Clinical News

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FDA Considers Sertindole, a Second-Generation Antipsychotic

Sertindole, an antipsychotic that was previously reviewed by the United States Food and Drug Administration (FDA) in the late 1990s, has recently been submitted as a new drug application for consideration for approval as a treatment for schizophrenia. Sertindole was originally approved in Europe in 1996 and was subsequently withdrawn due to concern about cardiac conduction adverse effects. Large, naturalistic clinical research reported no higher risk of cardiac effects above that of other available antipsychotics, and the drug was reapproved in 2000 for use in Europe. It will be of interest to learn how this proceeds.

FDA Approval of Deltoid Injection Site for Risperidone Microspheres

Based upon bioavailability and safety, tolerability studies that were presented at the May 2008 American Psychiatric Association Annual Meeting, the FDA has approved the administration of risperidone microspheres in the deltoid muscle in the arm—as an alternative choice to the current site of administration of the injection at the gluteal muscle in the buttocks. Risperidone microspheres have been available for the treatment of schizophrenia since 2003. This new injection would provide more flexibility for patients and clinicians. Once this becomes available, it will be interesting to know what percentage of patients already taking risperidone microspheres by gluteal injection "switch" to the new deltoid administration site.

New Maintenance Treatment Data on Antipsychotics

A study of asenapine given sublingually in comparison to placebo showed that asenapine reduced relapse in patients evaluated under double-blind conditions over twenty-six weeks. Asenapine is currently under review by the FDA. We have reviewed data from short-term trials of asenapine in earlier issues of ***Clinical Schizophrenia & Related Psychoses (CS).***

Long-acting injectable (LAI) olanzapine (at doses of 150 mg, 300 mg, or 450 mg every 4 weeks) was compared to a low dose (45 mg every 4 weeks) of long-acting injectable olanzapine in a 24-week, double-blind study of over 1,000 patients with schizophrenia who had previously been stabilized on oral olanzapine. The results were presented in September 2008 at the meeting of the European College of Neuropsychopharmacology (ECNP). The three therapeutic doses of long-acting injectable olanzapine were more effective for treating symptoms than the low-dose comparative treatment. The profile of adverse effects with long-acting injectable olanzapine was similar to oral olanzapine, with the notable exception of olanzapine LAI Post-Injection Syndrome. Olanzapine LAI is under consideration by the FDA.

New Study of Paliperidone Extended Release (ER) Tablets for Schizoaffective Disorder

Although prevalence estimates vary widely, schizoaffective disorder is still a relatively common condition among patients who are treated long term in the public mental health system. Surprisingly, there are few studies that address treatment options exclusively in this patient group. Most information is either extrapolated from studies of patients with schizophrenia and/or is derived from subanalyses of schizoaffective disorder subpopulations in large treatment studies. A recent study of 316 patients with well-characterized schizoaffective disorder compared 6 mg/day paliperidone ER, 12 mg/day paliperidone ER, and placebo over 6 weeks. The results were presented at the 2008 U.S. Psychiatric & Mental Health Congress. Patients receiving the higher dose of paliperidone improved significantly in their symptoms. The profile of adverse effects was similar to other studies of paliperidone in patients with schizophrenia.

TEOSS Study Rekindles Debate over First- versus Second-Generation Antipsychotics for Treatment of Schizophrenia

Recently published in *The American Journal of Psychiatry*, the TEOSS (Treatment of Early Onset Schizophrenia) study provides new comparative data on first- versus second-generation antipsychotics (FGAs version of SGAs) for the treatment of schizophrenia. In this study of childhood schizophrenia, 116 children/adolescents aged between 8 and 19 years were randomized to 8 weeks of treatment with olanzapine, risperidone, or molidone. Efficacy was generally similar across all three groups, with response rates of 50%, 46%, and 34% for patients receiving molidone, risperidone, and olanzapine, respectively. Olanzapine was associated

with an average 6 kilograms of weight gain compared with 3.6 kilograms with risperidone; molidone, chosen originally because of historical information suggesting that it had a low liability for weight gain, was not associated with weight gain in this study. This is the first comparative study of first- and second-generation antipsychotics in adolescents with schizophrenia. Although TEOSS has a smaller sample size (which may have impacted the capacity to determine comparative treatment efficacy across the three groups), it sits alongside CATIE and EUFEST as another important comparative study informing clinicians on the choices of antipsychotics across the range of older and newer drugs.

Sikich L, Frazier JA, McClellan J, Findling RL, Vitiello B, Ritz L, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. Am J Psychiatry 2008;165(11):1420-1431.

FGA versus SGA—and the Debate Rolls On!

Another meta-analysis adds to the debate about antipsychotics. Leucht and colleagues have conducted a large statistical analysis—meta-analysis—of some 150 published studies that compared FGAs and SGAs on efficacy and tolerability. Among the nine SGAs included in these studies, four drugs (clozapine, olanzapine, risperidone, amisulpride—an antipsychotic that is available in Europe) proved more efficacious than FGAs. Clozapine was the most robust, with an observed effect size in these comparative studies of 0.52, while aripiprazole and ziprasidone fared well in comparisons of weight liability, overall. SGAs were associated with more weight gain than haloperidol. When the comparison was made with low potency FGAs, however, the weight liability was similar. This important study confirms the impressions of many clinicians—that neither FGAs nor SGAs are truly distinct and homogeneous classes. One important implication, thereupon, is that treatment clinics are best considered as individualized for each patient. It is likely, however, that the debate over FGAs versus SGAs will continue to rage on for more time yet.

Leucht S, Corves C, Arbter D, Engel RR, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2008.

Deficits in Brain Derived Neurotrophic Factor (BDNF) at Birth and Later Risk of Schizophrenia

Obstetric complications (OCs) are seen in about twenty percent of the mothers of people who later go on to develop schizophrenia. Fetal distress, a "catch all" for fetal hypoxia, has been shown in some studies to be one of the OCs overrepresented in people with schizophrenia. In a recent study published in *Biological Psychiatry*, Cannon and colleagues examined Brain Derived Neurotrophic Factor (BDNF) from umbilical cord and maternal blood samples collected in a large cohort of people who later developed schizophrenia. Cannon and colleagues observed that BDNF was significantly reduced in those patients who experienced fetal hypoxia. These findings add to the weight of importance of OCs as an etiological event in schizophrenia. The study also provides important new data on BDNF and schizophrenia. There are now several studies showing BDNF reductions in patients with schizophrenia. There is also a growing literature in mood disorders showing that BDNF may be reduced in depression "restored" as the patient's mood is improved with antidepressant medications.

Cannon TD, Yolken R, Buka S, Torrey EF; Collaborative Study Group on the Perinatal Origins of Severe Psychiatric Disorders. Decreased neurotrophic response to birth hypoxia in the etiology of schizophrenia. Biol Psychiatry 2008;64(9):797-802.

Intriguing Study Links Middle-Ear Disease to Schizophrenia?

A very interesting study published in *The British Journal of Psychiatry* takes a second look at one of the oldest ideas about schizophrenia … that madness might be caused by irritation of the brain that could occur from middle-ear disease. This British study determined, from medical records of family practitioners, the rate of middle-ear disease in people who later developed schizophrenia. People who had middle-ear disease were over 3.6 times more likely to have a later diagnosis of schizophrenia (actually over 4 times more likely if the middle-ear disease was on the left side). However, the authors did not take into account respiratory infections or other viral assaults which might have contributed to the intriguing results of this study.

Mason P, Rimmer M, Richman A, Garg G, Johnson J, Mottram PG. Middle-ear disease and schizophrenia: case-control study. Br J Psychiatry 2008;193(3):192-196.

Clarification …

In the outstanding John Read paper on child maltreatment and psychosis that appeared in our last issue, the complete affiliation information for co-author Charles L. Whitfield should read as follows: Private practice of trauma psychology and addiction medicine; consultant and collaborating author, CDC, Atlanta, GA.