Armodafinil Shows Potential Benefit for Depressive Symptoms in Bipolar Disorder

Written by Brian Hoyle

Armodafinil 150 mg daily for 8 weeks as an adjuvant with mood stabilizers and/or antipsychotic drugs improved depressive symptoms associated with bipolar I disorder. The benefits, however, were not statistically significant compared with placebo. The findings of a multi-institutional, international, Phase 3, randomized, double-blind, placebo-controlled trial were presented by Caleb Adler, MD, University of Cincinnati, Cincinnati, Ohio, USA [APA 2014 (poster NR6-038); NCT01305408].

The study focused on depressive episodes of bipolar I disorder, which occur more frequently than the manic episodes [Kupka RW et al. *Bipolar Disord* 2007] and exact a toll on personal and work relationships [Calabrese JR et al. *J Clin Psychiatry* 2004]. The ability of armodafinil to bind to the dopamine transporter and inhibit dopamine reuptake [NUVIGIL (package insert). Frazer, PA: Cephalon, Inc; 2013] may be useful in treatment of bipolar I depression [Calabrese JR et al. *J Clin Psychiatry* 2010; Frye MA et al. *Am J Psychiatry* 2007].

Researchers screened 656 patients for the trial. All were aged 18 to 65 years, were diagnosed with bipolar I disorder, and were currently depressed for ≥2 weeks but ≤12 months despite a regimen of mood stabilizers for at least 4 weeks. Exclusion criteria included other Axis I or II disorders, psychotic symptoms or psychosis within 4 weeks of screening, suicidal ideation or a history of suicidal behavior, a Hamilton Anxiety Scale score ≥17 at baseline, and a documented drug or hypersensitivity reaction.

The 399 enrolled patients were randomly assigned to receive placebo (n=199) or armodafinil 150 mg/day (n=200). At baseline, 308 (77%) of patients were taking one mood stabilizer or antipsychotic. Patients in the two groups were similar in baseline demographic and bipolar illness characteristics (Table 1).

The primary efficacy assessment was the mean change from baseline to 8 weeks in the 30-item, clinician-rated Inventory of Depressive Symptomatology (IDS-C_{30}) score. Safety assessments

Peer-Reviewed Highlights From the

American Psychiatric Association 167th Annual Meeting

May 3-7
New York

Table 1. Baseline Demographic and Bipolar Illness Characteristics

	Placebo (n=199)	Armodafinil 150 mg/day (n=200)
Demographic Characteristics		
Age, years, mean (SD)	43.7 (11.6)	45.3 (11.3)
Males, n (%)	78 (39)	80 (40)
Race, n (%)		
White	176 (88)	182 (91)
Black	16 (8)	14 (7)
Other	7 (4)	4 (2)
Weight, kg, mean (SD)	81.2 (17.5)	80.7 (17.5)
Bipolar Illness Characteristics		
Time since start of current depressive episode, weeks, mean (SD)	12.1 (9.1)	12.3 (9.9)
Time since first depressive episode, years, mean (SD)	13.1 (9.7)	14.0 (9.2)
Time since first manic or mixed episode, years, mean (SD)	10.9 (9.0)	12.5 (9.5)
Hospitalization for bipolar depression, n (%)	137 (69)	127 (64)
Currently meets criteria for rapid cycling, n (%)	6 (3)	5 (3)

SD=standard deviation.

included adverse events, serious adverse events, vital signs, and laboratory data.

The baseline mean IDS-C_{30} scores were 42.4 and 43.5 in the armodafinil and placebo groups, respectively. The respective reduction in the score at 8 weeks was −20.8 and −19.4; the difference was not statistically significant (p=0.272). At 8 weeks, there were no clinically significant differences compared with baseline in serum chemistries, lipid profiles, and urinalysis parameters. Mean weight at 8 weeks was reduced in the armodafinil group by 0.5 kg and was increased in the placebo group by 0.3 kg.

Armodafinil was well tolerated. Adverse events were similar in the two groups; most were mild or moderate, and no deaths occurred.

The finding of a benefit of armodafinil that was not statistically significant from placebo calls for more research to conclusively determine the clinical value of the drug for treatment of bipolar I depression.

Vilazodone Effective and Safe in Major Depressive Disorder

Written by Brian Hoyle

A multicenter, randomized, double-blind, placebo-controlled trial involving more than 1100 patients with major depressive disorder (MDD) has affirmed the efficacy and safety of vilazodone (VLZ) 40 mg/day and indicated the acceptability of a dose of 20 mg/day. The poster presenter was Carl Gommoll, MS, Forest Research Institute, Jersey City, New Jersey, USA [APA 2014 (poster NR6-103)].

VLZ is a selective serotonin (5-HT) reuptake inhibitor and partial agonist of the 5-HT_{1A} receptor. Two prior placebo-controlled Phase 3 trials reported the efficacy and safety of a 40-mg/day dose [Khan A et al. *J Clin Psychiatry* 2011; Rickels K et al. *J Clin Psychiatry* 2009]. Researchers of a 52-week open-label study reported the long-term safety and tolerability of the same dose [Robinson DS et al. *J Clin Psychopharmocol* 2011].

The current study [NCT01473381] was conducted to confirm the results using this now-approved dose, as well as to assess the effectiveness, safety, and tolerability of a lower dose of 20 mg/day. The study was placebo-controlled and incorporated citalopram (CIT) 40 mg/day as an active control for assay sensitivity. The study phases consisted of a 1- to 4-week drug-free screening period, 10-week double-blind treatment, and 1-week double-blind down-taper. The 1162 patients were randomly assigned 1:1:1:1 to receive placebo, VLZ 20 mg/day, VLZ 40 mg/day, or CIT 40 mg/day, respectively.

Included patients were aged 18 to 70 years, met *DSM-IV-TR* criteria for MDD and had ongoing major depressive episodes, had Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥26 at screening and baseline, and were physically sound. Exclusion criteria included *DSM-IV-TR*-defined Axis I disorder other than MDD within the prior 6 months (excepting secondary diagnoses of comorbid generalized anxiety disorder, social anxiety, and/or specific phobia), defined suicide risk, absence of effect of ≥2 antidepressant drugs, and recent (within 2 weeks) use of psychoactive drugs or need for treatment with eszopiclone, zopiclone, or zaleplon.

The primary efficacy measure was MADRS total score. Secondary efficacy measures were Clinical Global Impressions-Severity (CGI-S) score and MADRS sustained response rate (≤12 for at least the last two clinic visits during the treatment period). CGI-Improvement and Hamilton Rating Scale for Anxiety (HAM-A) scores were also determined. Safety outcomes were adverse events, patient-monitored parameters, and ratings of suicidal ideation and sexual functioning.

The safety population comprised 281 placebo, 288 VLZ 20mg, 287 VLZ 40 mg, and 282 CIT patients. Patient demographics were generally similar between the groups. Approximately 70% of patients completed the study. The rate of discontinuation was significantly higher in the VLZ 40-mg/day group (34%) compared with the placebo (25%) group.

Compared with placebo, MADRS score improvement from baseline to Week 10 was significantly greater for VLZ 20 mg (least squares mean difference [LSMD], –2.57; adjusted p=0.0073) and VLZ 40 mg (LSMD, –2.82; adjusted p=0.0034) in the intent-to-treat population. CIT versus placebo had a similar pattern (LSMD, –2.74; p=0.0020), demonstrating assay sensitivity. In the same population, reductions in CGI-S scores were significantly greater than placebo for VLZ 20 mg (LSMD, –0.35; adjusted p=0.0073), VLZ 40 mg (LSMD,–0.33; adjusted p=0.0097), and CIT (LSMD, –0.35; p=0.0025). More patients met criteria for MADRS sustained response in the VLZ 20-mg (29.9%), VLZ 40-mg (33.5%), and CIT (31.1%) groups versus the placebo (26.3%) group; differences were not statistically significant.

All groups displayed similar adverse event (AE) profiles. Rates of treatment-emergent AEs (TEAEs) were similar for VLZ 20 mg (72.2%), VLZ 40 mg (77.4%), CIT (77.0%), and placebo (63.3%). TEAEs occurring in ≥5% of VLZ patients and twice placebo were diarrhea, nausea, vomiting, and insomnia. Majority of TEAEs were mild or moderate in severity. Serious AEs were reported in 2 placebo, 4 VLZ 20-mg, 4 VLZ 40-mg, and 6 CIT patients. One death occurred, in a patient receiving VLZ, which was not related to medication.