Bipolar Therapeutics Update 2014: A Tale of 3 Treatments

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In the 2010s, advances in the treatment of bipolar disorder slowed, with only 1 agent approved by the US Food and Drug Administration (FDA) for acute bipolar I depression (in 2013), compared to the robust progress in the 2000s, during which 7 agents were approved for acute mania, 2 for acute bipolar depression, and 6 for bipolar disorder preventive treatment. This slowing of progress may have been in part due to decreased pharmaceutical company enthusiasm for developing compounds for psychiatric indications,[1] as well as the tendency for periods of consolidation (development of derivative and better-tolerated treatments) to follow periods of rapid advances (development of efficacious novel treatments) in pharmacotherapy advancement.

Despite the substantial number of treatments approved by the FDA for bipolar disorder in the 2000s, important needs remained unmet, including the need for better-tolerated therapies (especially for treatments with lower propensities for yielding somnolence/sedation and weight gain) and additional treatments for acute bipolar depression. This update describes recent (2013–2014) events in bipolar disorder drug development, emphasizing information regarding 3 compounds (lurasidone, armodafinil, and cariprazine) that had, as of late 2014, 3 distinctive bipolar disorder treatment regulatory/availability outcomes in the US (FDA-approved and available on-label; FDA approval no longer pursued, but available off-label; and FDA approval status to be determined and not available, respectively).

Lurasidone

Lurasidone, a second-generation antipsychotic (SGA), is a benzoisothiazole derivative and is distinctive in that it is a serotonin 5-HT_7 receptor antagonist (consistent with putative procognitive effects), a serotonin 5-HT_{1A} receptor partial agonist (consistent with putative antidepressant effects), and an adrenergic α_{2C} receptor antagonist.[2,3] Like other SGAs, lurasidone is an antagonist at serotonin 5-HT_{2A} and dopamine D_2 receptors. Lurasidone has minimal affinities for histamine H_1 and muscarinic cholinergic receptors, consistent with a low risk of somnolence/sedation, weight gain, and anticholinergic side effects.

In a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in adults with acute bipolar I depression, lurasidone monotherapy compared with placebo had a favorable single-digit number needed to treat (NNT) for response (≥ 50% decrease in depression ratings) of 5, as well as a favorable double-digit number needed to harm (NNH) for akathisia of 15.[4,5] Therefore, lurasidone monotherapy compared with placebo was not only efficacious, but also more than twice as likely to yield benefit (response) than harm (akathisia). Moreover, in a different phase 3, multicenter, randomized, double-blind, placebo-controlled trial in adults with acute bipolar I depression, lurasidone adjunctive therapy (added to lithium or valproate) compared with placebo had a favorable single-digit NNT for response of 7 and a favorable double-digit NNH for nausea of 16.[5,6] Thus, lurasidone adjunctive therapy compared with adjunctive placebo was also more than twice as likely to yield benefit (response) than harm (nausea). As expected, somnolence and sedation were not commonly encountered with lurasidone, and ≥ 7% weight gain was seen in only 2.4% of patients with lurasidone monotherapy (vs 0.7% with placebo) and 3.1% with lurasidone adjunctive therapy (vs 0.7% with adjunctive placebo).[5]

Hence, lurasidone, whether administered as monotherapy or adjunctive therapy, appeared to have a favorable benefit/harm ratio that was not offset by reduction in efficacy, making it an important new treatment option for bipolar I depression. Indeed, in mid-2013, lurasidone was FDA approved for acute bipolar I depression in adults as monotherapy and as adjunctive therapy (added to lithium or valproate).

Armodafinil

Armodafinil is a low-affinity dopamine transporter inhibitor that was FDA approved in the 2000s for the treatment of excessive sleepiness in adults with narcolepsy, treated obstructive sleep apnea, and shift work disorder. Armodafinil has minimal affinities for histamine H_1 and muscarinic cholinergic receptors, consistent with a low risk of somnolence/sedation, weight gain, and anticholinergic side effects.

Three phase 3, multicenter, randomized, double-blind, placebo-controlled trials of adjunctive armodafinil (added to FDA-approved bipolar disorder preventive treatments) in adults with acute bipolar I depression had variable results. In the first trial, adjunctive armodafinil demonstrated efficacy for acute depression in adults with bipolar I disorder.[7] However, a second such trial was negative,[8] as was a third trial.[9,10]

In the first trial,[7] in adults with acute bipolar I depression, adjunctive armodafinil therapy (added to lithium, valproate, olanzapine, risperidone, aripiprazole, or mood stabilizer plus ziprasidone) compared with adjunctive placebo had a favorable single-digit NNT for response of 9 and a favorable double-digit NNH for anxiety of 29. Thus, armodafinil adjunctive therapy compared with placebo was not only efficacious, but also more than twice as likely to yield benefit (response) than harm (anxiety). As expected, somnolence/sedation and weight gain were not commonly encountered with armodafinil. However, in the second and third acute bipolar I depression trials, adjunctive armodafinil compared with adjunctive placebo did not demonstrate efficacy, although tolerability was adequate.[8–10]

Hence, adjunctive armodafinil had a favorable benefit/harm ratio that was offset by efficacy limitations, restricting its utility in bipolar I depression. Indeed, in mid-2013, the manufacturer of armodafinil (Teva Pharmaceutical Industries, Ltd.) announced that, based on an evaluation of the totality of results (1 positive and 2 negative phase 3, multicenter, randomized, double-blind, placebo-controlled trials), it would not proceed with regulatory filings for armodafinil for the treatment of major depression associated with bipolar I disorder.[11]

Despite the absence of an FDA bipolar I depression treatment indication, the prior FDA approval of armodafinil for the treatment of excessive sleepiness in adults with narcolepsy, treated obstructive sleep apnea, and shift work disorder made it available in the US. In view of the small number and tolerability limitations of FDA-approved acute bipolar depression treatments, clinicians and patients may determine that the established tolerability of adjunctive armodafinil makes it worth consideration in certain bipolar disorder patients (eg, in less clinically urgent cases of bipolar depression with minimal anxiety, psychomotor agitation, and insomnia but with prominent concerns regarding the risks of somnolence/sedation and weight gain), despite its efficacy limitations in acute bipolar I depression. Indeed, in the past, other treatments with adequate

tolerability but efficacy limitations such as lamotrigine or adjunctive antidepressants have been considered by some clinicians to be reasonable off-label alternative treatments for certain individuals with acute bipolar depression.[12]

Cariprazine

Cariprazine (RGH-188), an SGA, is a piperazine/piperidine derivative and is distinctive in that it is a robust dopamine D_3 receptor partial agonist.[13–15] In addition, cariprazine (like aripiprazole) is a partial agonist at dopamine D_2 receptors, and to a more limited extent at serotonin 5-HT_{1A} receptors, and is an antagonist at serotonin 5-HT_{2A} receptors, with limited affinity for histamine H_1 receptors and low affinity for muscarinic cholinergic receptors, consistent with a low risk of somnolence/sedation, weight gain, and anticholinergic side effects. Hence, the receptor actions of cariprazine suggest the possibility of a clinical profile with both similarities and differences compared to aripiprazole.

In a pooled analysis of two phase 3 multicenter, randomized, double-blind, placebo-controlled cariprazine monotherapy acute mania studies,[16,17] cariprazine (N = 492, mean dose = 7.2 mg/d) compared to placebo had a favorable single-digit NNT for response (≥ 50% decrease in mania ratings) of 6 but an unfavorable single-digit NNH for akathisia of 7. As expected, cariprazine had a low propensity for yielding somnolence/sedation and weight gain. It remains to be established whether cariprazine monotherapy has adequate tolerability, with a side effect profile more like that of aripiprazole than of older SGAs such as olanzapine, risperidone, and quetiapine. However, in a pooled analysis of the acute mania studies, akathisia was usually not problematic enough to yield discontinuation, so that cariprazine monotherapy compared to placebo had a favorable double-digit NNH for discontinuation due to akathisia of 34.[17] Moreover, in a 20-week study, among 402 bipolar I disorder patients taking open-label cariprazine (3–12 mg/d, mean = 6.2 mg/d), 32.6% had akathisia, but this led to discontinuation in only 4.7%. The rates of adverse effects of concern with other SGAs such as somnolence and ≥ 7% weight gain were only 5.7% and 9%, respectively.[18]

In late 2013, Gedeon Richter, Plc., and Forest Laboratories, Inc., announced that the FDA had issued a "complete response letter" (a letter conveying the FDA had not approved a New Drug Application in its current form) regarding cariprazine for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.[19] They reported that although the FDA had acknowledged that cariprazine had demonstrated effectiveness in the treatment of schizophrenia and mania associated with bipolar disorder, the Agency indicated that more information (including the optimal dose to avoid potential side effects) would be needed for approval. Thus, as of late 2014, the ultimate regulatory/availability status of cariprazine (which had not been FDA approved for any indication and thus was not available in the US) remained to be determined.

Conclusion

In conclusion, as of late 2014, lurasidone had been FDA approved for acute bipolar I depression and marketed in the US for that indication. In contrast, adjunctive armodafinil had not been FDA approved for acute bipolar I depression and had not been marketed in the US for that indication, with the manufacturer having announced that bipolar I depression approval will no longer be pursued. However, armodafinil remained FDA approved to improve wakefulness in adults with excessive sleepiness associated with treated obstructive sleep apnea, narcolepsy, or shift work disorder and marketed in the US for those indications. Finally, cariprazine had not been FDA approved or marketed in the US for acute mania (or for that matter, for any indication), although regulatory filing for schizophrenia and acute mania had not been discontinued.

Taken together, the data suggest that progress in therapeutics in the 2010s, despite substantial slowing compared to the 2000s, has remained sufficient to sustain hope that significant advances that permit ongoing improvement in outcomes for patients with bipolar disorder will continue.

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