MEETING HIGHLIGHTS

American Psychiatric Association

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At this year’s 161st Annual Meeting of the American Psychiatric Association, from May 3 to 8, 2008, in Washington, DC, researchers presented data on new atypical antipsychotic medications (iloperidone and asenapine) with an efficacy comparable to that of older atypical agents but with more benign side-effect profiles in schizophrenia and bipolar disorder. In addition, among studies of post-traumatic stress disorder in veterans returning from tours of duty in Iraq, preliminary results for medications in combination with virtual reality exposure therapy show strong promise.

New Atypical Agents and Virtual Reality with Drug Therapy

Iloperidone in Schizophrenia
• Peter J. Weiden, MD, Center for Cognitive Medicine, University of Illinois, Chicago, Ill.
• Stephen M. Stahl, MD, PhD, University of California, San Diego, and La Jolla, Calif.

With an efficacy comparable to that of other approved atypical antipsychotic agents and a favorable side-effect profile, iloperidone (Fanapta, Vanda Pharmaceuticals) may be a welcome treatment option for patients with schizophrenia, according to phase 3 clinical trial results. Iloperidone, a mixed D2/5-HT2 antagonist, is currently under review by the Food and Drug Administration (FDA). In November 2007, the FDA accepted Vanda’s New Drug Application for iloperidone.

There is still a “huge” unmet need for treatment alternatives in this population, according to Dr. Weiden. His study enrolled 593 adult patients admitted for acute exacerbations of schizophrenia meeting specific requirements on the Positive and Negative Syndrome Scale (PANSS). In the randomized, four-week, double-blind, placebo-controlled trial, the active arms received iloperidone 24 mg/day and ziprasidone (Geodon, Pfizer) 160 mg/day. Endpoints were changes in PANSS scores, Brief Psychiatric Rating Scale (BPRS) scores, and in Clinical Global Impression–Severity (CGI–S) Scale scores.

An analysis showed significant and similar improvements relative to placebo in PANSS-T (total) scores for both agents: iloperidone, –12.0 (P = 0.006) and ziprasidone, –12.3 (P = 0.012). PANSS-P (positive) and PANSS-N (negative) scores for iloperidone and ziprasidone also improved, compared with baseline scores (P < 0.001 and P = 0.036, respectively). BPRS and CGI–S scores improved significantly for both agents compared with placebo. Dr. Weiden concluded that iloperidone demonstrated “an attractive efficacy profile.”

A second study, a pooled analysis of nine phase 2 and 3 trials found a favorable metabolic profile for iloperidone. Dr. Stahl said that weight gain with iloperidone was similar to that with risperidone (Risperdal, Janssen): a weight change of 7% or more in 13.5% of patients in short-term studies and in 23.2% of patients in long-term studies.

Iloperidone showed modest weight gain but is pretty much neutral with respect to metabolic index, glucose, total cholesterol, and triglycerides,” Dr. Stahl said, noting also that triglycerides actually improved (~17.7 mg/dL for both short-term and long-term studies).

“As triglycerides are a fairly sensitive indicator of whether or not you’re getting insulin resistance,” he said. “I think the most interesting thing about this drug is that it does not cause extrapyramidal symptoms [EPS] or akathisia.”

Dr. Stahl commented that he thought that iloperidone, if approved, would be a “switch” drug, not a starting drug, because it is titrated slowly and would be prescribed for patients who have problems with tolerability or efficacy with other atypical antipsychotic agents.

In an interview, Dr. Weiden concurred, underscoring that low EPS rates “are a major strength of this medicine.”

Asenapine in Bipolar Disorder
• Roger S. McIntyre, MD, Associate Professor of Psychiatry, University of Toronto, Ontario, Canada

A review of clinical trials in the Olympia Program of asenapine, an atypical antipsychotic agent acquired by Schering-Plough from Organon, revealed efficacy and safety in both acute and extended therapy for bipolar disorder. A double-blind, nine-week extension trial of bipolar mania (ARES 7501006), according to lead investigator Dr. McIntyre, included more than 500 patients with acute manic or mixed episodes of bipolar I disorder who had completed an earlier three-week placebo-controlled trial with olanzapine (Zyprexa, Lilly) to verify assay sensitivity. The extension trial tested asenapine directly for non-inferiority with olanzapine, a drug that is usually considered the gold standard for this indication.

Patients continued their earlier doses (asenapine 10 mg twice daily on day one, 5 or 10 mg twice daily thereafter; and olanzapine 15 mg once daily on day one, 5 to 20 mg thereafter). However, patients who had received placebo were given asenapine. The primary outcome measure was the change in total scores of the Young Mania Rating Scale (YMRS) on day 84. Patients completing this trial were eligible for a double-blind, 40-week extension, bringing follow-up to 52 weeks.

YMRS scores declined by 24.4 with asenapine and by 23.9 with olanzapine, thereby confirming non-inferiority for asenapine, Dr. McIntyre said. Responses (with total YMRS scores reduced by 50% or more) and remissions (scores of 12 or less at the endpoint) were also similar for asenapine and olanzapine (approximately 90% for both parameters in both groups).

CGI–Bipolar Disorder (CGI–BP) Severity of Mania scores were “much or very much improved” in about 80% of patients. continued on page 367
Treatment-related adverse events (63%) and EPS (13%) were similar for both drugs, but clinically significant weight gain (7% or more above baseline weight) occurred more often with olanzapine (30.6%) than with asenapine (16.9%). In the 40-week extension study among 218 patients continuing the same dosages, response and remission rates remained similar for both treatments, but they had increased to nearly 100%.

Dr. McIntyre stated, “I think it’s axiomatic that the longer an individual remains on therapy, the more the likelihood of response and remission increase.”

Weight gain remained higher with olanzapine (55.1%) than with asenapine (36%). The frequency of metabolic syndrome increased in the olanzapine patients (from 20% at baseline to 29.9%) but decreased in the asenapine patients (from 26.4% at baseline to 23.4%). The incidence of EPS increased to 35.4% with asenapine but to a lesser degree with olanzapine, to 18.7%.

**Virtual Reality Therapy for Post-traumatic Stress Disorder in Iraq War Veterans**

- Barbara Rothbaum, PhD, Professor of Psychiatry, Emory University School of Medicine, Atlanta, Ga.

The combination of virtual reality, psychotherapy, and pharmacotherapy reduced the magnitude of startle (a response to an unexpected stimulus) by a significant 75% in 24 veterans with post-traumatic stress disorder (PTSD). Heightened acoustic startle, a symptom of hyperarousal, is common in these patients.

Participants were exposed to virtual reality therapy that was tailored to their own experience. They received d-cycloserine (Seromycin, Lilly) (a broad-spectrum antibiotic that aids in extinguishing fear memories) or alprazolam (Xanax, Pfizer), an antianxiety medication. Ultimately, 150 patients are scheduled to be enrolled in the National Institutes of Mental Health study.

The virtual reality sessions consisted of two-minute video clips of scenes depicting the Iraq theater of combat from the viewpoint of a soldier either in a Humvee or on foot patrol. A platform with a “base shaker” (a powerful speaker beneath the patient’s seat) simulated the vibrations of an improvised explosive device. Odors of diesel fuel and burning rubber, sounds of explosions, ricocheting bullets, helicopters, and shouts and cries contributed further to verisimilitude. Dr. Rothbaum explained that these sessions, followed by therapy sessions, are designed to repeat traumatic memories until physical and emotional responses diminish. Acoustic startle was assessed before treatment, immediately after treatment, and at three and six months after treatment. All subjects manifested robust startle responses before treatment. In a preliminary report of results, Dr. Rothbaum said that most subjects were doing well; their PTSD symptoms had fallen into the nonclinical range. Startle magnitude decreased by 75% during the course of treatment and reached a nadir six months after treatment.

Similar declines were seen in Clinician-Administered PTSD Scale (CAPS) scores. Although the analysis has not yet compared d-cycloserine and alprazolam effects, Dr. Rothbaum did note that, in her experience, the effectiveness of two virtual reality sessions with d-cycloserine was as great as eight sessions of virtual reality without medication. The planned completion date of the study is late August 2011.