P01-188

A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF DIVALPROEX AND OLANZAPINE IN BIPOLAR I DISORDER, MIXED EPISODE

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Aims: This unique study of treatment of the mixed state of bipolar I disorder using simultaneous depression and mania response criteria compared divalproex monotherapy versus olanzapine augmentation in a 6-week, randomized, double-blind trial.

Methods: Patients (age 18-60 years) with 14-28 days of divalproex monotherapy (blood levels of 75-125 µg/mL) were randomized to augmentation with olanzapine 5-20 mg/day or placebo. Data collected included: Hamilton Depression Rating Scale (HDRS), Young Mania Rating Scale (YMRS), Clinical Global Impression for Bipolar Illness (CGI-BP), hospitalizations, concomitant medications, and adverse events (AEs). Primary co-objectives were comparisons of baseline to endpoint changes in HDRS and YMRS. Secondary objectives included comparisons of times to onset (25% reduction) and response (50% reduction) in both HDRS and YMRS, change in CGI-BP, hospitalizations, and safety.

Results: Patients were 59% female, 51% Caucasian, 33% African American, and 14% Hispanic with mean standard deviation (SD) HDRS and YMRS scores of 22.2 (4.5) and 20.9 (4.4). Mean standard error (SE) score changes for the olanzapine (n=100) or placebo (n=101) arms, respectively, were: HDRS, -9.37 (.55) and -7.69 (.54), p=.022; YMRS, -10.15 (.44) and -7.68 (.44), p< .001; and CGI-BP, -1.34 (.11) and -1.06 (.11), p=.056. Times-to-onset (median 7 vs 14 days) and response (median 25 vs 49 days) were significantly shorter for olanzapine augmentation. One olanzapine patient required hospitalization (p=1.0). Treatment-emergent AEs were consistent with previously-published rates.

Conclusion: Six-week olanzapine treatment augmentation was associated with greater and earlier reduction of manic and depressive symptoms in mixed episode patients on divalproex treatment.

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