Combo Drug Approved for Resistant Depression

BY DIANA MAHONEY

The Food and Drug Administration's recent approval of Eli Lilly's olanzapine/fluoxetine combination drug Symbyax for recalcitrant depression has been hailed as an important advance in the management of patients with major depressive disorder, but some experts still advise proceeding with caution.

Already approved for the treatment of bipolar depression, Symbyax is the first agent to be approved for acute therapy of treatment-resistant depression.

Approval of the combination antipsychotic/antidepressant was based on data from five trials demonstrating significant reductions in mean total Montgomery-Åsberg Depression Rating Scale (MADRS) scores relative to either fluoxetine alone or olanzapine alone among patients who met DSM-IV criteria for major depressive disorder (MDD) and who previously did not respond to two antidepressants of adequate dose and duration.

The data about weight gain with the combination therapy 'merit an important discussion.'

DR. PHILIP

The studies evaluated fixed-combination doses ranging from 6 mg to 18 mg for olanzapine and 25 mg to 50 mg for fluoxetine, according to a press release from Eli Lilly & Co.

In an integrated analysis provided to the FDA by Eli Lilly, the reduction from baseline in mean MADRS scores for the combination drug vs. fluoxetine alone and olanzapine alone was –12.2 vs. –8.5 and –7.7, respectively. The remission rates for the combination, fluoxetine only, and olanzapine only were 25.5%, 17.3%, and 14.0%, respectively.

Pooled data from safety studies showed that, among the adverse events reported in at least 5% of the patients taking the combination drug, weight gain, increased appetite, dry mouth, somnolence, and fatigue were reported at twice the rate of patients in the placebo group.

Considering the large number of patients with treatment-resistant MDD—up to 35% of patients with depression, according to the data provided by Eli Lilly—the approval of the combination therapy is an important development, said Dr. Noah S. Philip of Brown University, Providence, R.I., who has studied the off-label use of atypical antipsychotic drugs in the treatment of depression.

"As the [Sequenced Treatment Alternatives to Relieve Depression] trial demonstrated, approximately one-half of patients respond and one-third remit during their first antidepressant trial, so more options are clearly needed, and use of the atypical antipsychotics as augmenting agents for depression is an increasing pattern to fill this important need."

However, he noted, "there are still no trials comparing these newer, and much more expensive, augmentation strategies to other … strategies such as lithium, T3, or bupropion augmentation."

There have also been concerns that definition of treatment-resistant depression in the olanzapine/fluoxetine combination studies might be too lax. "Operationally, the definition of treatment-resistant depression is the failure of at least two previous trials in the current depressive episode [as in the data presented by Lilly to the FDA]," Dr. Philip said. "Other definitions include failure from at least two separate classes of antidepressants within a current major depressive episode, verified by scales such as the Antidepressant Treatment History Form, as well as failed trials of psychotherapy."

In addition, Dr. Philip said, the data about weight gain with the combination therapy "merit an important discussion. Lilly's data showed that 56% of patients who received olanzapine/fluoxetine combination in longer term treatment (up to 76 weeks) had a more than 7% increase in weight from their baseline, and that patients with early weight gain [first 6 weeks] were more likely to gain even more weight," he said (J. Clin. Psychiatry 2005;66:1468-76). ■