Aripiprazole for the Treatment of Depression in MDD—Selected Posters

Over 60% of patients with major depressive disorder (MDD) who are treated with standard antidepressant therapy (ADT) do not achieve remission. The efficacy and safety of aripiprazole as adjunctive therapy recently have been demonstrated in patients who had an inadequate response to initial ADT [Berman RM et al. *J Clin Psychiatry* 2007; Marcus RN et al. *J Clin Psychopharmacol* 2008].

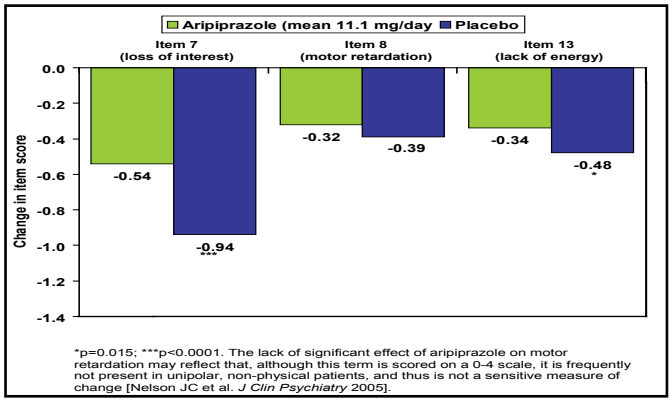
Posters that were presented during the APA annual meeting reported additional analysis of data from the above studies, which were identical 14-week trials that consisted of an 8-week prospective treatment phase with ADT and a 6-week randomized, placebo-controlled phase in which patients received either adjunct aripiprazole (n=375; mean dose 11.1 mg/day) or adjunct placebo (n=368). Only patients who failed to achieve an adequate response (<50% reduction on HAM-D17 Total, HAM17 ≥ 14, and CGI-I ≥3) with ADT entered the randomized phase.

Carlson BX et al. (NR3-014) reported that patients who were treated with adjunct aripiprazole for 6 weeks experienced a 1.75-kg increase in weight versus 0.38 kg in placebo patients (p<0.001). Common treatment-emergent adverse events that were seen more often in aripiprazole versus placebo patients included akathisia (28.8%), restlessness (12.1%), insomnia (8.1%), fatigue (8.4%), blurred vision (5.7%), and constipation (4.6%). The majority of akathisia events that were experienced was mild/moderate and rarely led to discontinuation; 52% resolved by the study end and 80% resolved following a dose reduction.

In an analysis of difficult-to-treat core symptoms of depression, Nelson JC et al. (NR3-022) reported that adjunctive aripiprazole produced significantly greater improvement in loss of interest (p=0.0001) and lack of energy (p=0.015) but not motor retardation (Figure 1). Overall composite score for these items, as well as HAM-D17 total score, was significantly improved with aripiprazole versus placebo (-1.61 vs -1.12; p <0.001 and -7.1 vs -4.7; p<0.001, respectively).

Reimherr FW et al. (NR3-039) reported that aripiprazole significantly (p<0.001) improved 8 of 10 MADRS line items, including apparent sadness, reported sadness, lassitude, and inability to feel, as early as 1 week after beginning treatment; pessimistic and suicidal thoughts improved within 2 weeks. Reduced sleep and appetite improved gradually with aripiprazole and reached significance (p<0.001) by Week 6.

Figure 1. Mean Change from Baseline (End of Week 8) to Endpoint (Week 14) in HAM-D Composite Drive Score Items.



For a subset of patients who were defined as anxious or having atypical depression, Trivedi MH et al. (NR3-074) reported that aripiprazole produced significantly (p<0.05) greater improvement in MADRS total score versus placebo. Response and remission rates also were significantly (p<0.05) higher in the aripiprazole treatment group.

Tran QV et al. (NR3-097) presented data that showed that the mean reduction in MADRS total score was significantly greater in patients with MDD who received adjunctive aripiprazole versus placebo (-8.67 vs -5.73; p<0.001). A subpopulation analysis revealed no treatment-by-subgroup interaction.

Overall, adjunctive aripiprazole appears to be an efficacious, safe, and well-tolerated treatment for the core symptoms of depression in patients who are resistant to ADT.

Impact of Depression on Fibromyalgia Treatment – Selected Posters

Fibromyalgia is a chronic disorder that affects approximately 3.4% of women and 0.5% of men in the United States. It is characterized as widespread musculoskeletal pain, fatigue, and a reduced threshold for pain. Treatment can be complicated by the comorbid depressive moods that often accompany fibromyalgia. Three double-blind, placebo-controlled studies examined the correlation between treatment effect on pain and levels of depression/anxiety in fibromyalgia patients.

Arnold L et al. (NR7-090) presented pooled data from 3 trials that compared pregabalin 150, 300, 450, and

600 mg/day with placebo after 8-14 weeks of treatment in >1500 fibromyalgia patients. Significant ($p<0.001$) reductions in pain (≥30% reduction on the pain diary score) with 450 and 600 mg/day doses of pregabalin were reported at the study endpoint. Significant changes, relative to baseline, were also seen on the Hospital Anxiety and Depression Scale (HADS) (450 and 600 mg doses; $p<0.01$), the Multidimensional Assessment of Fatigue (MAF), and the Patient Global Impression of Change (PGIC) (all $p<0.05$). Patients also reported significant ($p<0.001$) improvement in sleep quality (300-600 mg doses). Changes in pain relative to sleep and PGIC scores were highly correlated, pain and MAF were moderately correlated, while pain and HAD scores had little correlation. Adverse events occurring in greater frequency in pregabalin-treated patients were dizziness, somnolence, weight increase, blurred vision, and dry mouth.

Gendreau RM et al. (NR7-091) evaluated the impact of baseline depression severity on the efficacy of milnacipran (100 or 200 mg/day) as treatment for fibromyalgia in a 6-month study. Milnacipran (100 and 200 mg/day) significantly improved the composite score for pain (≥30% reduction on the pain diary score + PGIC score) at 3 ($p<0.03$) and 6 months ($p<0.05$). Maximum pain relief was achieved within 9 weeks of beginning treatment and was maintained for the duration of the study. Pain relief was independent of depression, as indicated by baseline Beck Depression Inventory scores. Mild to moderate nausea and headaches were commonly reported adverse events among all patients.

Arnold LM et al. (NR3-069) presented pooled data from 4 duloxetine (combined scores for 60 or 120 mg/day) studies in fibromyalgia patients with and without depression. Significant ($p<0.05$) improvement versus placebo was noted on the Brief Pain Inventory average score, the Fibromyalgia Impact Questionnaire, the clinician GI-S and patient GI-I scores in patients with and without comorbid depression beginning at Week 1. HAM-D17 scores showed significant improvement in depressed patients (-5.77 vs -4.39; $p<0.05$) who were treated with duloxetine versus placebo. Common adverse events included nausea, headache, constipation, and somnolence, which were significantly ($p<0.05\%$) higher with duloxetine in both depressed and nondepressed patients.

All three drugs improved pain, patients' impression of change in their disease state, and their self-reported ability to function, regardless of their baseline depression score.

Insights from the Antidepressant BRITE-MD Trial: Predicting Response

Results from the BRITE-MD (Rapid Identification of Treatment Effectiveness in Major Depression) study suggest that the use of frontal quantitative EEG (fqEEG) could be used as a biomarker to predict treatment outcome with the antidepressant escitalopram (ESC).

In this open-label study of adults with DSM-IV-defined major depressive disorder, all subjects initially received ESC (10 mg/day) for a period of one week. Subjects were then randomized to either: 1) continued treatment with ESC; 2) bupropion XL (BUP; 300 mg/day); or 3) augmentation of ESC with BUP, for an additional 7 weeks (n=220). Subjects were assessed for severity of depression using the HAM-D-17 instrument, as well as 4-channel fqEEG. Study endpoints were Response (≥50% decline in HAM-D) and Remission (final HAM-D ≤7).

The predictive metric that was used in the study consisted of a composite EEG index—the Antidepressant Treatment Response (ATR)—which was developed to predict clinical response using fqEEG from baseline to Week 1.

Results at 7 weeks showed that the response rates for those patients who remained on the ESC initial treatment was higher for ATR-predicted responders than for ATR-predicted non-responders (68% vs 28%; $p=0.001$). This predictive ability also was seen amongst ESC patients who achieved remission, wherein ATR-predicted remitters occurred at a higher rate than the ATR-predicted non-remitters (50% vs 21%; $p=0.01$). For patients who were identified as ATR-predicted non-responders at one week and then randomized to BUP, a higher response rate was achieved as compared with those who remained on ESC (53% vs 28%; $p=0.034$). ATR-predicted non-responders who received BUP augmentation had a numerically higher response rate than those who remained on ESC for the entire study period (33% vs 28%); however, these results were not significant.

Though not yet definitive, the findings of BRITE-MD suggest that an ATR index at Week 1 of ESC treatment may help guide antidepressant selection, potentially leading to improved outcomes of antidepressant therapy.

For additional information, please visit: www.BRITE-MD.org.