Li or VPA ≥ 28 d) for 3–14 days - open-label extension (lurasidone 20–120 mg/d), flexible dose, 24 weeks	**Primary efficacy measure** - Baseline-to-endpoint change in MADRS score **Secondary efficacy measures** - Baseline-to-endpoint change in CGI-BP-S score - Response: ≥50% reduction in MADRS - Remission: MADRS score ≤ 12 at endpoint - HAM-A - QIDS-SR$_{16}$ - Q-LES-Q-SF - SDS	**Primary outcomes** - Significant improvement in MADRS score at week 6 with lurasidone (−15.4 for both) vs. placebo (−10.7) **Secondary outcomes** Significant improvement in (lurasidone vs. placebo): - CGI-BP-S scores - Response - Remission - QIDS-SR$_{16}$ - HAM-A - SDS - Q-LES-Q-SF	Common AEs: - Nausea - Headache - Akathisia - Insomnia - Somnolence - Sedation Small changes in: - Glucose - Prolactin - Body weight - Cholesterol - Low rates of treatment-emergent mania
Poster presented at the American Psychiatric Association Meeting in Philadelphia, Pennsylvania. May 2012.[11]	**Subjects** - n = 340 - age: 18–75 - Li: 0.6–1.2 mEq/L, VPA 50–125 ug/mL at screening - Rest of the criteria same as above **Study** - Adjunctive therapy - 6-week, double-blind, lurasidone (20–120 mg/d) + Li or VPA (n = 179) OR placebo + Li or VPA (n = 161) - Screening (Li or VPA ≥ 28 d) for 3–14 days - Open-label extension (lurasidone 20–120 mg/d) flexible dose, 24 weeks	**Primary efficacy measure** - Baseline-to-endpoint change in MADRS score **Secondary efficacy measures** - Baseline-to-endpoint change in CGI-BP-S score - Response: ≥50% reduction in MADRS - Remission: MADRS score ≤ 12 at endpoint - HAM-A - QIDS-SR$_{16}$ - Q-LES-Q-SF - SDS	**Primary outcomes** - Significant improvement in MADRS score with lurasidone + Li/VPA (−17.1) vs. placebo (−13.5) **Secondary outcomes** Significant improvement in (lurasidone + Li/VPA vs. placebo): - CGI-BP-S score - Response - Remission - QIDS-SR$_{16}$ - HAM-A - SDS - Q-LES-Q	- Same as above

Table 1. Continued

	Olanzapine			
Reference	Design	Measures	Results	Adverse effects
Tohen M, McDonnell DP, Case M, Kanba S, Ha K, Fang YR, Katagiri H, Gomez JC 2012 British J of Psychiatry[3]	**Subject** - N = 514 - Bipolar I disorder depression (DSM-IV-TR) - Age: 18–65 - Depressive episode for ≤ 90 days - Total HRSD-17 score ≥ 18 - ≥1 manic or mixed episode in the past 6 years. **Study** - Randomized, double-blind, placebo-controlled - Phase 3 trial of Olanzapine (5–20 mg/d) or placebo for 6 weeks in 2:1	**Primary efficacy measure** - Change in baseline-to-endpoint MADRS **Secondary efficacy measures** - CGI-BP - HRSD-17 - YMRS Response rate (≥50% reduction in MADRS at endpoint) - Recovery (MADRS ≤ 12 for ≥ 4 weeks) - Remission (*a priori* MADRS ≤ 12) (*post hoc* MADRS ≤ 8)	**Primary outcome** - Significant improvement in MADRS with olanzapine **Secondary outcomes** Significant improvement in (olanzapine vs. placebo): - HRSD-17 - YMRS - CGI-BP - Response - Remission - No significant difference in remission rate between olanzapine vs placebo	- Significant more people treated with (69.7%) had ≥ 1 treatment-emergent adverse events vs placebo (54.4%) Significant mean increase in: - Fasting cholesterol - Triglycerides - Weight - Body weight (≥7% body weight) Abnormally high levels of: - Alanine aminotransferase, aspartate - Aminotransferase - Gamma-glutamyl transpeptidase - Prolactin - Abnormally low neutrophils
Tohen M, Katagiri H, Fujikoshi S, Kanba S. 2013 J of Affective Disorders[4]	**Subjects** - N = 1214 (olanzapine = 690, placebo = 524) *Study 1:* - Bipolar I disorder depression (DSM-IV) - Both genders - Age: ≥18 - Total MADRS ≥ 20 at screening - ≥1 manic or mixed episode history *Study 2:* - ≤90 days of depressive episode - HAMD-17 (≥18) - East Asian countries (ie, Japan, Korea, etc) - The rest is same as above **Design** 1) 8 week, randomized, double-blind, placebo-controlled. olanzapine (5–20 mg/d) or placebo (or OFC) in 4:4:1 2) 6 week, randomized, double-blind, placebo-controlled, olanzapine monotherapy (5–20 mg/d) or placebo in 2:1	**Primary efficacy measures** - Baseline-to-endpoint change in MADRS total score - Changes in total MADRS score, MADRS-6 score, individual MADRS item scores from baseline. **Secondary efficacy measures** - MADRS-6 subscale - Individual MADRS item scores (Bech *et al*, 2002; Thase *et al*, 2012)	**Primary outcome** - Significant lease square mean change in MADRS with olanzapine (−13.77) vs placebo (−10.15) **Secondary outcomes** - Significant least squares mean change in MADRS-6 subscale score (olanzapine vs placebo) - Significant improvement in individual MADRS item scores except concentration difficulties and suicidal thoughts (olanzapine vs placebo)	- Not listed

Table 1. Continued

	Olanzapine			
Reference	Design	Measures	Results	Adverse effects
Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Mitchell PB, Centorrino F, Risser R, Baker RW, Evans AR, Beymer K, Dube S, Tollefson GD, Breier A 2003 Arch Gen Psychiatry[2]	<u>Subjects</u> - n = 833 - Bipolar I disorder I depression (MADRS ≥ 20, DSM-IV) - Age: ≥18 - ≥1 manic or mixed episode history <u>Study</u> - 8-week, double-blind, randomized, controlled, multi-site - Treatment with placebo (n = 377) or olanzapine (5–20 mg/d, n = 370) or OFC (6 and 25, 6 and 50, or 12 and 50 mg/d olanzapine and fluoxetine, n = 86)	<u>Primary efficacy measure</u> - Changes in MADRS total score <u>Secondary efficacy measures</u> - CGI-BP-S - YMRS - HAM-A - Response (≥50% improvement in MADRS total score from baseline-to-endpoint, ≥ 4 weeks) - Remission (MADRS total score ≤ 12 at end-point or ≥ 4 weeks)	<u>Primary outcomes</u> (Olanzapine, OFC vs placebo): - Significant improvement in depressive symptoms (week 1 onward); greater improvement with OFC than olanzapine alone - Decrease in MADRS total scores by 11.9, 15.0, and 18.5 in placebo, olanzapine, and OFC <u>Secondary outcomes</u> Significant improvements in (OFC, olanzapine vs. placebo): - Remission rate - Response rate - Inner tension - Reduced sleep - Reduced appetite - CGI-BP-S - HAM-A - Reported/apparent sadness - Inability to feel - Pessimistic thoughts - No sig. difference in treatment-emergent mania and YMRS between 3 groups	**Olanzapine** - Somnolence **OFC** - High rates of nausea and diarrhea - Discontinuation time (placebo: 41 days, olanzapine: 56 days, OFC: 65 days)

Table 1. Continued

		Quetiapine		
Reference	Design	Measures	Results	Adverse effects
Weisler RH, Calabrese JR, Thase ME, Arvekvist R, Stening G, Paulsson B, Suppes T. 2008 J Clin Psychiatry[7]	**Subjects** - Bipolar I disorder (DSM-IV) (n = 694) with a major depressive episode - HDRS total score ≥ 20 - HDRS item 1 score ≥ 2 - YMRS ≤ 12 - Age: 18–65 **Study** - *Post hoc*, 2 double-blind, randomized, placebo-controlled studies - Quetiapine 300 or 600 mg/d or placebo (1:1:1) for 8 weeks	**Primary efficacy measure** - Baseline-to-endpoint change in MADRS total score **Secondary efficacy measures** - Response (≥50% reduction in baseline-to-endpoint MADRS score) - Remission (reduction in MADRS score to ≤12) - Baseline-to-end change in MADRS items, HAM-D total scores, HAM-D items 1 and 3 scores, HAM-A, CGI-S-, CGI-I, Q-LES-Q SF	**Primary outcome** - Significant improvement in mean MADRS total scores with quetiapine vs placebo (300 mg/d: −19.4, 600 mg/d: −19.6, placebo: −12.6) **Secondary outcomes** Significant improvement in (quetiapine vs. placebo): - Response - Remission - CGI-S - CGI-I - Anxiety - Q-LES-Q-SF - PSQI - No sig. improvement in SDS	**Quetiapine** - Dry mouth - Somnolence - Sedation - Dizziness - Constipation - EPS-related adverse events - Greater mean weight gain - Greater treatment-emergent mania - Adverse effects resulted in only a low withdrawal rate
McElroy SL, Weisler RH, Chang W, Olausson B, Paulsson B, Brecher M, Agambaram V, Merideth C, Nordenhem A, Young AH 2010 J Clin Psychiatry[8]	**Subjects** - N = 740 (bipolar I disorder 1: 478, bipolar II disorder: 262) - Bipolar I disorder (n = 478) or 2 patients (n = 262) with major depressive episodes (DSM-IV) - Age: ≥18 - HDRS total score ≥ 20 - HDRS item 1 score ≥ 2 - YMRS ≤ 12 **Study** - Randomized, parallel-group, multicenter, double-blind, placebo-controlled - 8 week treatment with 300 mg/d quetiapine (n = 245), 600 mg/d quetiapine (n = 247), paroxetine 20 mg/d (n = 122), placebo (n = 126) in 2:2:1:1	**Primary efficacy measure** - Baseline-to-endpoint change MADRS total score **Secondary efficacy measures** - Response (≥50% reduction in MADRS total score baseline-to-endpoint) - Remission (MADRS total score ≤ 12 at week 8) - Change in MADRS individual item scores - MADRS item 10 score - HDRS total score - HDRS item 1 score - CGI-BP-S score - CGI-BP-C score - HARS - SDS - Q-LES-Q	**Primary outcomes** - Mean change in MADRS total baseline-to-endpoint scores (quetiapine 300: −16.19, quetiapine 600: −16.31, paroxetine: −13.76, placebo: −12.60) - Sig. reduction in MADRS total score with quetiapine but not with paroxetine **Secondary outcomes** - Improvements in most secondary measures seen with quetiapine (both doses) but not with paroxetine Significant improvements in (quetiapine vs. placebo; not with paroxetine): - All MADRS individual items - Suicidal thoughts Number of responders - CGI-BP-S Significant improvements in: - Remission (600 mg/d quetiapine vs. placebo) - HARS total score (quetiapine and paroxetine vs placebo)	**Quetiapine (both doses)** - Dry mouth - Somnolence - Sedation - Dizziness **Paroxetine** - Dry mouth - Sedation - Headache - Insomnia - Nausea - Lower incidence of change in mania with quetiapine vs placebo or paroxetine - Adverse events leading to discontinuation (paroxetine > 600 mg/d quetiapine > 300 mg/d quetiapine > placebo) - Lowest incidence of serious AE in 300 mg/d quetiapine, but highest with paroxetine (depression, atrial fibrillation, BD I, cellulitis, hypomania, mania, etc)

Table 1. Continued

	Quetiapine			
Reference	Design	Measures	Results	Adverse effects
Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, Paulsson B, Brecher M 2010 J Clin Psychiatry[9]	**Subjects** - n = 802 - Bipolar I depression (n = 499), bipolar II depression (n = 303) - With or without rapid-cycling (4–8 episodes/yr) - Recent major depressive episode - HDRS score ≥ 20 - HDRS item 1 score ≥ 2. - Age: 18–65 (mean = 42.2) - 59.3% women **Study** - Double-blind, placebo-controlled, randomized, multicenter, parallel-group, fixed-dose - 8 week treatment with quetiapine [300 mg/d (n = 265); 600 mg/d (n = 268)], Li [600–1800 mg/d (n = 136)] or placebo (n = 133) in 2:2:1:1 ratio	**Primary efficacy measure** - Change in MADRS total score. **Secondary efficacy measures** - Response (≥50% reduction in MADRS total score) - Remission (MADRS total score ≤12) - CGI - MADRS individual items - MADRS item 10 (suicidal thoughts) - HDRS total score - HDRS item 1 (depressed mood) - CGI-BP-S - HARS - SDS - MOS-Cog	**Primary outcomes** - Mean MADRS total score change (quetiapine 300: −15.4; quetiapine 600: −16.1; Li: −13.6; placebo: −11.8) - Significant more efficacy in MADRS total score (quetiapine 600 mg/d > Li) **Secondary outcomes** Significant improvements in (quetiapine vs. placebo; not with Li): - Response and remission rates (both doses) - HDRS (both doses) - CGI-BS-I/C (both doses) - HARS (both doses) - SDS (600 mg/d quetiapine vs placebo) - MOS-Cog (600 mg/d quetiapine vs placebo)	- Incidence of serious AEs was low and similarly distributed across the treatment groups - Low rates of treatment-emergent mania and suicidal thoughts in all treatment groups **Quetiapine** - Somnolence - Dry mouth - Dizziness **Li:** - Nausea
Calabrese JR, Keck PE, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J 2005 Am J Psychiatry[10]	**Subjects** - N = 542 - Bipolar I disorder (n = 360), bipolar II disorder (n = 182) - Major depressive episode (DMS-IV) **Study** - Randomized, double-blind, placebo-controlled - Quetiapine (600 or 300 mg/day) or placebo for 8 weeks	**Primary efficacy measure** - Mean change in baseline-to-endpoint MADRS **Secondary efficacy measures** - HAM-D - CGI-BP-S - HAM-A - PSQI - Q-LES-Q - Response: ≥50% reduction in MADRS - Remission: MADRS score ≤ 12 at endpoint	**Primary outcome** - Significant improvement in MADRS total scores in both quetiapine doses (week 1 onward) vs placebo **Secondary outcomes** Significant improvements in (quetiapine vs placebo): - Response - Remission - MADRS items - Treatment-emergent mania similar between quetiapine and placebo groups	In ≥ 10% of all patients with no sig. difference: - Dry mouth - Sedation - Somnolence - Dizziness - Fatigue - Constipation - Headache - Nausea - Upper respiratory infection Overall study discontinuation rate: - Placebo < 300 mg/d quetiapine < quetiapine 600 mg/d

Table 1. Continued

Reference	Quetiapine			
	Design	Measures	Results	Adverse effects
Cutler AJ, Datto C, Nordenhem A, Minkwitz M, Acevedo L, Darko D. 2011 Clinical Therapeutics[5]	**Subjects** - Bipolar I disorder (DSM-IV-TR) - With or without rapid cycling - Recent manic or mixed episode - Age: 18–65 - At least 1 manic episode in the 5 years prior to the recent index episode - At screening, YMRS total score ≥ 20 and YMRS item score ≥ 4 on 2 core manic items, CGI-BP-S ≥ 4 **Study** - Randomized, parallel-group, double-blind, placebo-controlled for 3 weeks - Placebo (n = 159) or quetiapine XR (n = 149) (day 1: 300 mg; day 2: 600 mg; day 3–end: 400–800 mg flexible dose) in 1:1 ratio	**Primary efficacy measure** - Change in the baseline-to-endpoint YMRS total score **Secondary efficacy measures** - YMRS response (≥50% reduction in score) - Remission: (YMRS ≤ 12 at endpoint) - CGI-BP-S/C (baseline to week 3) - CGI-BP-C score of 1 or 2 at endpoint - Change in baseline-to-endpoint YMRS item scores	**Primary Outcome** - From day 4 until the end, significant improvement in manic symptoms with quetiapine XR vs placebo (least square mean change: −14,34, −10.52 for quetiapine XR and placebo, respectively) **Secondary outcomes** Significant improvements in (quetiapine XR vs. placebo): - CGI-BP-S/C scores - Response rate - Remission rate	Overall discontinuation rate: - placebo < quetiapine XR (difference of 0.4%) - Mostly mild to moderate adverse effects **Quetiapine XR** - Dry mouth - Somnolence - Sedation **Placebo** - Headache - Sedation - Dry mouth Higher rates of serious adverse events (ie, suicidal ideation) in placebo vs quetiapine XR
Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese J. 2006 J Clin Psychopharmacol[6]	**Subjects** - Bipolar I or II depression (DSM-IV) - N = 509 - Age: 18–65 - At screening, HAM-D ≥ 20, HAM-D item 1 score ≥ 2, YMRS score ≤ 12. **Study** - Double-blind, placebo-controlled, randomized, fixed-dose - Quetiapine (300 or 600 mg/d) or placebo for 8 weeks - Same design as BOLDER I study - Use of lorazepam and zolpidem permitted	**Primary efficacy measure** - Change in baseline-to-endpoint MADRS total score **Secondary efficacy measures** - HAM-D - Individual MADRS items - HAM-A - CGI - Response (≥50% reduction in MADRS score) - Remission (MADRS score ≤ 12) - SDS - Q-LES-Q-SF	**Primary outcomes** - Significant improvement in MADRS total scores with quetiapine (both doses) vs placebo from week 1 until the end (mean change in MADRS total score: placebo: −11.93; quetiapine 300 mg/d: −16.94; quetiapine 600 mg/d: −16.00) **Secondary outcomes** - Therapeutic effect sizes (quetiapine 300 mg/d: 0.61; quetiapine 600 mg/d: 0.54) Significant improvements in (quetiapine vs placebo): - HAM-D score - Response rates - Remission rates - CGI Severity Scale - CGI Improvement Scale - SDS - Greater decrease in HAM-A score with quetiapine (both doses) vs placebo - Greater improvement in Q-LES-Q-SF score with quetiapine (both doses) vs. placebo	- Completion rates (placebo > quetiapine 300 mg/d > quetiapine 600 mg/d) Observed in all 3 groups: - Dry mouth - Sedation - Somnolence - Dizziness - Fatigue - Headache - Constipation - Nausea

Table 1. Continued

Modafinil				
Reference	Design	Measures	Results	Adverse effects
Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE, Walden J, Leverich GS, Altshuler LL, Nakelsky S, Hwang S, Mintz J, Post RM. 2007 Am J Psychiatry[16]	**Subjects** - Age: 18–65 - n = 85 - BD I or II (DSM IV, IDS) - Nonresponsive to mood stabilizer and with or without antidepressant treatment **Study** - Multisite, randomized, DB, placebo-controlled - 6 week treatment with adjunctive modafinil (n = 41) or placebo (n = 44) - Week 1: 100 mg modafinil or placebo/d - Weeks 2–6: 200 mg modafinil or placebo/d	**Primary efficacy measure** - Score change in IDS from baseline-to-endpoint **Secondary efficacy measures** - Clinical response (50% reduction in DIS score after week 6) - Remission (final IDS < 12) - Depression (Change in CGI-BP baseline-to-endpoint) - Fatigue and energy-level (Change in 4 IDS questions baseline-to-endpoint) - Hypomania (YMRS score > 13)	**Primary outcome** - Significant improvement with modafinil compared to placebo **Secondary outcomes** Significant improvements in (modafinil vs placebo): - Depressive symptoms (CGI-BP) - Response and remission rates - Fatigue - Energy - No significant change in hypomania or mania - No difference in IDS score between groups at endpoint - Response rate higher in BD I or placebo than BD II	- No significant baseline-to-endpoint difference in heart rate, blood pressure, or weight between groups **Modafinil vs placebo**: - Headache (4 vs 1) - Hypomania (1 vs 4) - Nausea (1 vs 1) - Dyspepsia (0 vs 2 - Infection (0 vs 1) - Insomnia (2 vs 0) - Rapid heart rate (1 vs 0)
Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA 2010 J Clin Psychiatry[17]	**Subjects** - Age: 18–65 - n = 257 - Men and women - Major depressive episode (QIDS-SR$_{16}$, CGI-BP, YMRS) + BD I (DSM-IV-TR) - Nonresponsive to previous treatment with 1 or 2 of: Li (≥0.6 mEq/L plasma), olanzapine (≥5 mg/d), or valproic acid (≥50 ug/ml plasma) **Study** - Randomized, multicentre, DB, placebo-controlled, fixed-dosage - Adjunctive armodafinil (150 mg/d, n = 128) or placebo (n = 129) treatment (once a day) for 8 weeks - For safety, if necessary dosage decrease to 100 mg/d	**Primary efficacy measure** - Mean change from baseline-to-endpoint visit in total IDS-C$_{30}$ score **Secondary efficacy measures** Change from baseline in: - MADRS - IDS-C$_{30}$ - HARS - CGI-BP - QIDS-SR$_{16}$ - Q-LES-Q-SF	**Primary outcomes** - Significant baseline-by-treatment interaction in IDS-C$_{30}$ score - Greater improvement in adjunctive armodafinil compared to placebo **Secondary outcome** - No difference between groups	In both armodafinil and placebo: - Headache - Insomnia - Diarrhea - Restlessness - Anxiety - Hypomania No association between adjunctive armodafinil and increased incidence or severity of mania, metabolic changes, depression, or suicidality

Table 1. Continued

Reference	Lamotrigine			
	Design	Measures	Results	Adverse effects
Van der Loos MLM, Mulder PGH, Hartong EGThM, Blom MBJ, Vergouwen AC, de Keyzer HJUEM, Notten PJH, Luteijin ML, Timmermans MA, Vieta E, Nolen WA 2009 J Clin Psychiatry[12]	Subjects - N = 124 - Age ≥ 18 - Bipolar I/II disorder (DSM-IV) - Current major depressive episode (MINI-Plus) - MADRS score ≥ 18 - CGI-BP depression severity score ≥ 4 - Receiving lithium treatment (0.6–1.2 mmol/L) ≥ 2 weeks before the study Study - Double-blind, multicenter, placebo-controlled - Lamotrigine (200 mg/d) or placebo adjunctive to existing lithium treatment - Subjects assigned to lamotrigine (n = 64) or placebo (n = 60) in a 1:1 ratio for 8 weeks	Primary efficacy measure - Change in baseline-to-endpoint in MADRS total score Secondary efficacy measures - Response (≥50% reduction in MADRS total score or change in CGI-BP compared to baseline) - Mania or hypomania	Primary outcome - Mean change in baseline MADRS total scores (placebo: −11.03; lamotrigine: −15.38) Secondary outcomes - Significant greater response with lamotrigine vs placebo (lamotrigine: 51.6%; placebo: 31.7%) - No significant CGI-BP score in change of depression (lamotrigine: 64.1%; placebo: 49.2%) - 7.8% from lamotrigine group and 3.3% from placebo group switched to mania or hypomania	- Mostly mild to moderate adverse effects - No significant difference in adverse effects between the two groups ≥5% in either group (lamotrigine and placebo, respectively) - Headache - Fatigue - Nausea - Flu-like symptoms - Insomnia - Tremor - Skin problems/mild rash - Dizziness Abdominal pain - Back pain - Rash - Joint/muscle pain - Agitation
Van der Loos MLM, Mulder P, Hartong EGThM, Blom MBJ, Vergouwen AC, van Noorden MS, Timmermans MA, Vieta E, Nolen WA 2011 Bipolar Disorders[13]	Subjects - n = 124 - Bipolar I/II disorder - MADRS score ≥18 - Receiving lithium treatment (0.6–1.2 mmol/L) Study - Randomized, double-blind, placebo-controlled - Lamotrigine (n = 64; 200 mg/d) or placebo (n = 60) adjunctive to lithium treatment for 8 weeks - Paroxetine (20 mg/d) (open label) administered to nonresponders (n = 37) for another 8 weeks in addition to lamotrigine or placebo treatment - Patients followed until week 68 - Benzodiazepines (2 mg lorazepam equivalents/d) allowed.	Primary efficacy measure - Change in baseline-to-endpoint MADRS total score Secondary efficacy measures - Responder status (CGI-BP depression or mania score < 4) - Time of first relapse after reaching responder status	Primary outcome - Significant improvement in MADRS total score with lamotrigine (−15.37) vs placebo (−11.16) at week 8. - Further improvement in MADRS total score with paroxetine but not significant between paroxetine + placebo or paroxetine + lamotrigine Secondary outcomes - Longer relapse time with lamotrigine (median time 10 months) vs. Placebo (median time 3.5 months) - Higher responder status in lamotrigine group vs. placebo	- 5 serious adverse effects in total (3 in the placebo group and 2 in the lamotrigine group) - No significant difference between the prevalence of adverse effects between the lamotrigine and placebo groups ≥5% of patients in either group: - Pulmonary problems - Hallucinations - Blurred vision - Joint/muscle pain - Throat problems - Headache - Nausea - Insomnia - Flu-like symptoms - Hypertension - Abdominal pain - Back pain - Coordination problems - Eye problems

Table 1. Continued

	Ketamine			
Reference	Design	Measures	Results	Adverse effects
Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, Kammerer WA, Quezado Z, Luckenbaugh DA, Salvadore G, Machado-Vieira R, Manji HK, Zarate CA 2010 Arch Gen Psychiatry[14]	Subjects - n = 18 - BD (DSM-IV, >20 MADRS) - Treatment resistant maintained with Li or valproate - Age: 18–65 - Current major depressive episode of at least 4 weeks Study - Randomized, PC, DB, CO, single-center, add-on study - IV infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo on 2 days 2 weeks apart combined with Li or valproate only - Li or valproate administered weekly	Primary efficacy measure - MADRS at baseline (60 min before infusion), 40, 80, 110, 230 min, days 1, 2, 3, 7, 10, and 14 after infusion Secondary efficacy measures - HDRS - BDI - VAS - HAM-A - BPRS - CADSS - YMRS	Primary outcomes - Significant improvement in depressive symptoms with ketamine compared to placebo (40 min–day 3; Largest effect at day 2) - No significant difference b/w 2 groups (baseline, day 7 onward) Secondary outcomes Fewer depressive symptoms with ketamine - BDI (40 min–day 3 and at day 14) - VAS (40 min–day 3) Less anxiety with ketamine - HAM-A (at 40 min, at 230 min–day 3) - VAS (40 min–day 2) Manic symptoms: Sig. decline with ketamine (YMRS, 80 min–day 2)	- No serious adverse effect 10% of ketamine or placebo groups: - Woozy/loopy - Lethargic/drowsy - Cognitive impairment - Fear or anxiety - Nausea - Dizziness - Odd sensations - Blurred vision - Headache Ketamine vs. placebo - Manic symptoms (1 vs. 1) Ketamine only (≥10%) - Dissociative symptoms* (most common, at 40 min) - Feeling strange - Dry mouth - Tachycardia - Inc. blood pressure No adverse event sig. different b/w 2 groups (80 min onward)

Table 1. Continued

	Ketamine			
Reference	Design	Measures	Results	Adverse effects
Zarate CA, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, Selter J, Marquardt CA, Liberty V, Lukenbaugh DA 2012 Biol Psychiatry[15]	<u>Subjects</u> - n = 15 - Mean age: 46.7 - Female: 8 - BD I or II (DSM-IV) - Depression maintained despite Li or valproate <u>Study</u> - Randomized, controlled, DB, CO, PC, single-centered - IV infusion of ketamine hydrochloride (0.5 mg/kg) or saline administered on 2 days, 2 weeks apart, combined with Li or valproate	<u>Primary efficacy measure</u> - Depressive symptoms (MADRS) measured at baseline (60 min before infusion), 40, 80, 110, and 230 min after infusion and days 1, 2, 3, 7, 10, and 14 after infusion <u>Secondary efficacy measures</u> - HDRS - BDI - VAS - HAM-A - BPRS - CADSS - YMRS	<u>Primary outcomes</u> - Significant improvement in depressive symptoms and suicidal ideation with ketamine compared to placebo (40 min to day 3) - No significant difference b/w groups at baseline, days 7, 10, and 14 <u>Secondary outcomes</u> - Significant difference in HDRS (40 min to day 2) - Significant difference in BDI and VAS (40 min to day 14)	- No serious adverse effect <u>10% of ketamine or placebo groups:</u> - Woozy/loopy - Lethargic/drowsy - Cognitive impairment - Fear or anxiety - Nausea - Dizziness - Odd sensations - Blurred vision - Headache - Drowsiness or sedation - Early morning awakening - Difficulty falling asleep <u>Ketamine only:</u> - Dry mouth - Dizziness/faintness - Flatulence - Dissociative symptoms* (most common, at 40 min)

MADRS: Montgomery–Åsberg Depression Rating scale; YMRS: Young Mania Rating Scale; CGI-BP: Clinical Global Impression-Bipolar version; HAM-A: Hamilton Anxiety Scale; QIDS-SR$_{16}$: Quick Inventory of Depressive Symptomatology; Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction-Short Form; SDS: Sheehan Disability Scale; BMI: Body Mass Index; HRSD-17, HAMD-17: Hamilton Rating Scale for Depression; MMRM: Mixed-effects Model Repeated Measures; HARS: Hamilton Anxiety Rating Scale; PSQI: Pittsburg Sleep Quality Index; MOS-Cog: Medical Outcomes Study Cognitive Scale; BDI: Beck Depression Inventory; Quetiapine XR: Quetiapine Extended Release; VAS: Visual Analog Scales; BPRS: Brief Psychiatric Rating Scale; CADSS: Clinician Administered Dissociative Scale; IDS: Inventory of Depressive Symptoms.

Mental Disorders, 4th edition, text revision (DSM-IV-TR)-defined major depressive episode in individuals diagnosed with bipolar I disorder with or without rapid cycling, and without psychotic features. The MADRS total score at baseline was ≥20 at screening and YMRS score ≤12. The primary efficacy parameter was a change from baseline in total MADRS score at week 6. All eligible subjects had to have had lithium or valproate for at least 28 days prior to entry.[11]

A total of 331 subjects were assigned to lurasidone (n = 164 at 20–60 mg per day; n = 167 at 80–120 mg per day; n = 168 assigned to placebo). The percent of subjects that discontinued were similar across groups (ie, 26% of total participants in the 2 lurasidone groups and 25% for placebo). The modal dose of lurasidone in the 20–60 mg group was 20 mg per day, while the modal dose in the 80–120 mg group was 80 mg per day.[11]

The change from baseline in the total MADRS score Mixed-Effects Model Repeated-Measures (MMRM) was significantly greater (ie, –15.4 for both lurasidone groups and –10.7 for placebo) in the lurasidone-treated groups. Both lurasidone-treated groups exhibited significant reductions in MADRS scores at all visits except week 1. Significant change from baseline was also noted for both lurasidone groups on the CGI-BP-S at endpoint (ie, all visits for the 80–120 mg group and all visits except week 1 for the 20–60 mg group). The response rates were higher in both lurasidone-treated groups vs placebo with a number needed to treat (NNT) = 5. Moreover, remission rates were also significantly higher for both lurasidone groups with NNT = 6 and 7 for the lower and higher doses of lurasidone, respectively. Evidence of efficacy was also evident as measured by the Hamilton Anxiety Rating Scale (HAM-A) and Quick Inventory of Depressive Symptomology-Self Report (QIDS-SR) with significant reductions in both lurasidone groups vs placebo. Significant improvements were also noted in measures of function [ie, Sheehan Disability Scale (SDS)] and quality of life [ie, Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF)].[11]

There were no significant changes between the 2 lurasidone groups and placebo in weight, body mass index (BMI), fasting cholesterol, triglycerides, and glucose. The most commonly reported adverse events were nausea, headache, akathisia, insomnia, somnolence, and sedation.[11]

The adjunctive trial had a similar study design and was a randomized, double-blind, placebo-controlled trial that compared adjunctive lurasidone 20–120 mg per day to adjunctive placebo. Lurasidone was started at 20 mg per day and increased to 60 mg per day. All subjects were required to take lithium (0.6–1.2 mEq/L) or valproate (50–125 µg.mL) for ≥28 days. The double-blind phase was also followed by an open-label extension, flexibly dosed (ie, lurasidone 20–120 mg/day) for 24 weeks. Eligibility criteria as well as primary and secondary endpoints were similar to the monotherapy trial.[11]

A similar number of individuals was assigned to adjunctive lurasidone (n = 179) and placebo (n = 161) with a similar percentage receiving lithium or valproate (50%/50% and 45%/54% in the lurasidone and placebo group, respectively). The overall rate of discontinuation was similar in the lurasidone and placebo groups (ie, 22% and 18%, respectively). The mean plasma concentration of lithium at endpoint was 0.7 mEq/L in both groups, and for valproate it was similar at 71.1 and 72.4 µg/mL in the placebo and valproate groups, respectively.[11]

The least square mean change from baseline from MMRM was significantly greater in the adjunctive lurasidone group (–17.1) vs the adjunctive placebo group (–13.5). The first observation week wherein the adjunctive lurasidone group separates from placebo was at week 3. Evidence of efficacy as measured by CGI-BP-S was also evident at endpoint for the adjunctive lurasidone group and at each observation point except week 1. The response and remission rates were significantly higher in the lurasidone treated group with an NNT = 7 for both outcomes, respectively. Further evidence of efficacy was apparent on the QIDS-SR, HAM-A, SDS, and Q-LES-Q-SF. There was no evidence of treatment-emergent mania; with only 1 subject in each group meeting *a priori* criteria (ie, YMRS ≥16 on any 2 consecutive visits, or at final assessment). There were no significant between-group differences on change from baseline on total weight, BMI, fasting cholesterol, triglycerides, or glucose. There was a significant median change from baseline in prolactin in the lurasidone treated group (ie, 3.8 ng/mL) versus the placebo group (0.0 ng/mL) (2.8 ng/mL vs –0.1 ng/mL; 5.1 ng/mL vs. 0.2 ng/mL in the lurasidone vs. placebo groups in males and females, respectively). The most common adverse events were nausea, headache, somnolence, tremor, akathisia, and insomnia with differences between the lurasidone and placebo treated groups, which were <7% apart for all adverse events.[11]

Lamotrigine

The anticonvulsant lamotrigine was approved for maintenance treatment of bipolar I disorder. Despite replicated evidence supporting the efficacy of lamotrigine in improving secondary outcome measures, lamotrigine failed to show consistent improvement on the primary outcome measure (eg, change in MADRS baseline-to-endpoint score) in acute bipolar depression trials. A significant positive result in the primary

efficacy measure was reported, however, in a meta-analysis of 5 studies.[12]

The primary objective of the 8-week, randomized, double-blind study was to assess the therapeutic effects of lamotrigine adjunctive to the existing lithium treatment in individuals with bipolar depression. The study included 124 eligible subjects, who were diagnosed with bipolar I or II disorder as outlined by DSM-IV-TR criteria. At the time of screening, the participants were required to have a score of at least 18 on the MADRS and 4 on the CGI-BP-S depression scale. Subjects were treated with lithium (0.6–1.2 mmol/L, plasma level) for at least 2 weeks prior to the study. Eligible subjects were then assigned to lamotrigine (200 mg/d, n = 64) or placebo (n = 60). Benzodiazepines (2 mg lorazepam equivalents per day) were permitted throughout the investigation.[12]

Mean change in baseline MADRS total score was greater in the lamotrigine group (–15.38) when compared to placebo (–11.03). Response rate was defined as greater than 50% reduction in MADRS total score or change in CGI-BP-S depression by less than or equal to 2 compared to baseline. Response rate was significantly higher in the lamotrigine group compared to the placebo group (51.6% and 31.7%, respectively, for MADRS score and 64.1% and 49.2, respectively, for CGI-BP-S score). Few subjects showed a switch to mania or hypomania (7.8% in the lamotrigine and 3.3% in placebo). Adverse events were mild to moderate with no significant difference in their frequency between the 2 groups. Headache, fatigue, and nausea were commonly reported side effects.[12]

In another study, van der Loos et al[13] observed the long-term effects of the aforementioned study over the span of 68 weeks. Eligibility criteria for subjects were identical to the one described above. After 8 weeks of treatment with lamotrigine, the nonresponders identified by the CGI-BP depression or mania score lower than 4 were treated with open-label paroxetine (20 mg/day) for another 8 weeks in addition to the ongoing lamotrigine or placebo treatment. Responders were followed until week 68 or until a relapse of manic or depressive episode.[13]

Significant improvement in MADRS total score was observed in the lithium–lamotrigine group compared to the lithium–placebo group (–15.37 and –11.16, respectively) after the first 8 weeks; however, adjunctive paroxetine to nonresponders (n = 37) did not yield a significant difference in MADRS total score between the lithium–lamotrigine–paroxetine and the lithium–placebo–paroxetine groups (–17.91 and –15.40, respectively). The median time to recurrence was longer in the lamotrigine group (10 months) compared to the placebo group (3.5 months). The probability of no recurrence, as well as the percentage of responders, were higher in the lamotrigine group compared to the placebo group throughout the study period.[13]

Ketamine

Glutamate receptor dysfunction is implicated in the pathophysiological course of bipolar depression. Recent studies have demonstrated that ketamine, an N-methyl-D-aspartate (NMDA) agonist, exerts immediate antidepressant effects.[14] The primary goal of a randomized, placebo-controlled, double-blind, cross-over study was to evaluate the effect of ketamine vs placebo in individuals with treatment-resistant bipolar depression.[14] Eligible subjects were required to be diagnosed with DSM-IV-TR-defined bipolar I or II depression with a minimum MADRS score of 20. Participants were required to have used at least 1 antidepressant and resistant to either lithium (0.6–1.2 mEq/L) or valproic acid (50–125 µg/mL) treatment lasting at least 4 weeks. Eligible subjects were then randomly assigned to, and treated with, intravenous infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo on 2 different test days that were 2 weeks apart. The single intravenous infusion of ketamine was combined with either lithium or valproate treatment.[14]

For all subjects, the MADRS scores were measured at baseline (60 min before infusion); 40, 80, 110, and 230 minutes; and days 1, 2, 3, 7, 10, and 14 after the infusion. Significantly fewer depressive symptoms were observed with ketamine compared to placebo (P < 0.01) 40 min following infusion from day 1 to day 3. The largest effect size (0.80) was reported on day 2, postinfusion. No significant difference between ketamine and placebo was observed from baseline and day 7 thereafter. A decrease in depressive symptoms with ketamine was also seen in the results obtained by the Beck Depression Inventory (BDI) and the Visual Analog Scales (VAS). Significantly fewer anxiety and manic symptoms were observed intermittently with ketamine treatment starting at 40 minutes and 80 minutes postinfusion, respectively.[14]

The robust antidepressant effects of ketamine were replicated in another study of similar design, where 15 patients diagnosed with bipolar I or II depression received ketamine hydrochloride or saline intravenous infusion. With the exception of the appetite and sleep items, 8 out of 10 individual MADRS items showed improvement with ketamine treatment compared to placebo. The median response time to ketamine was 40 min, whereas the mean relapse time was 4.5 days. Subjects (N = 15) met remission criteria (defined as a MADRS score <10) from 40 minutes until day 3 post-infusion. Moreover, ketamine treatment reduced suicidal ideation when compared to placebo and was reflected in MADRS, HDRS, and BDI scores.[15]

The most common side effects reported were dissociative symptoms (40 min post-infusion), sensation of oddity, dry mouth, tachycardia, and increased blood pressure. No serious adverse events were reported. No significant difference in adverse events between ketamine and placebo were observed following the 80-min assessment.[14]

Modafinil Armodafinil

Modafinil is not an FDA-approved treatment for bipolar depression; however, it is approved for the treatment of excessive sleepiness, which is often a characteristic of bipolar depression. The antidepressant effect of modafinil in bipolar depression has been studied. In 1 randomized, double-blind, placebo-controlled study, 85 eligible subjects diagnosed with bipolar I or II depression as outlined by DSM-IV-TR criteria, unresponsive to mood stabilizers, were treated with modafinil (n = 41) or placebo (n = 44) for 6 weeks. All subjects received 100 mg/day at week 1, which was increased to 200 mg/day at week 2 and every week thereafter.[16]

The primary efficacy measure was a change in the Inventory of Depressive Symptoms (IDS) score from baseline to endpoint. Significant reductions in total IDS score, 4-item IDS subset score, and CGI-BP depression severity were observed in the modafinil vs placebo group. A significantly greater percentage of subjects in the modafinil group (43.9%) achieved at least a 50% reduction in their IDS score compared to placebo (22.7%). Significantly greater response (greater than 50% reduction in IDS score at endpoint) and remission (final IDS score <12) rates (44% vs 39% and 23% vs 18%, respectively) were observed with modafinil compared to placebo. The frequency of treatment-emergent hypomania or mania did not differ significantly between the modafinil and placebo groups.[16]

A separate 8-week, randomized, double-blind, placebo-controlled study evaluated the efficacy of armodafinil as a treatment for bipolar I depression. Two hundred fifty-seven subjects participated in the study. Subjects unresponsive to previous treatment with lithium (≥0.6 mEq/L plasma), olanzapine (≥5 mg/day), or valproic acid (≥50 μg/mL plasma) were randomized to adjunctive armodafinil (n = 128, 150 mg/day) or placebo (n = 129).[17]

Mean change from baseline to endpoint values on the 30-item IDS (IDS-C_{30}) was used as the primary efficacy measure. Individuals receiving armodafinil displayed a greater mean change from baseline to endpoint on the IDS-C_{30} when compared to placebo (–15.8 and –12.8, respectively). Depressive symptomatology improved with armodafinil treatment compared to placebo as measured by the total IDS-C_{30} scores without reaching statistical

significance. No statistically significant improvement in remission (24% vs 18%) or response rates (37% vs 38%) was observed with armodafinil or placebo during the final 4 weeks. Armodafinil treatment did not yield any significant improvement on any secondary measures (ie, HARS, MADRS, CGI-BP, Q-LES-Q-SF, and QIDS-SR_{16}),[17] leaving it uncertain whether armodafinil can be considered a reliable treatment in bipolar depression.

Adverse events were categorized as mild to moderate. The most common adverse events reported with armodafinil treatment were headache, hypomania, infection, nausea, pepsia, insomnia, and rapid heart rate.[16] There was no significant difference in the percentage of the subjects who discontinued treatment due to adverse events in the armodafinil (13%) and placebo groups (9%).[17]

Summary and Conclusion

Three agents are now currently FDA-approved for the acute treatment of bipolar depression. The efficacy of OFC and quetiapine XR is also established in bipolar depression. Lurasidone is the only FDA-approved treatment established as efficacious for monotherapy as well as adjunct to lithium or divalproex.

The major limitations of OFC and quetiapine are sedation, propensity toward clinically significant weight gain, and metabolic disruption. The observation that individuals with BD are differentially affected by overweight/obesity, diabetes mellitus type II, and metabolic syndrome, as well as excess and premature mortality (largely due to cardiovascular disease), underscores the hazards posed by iatrogenic weight gain. The relatively low number needed to harm (NNH) for weight gain significantly reduces the overall therapeutic index (ie, NNT/NNH) and acceptability of the treatment. Lurasidone has minimal propensity to weight gain and appears metabolically neutral, which will be a significant advantage. The evidence of efficacy as monotherapy and as an adjunct has translational value, as many individuals with BD are treated with polypharmacy even in circumstances where the most adequate initial treatment approach is monotherapy.

Evidence for failed/negative studies with ziprasidone, aripiprazole, rispiridone, and cariprazine provide robust evidence indicating that although all antipsychotic treatments appear to be anti-manic, they may not be antidepressant. This observation provides the basis for differentiating atypical antipsychotics based on their efficacy in BD, notably bipolar depression, as well as their overall tolerability and safety profile.

With the introduction of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), there will be interest in evaluating the efficacy

of the currently approved FDA agents, as well as others, in bipolar depression (and mania) with mixed features. In the interim, the algorithmic measurement-based approach when stratifying treatments for bipolar depression should give priority to those agents that are FDA-approved. The evidence for conventional antidepressant medication in bipolar depression is mixed; notwithstanding the absence of compelling replicated evidence of efficacy in bipolar depression, it is likely the case that subpopulations of individuals with bipolar disorders may benefit from conventional antidepressants without the harm of mood destabilization.[18] Moreover, the hazards for mood destabilization in susceptible mood populations remains a real risk, along with the most often observed outcome being inefficacy. Lamotrigine is well-tolerated, and its efficacy in bipolar depression is most compelling as an adjunct to lithium and in recurrence prevention. Efficacy for ketamine and modafinil/armodafinil are also suggested, but not established at this time. The selection of treatments in bipolar depression also needs to pay close attention to adverse event profiles in the short- and long-term with a particular emphasis on propensity for engendering and/or worsening medical comorbidity.

Disclosures

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1. Helena is a 24-year-old patient with bipolar II presenting with depression. She has had a very limited response to lamotrigine for the past 2 months and is wondering what other treatment options are available for bipolar depression. Although there is evidence from a 6-week randomized, double-blind, placebo-controlled study supporting its efficacy in bipolar depression, which of the following treatments are not currently FDA-approved for this indication?

    A. Quetiapine monotherapy
    B. Olanzapine monotherapy
    C. Lurasidone monotherapy

2. Frank is a 54-year-old male patient with bipolar depression. He is having partial response to treatment with valproate, but you would like to add an adjunctive agent to further improve his depressive symptoms. Which of the following agents is FDA-approved as both a monotherapy and as an adjunct to mood stabilizers for the treatment of bipolar depression?

    A. Lurasidone
    B. Olanzapine–fluoxetine combination
    C. Lamotrigine
    D. All of the above
    E. None of the above

3. Tina is a 41-year-old patient with untreated bipolar depression. She is currently overweight (BMI = 32) and has a history of hypercholesteremia. Compared to placebo, the atypical antipsychotic lurasidone has shown significantly greater changes in:

    A. Weight
    B. Triglyceride levels
    C. Fasting cholesterol
    D. All of the above
    E. None of the above

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