

11th International Congress For Schizophrenia Research

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The 11th International Congress for Schizophrenia Research took place this year in Colorado Springs, Colorado, from March 28 to April 1, 2007. This year's biennial conference, 20 years after the initial ICSR meeting, again served as a venue for active researchers in neuro-

science, cognitive neuroscience, basic and clinical psychopharmacology, psychosocial interventions, and genetics. In this article, a hormonal treatment, a novel antipsychotic agent, and a substance abuse study are discussed.

Transdermal Estrogen

Presenter: Jayashri Kulkarni, PhD, Professor of Psychiatry, Monash University, Melbourne, Australia

Among women meeting criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder, treatment with a transdermal estrogen patch seems to have the potential to reduce positive, negative, and general symptoms of psychopathology.

Presenting the results of a study of 102 women, Dr. Kulkarni observed that postpartum and menopausal hormonal changes can make women more vulnerable to either a first episode or a relapse of psychosis. Women in her study met the criteria for schizophrenia, as specified in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*); schizoaffective disorder; or schizophreniform disorder. All patients had Positive and Negative Syndrome Scale (PANSS) scores indicating acute illness (60 or above).

The patients were randomly assigned, in a double-blind fashion, to receive the estradiol transdermal patch (100 mcg) or placebo for 28 days. Each woman continued to receive antipsychotic medications.

In the estradiol group of patients, but not in the placebo group, PANSS general psychopathology symptoms decreased significantly from baseline (with estradiol, $P < 0.001$; with placebo, $P = 0.79$). Differences between the groups were significant ($P = 0.004$). PANSS total symptoms scores were similarly reduced in the estradiol group only.

"These findings open the door for a preventive role for estrogen in women with schizophrenia who deteriorate in periods of hormonal change," Dr. Kulkarni concluded.

However, she pointed out that because of known risks of long-term hormone therapy, she was also evaluating selective estrogen receptor modulators (SERMs) as a therapy for schizophrenia in women. SERMs, sometimes called "brain estrogens," do not affect breast or ovarian tissues. Initial experience with raloxifene (Evista, Eli Lilly) 60 mg daily suggests that a higher dose (120 mg), now being tested, might be effective.

Bifeprunox Mesilate and Risperidone

Presenter: Herbert Y. Meltzer, MD, Professor of Psychiatry, Vanderbilt University Medical Center, Nashville, Tennessee

Researchers testing a novel atypical antipsychotic agent, bifeprunox mesilate (Solvay/Wyeth), described its side-effect profile as "exceptionally benign." Bifeprunox is a highly potent partial dopamine D_2 agonist with moderately potent serotonin 5-HT_{1A} agonist activity. Its lack of affinity for 5-HT_{2A} and 5-HT_{2C}, muscarinic, or histaminergic receptors may account for its lack of cardiometabolic symptoms (weight gain and adverse lipid changes) and extrapyramidal symptoms (tardive dyskinesia), which are common with other atypical and typical antipsychotic agents, respectively. A New Drug Application for bifeprunox was submitted to the Food and Drug Administration (FDA) in October 2006.

Dr. Meltzer's double-blind study included patients with a mean age of approximately 38 years who met the *DSM-IV* criteria for schizophrenia and who were experiencing an acute exacerbation. Patients were randomly assigned to receive once-daily bifeprunox (30 or 40 mg, $n = 148$ for each), placebo ($n = 148$), or risperidone (Risperdal, Janssen) 6 mg ($n = 154$) for six weeks. All patients were hospitalized for a minimum of 10 days after randomization.

The primary efficacy endpoint was the change in PANSS scores from baseline.

Both bifeprunox 30 mg and risperidone 6 mg produced significant reductions in PANSS scores, compared with the baseline scores, at each weekly assessment. On the basis of this and other research, Dr. Meltzer noted, the bifeprunox recommended dose would be 20 mg daily. Although there was a larger improvement in efficacy with risperidone (a decline of about 19 points in PANSS scores and 13 points with bifeprunox 30 mg), he said that the difference in efficacy between the agents was unlikely to be clinically significant. The numbers of patients who dropped out of the study because of a lack of efficacy, he emphasized, were roughly comparable: 14 of 148 patients receiving bifeprunox 30 mg and 10 of 154 receiving risperidone 6 mg.

An analysis of side effects, however, clearly revealed advantages with the new agent. Patients receiving bifeprunox

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Meeting Highlights: International Congress for Schizophrenia Research

experienced a mean weight loss of approximately 1 kg, compared with those receiving placebo ($P = 0.001$). Those receiving risperidone gained nearly 1.5 kg ($P = 0.0003$ versus placebo).

Mean plasma glucose levels dropped by nearly 5 mg/dL with bifeprunox 30 mg and increased by more than 1 mg/dL with risperidone 6 mg. Similarly, plasma prolactin levels decreased significantly with bifeprunox and increased significantly with risperidone.

“The main point is that bifeprunox has probably the most benign side-effect profile of any of the atypical antipsychotic agents and certainly is more benign than the typicals,” Dr. Meltzer concluded.

A pioneer in the field of atypical antipsychotic agents, Dr. Meltzer was enthusiastic about the potential utility of bifeprunox, as he stated in an interview:

“Because efficacy is essentially the same among the atypical antipsychotic agents, I think most physicians and patients make treatment decisions based on side-effect profile. With schizophrenia occurring in 1% of the population, that’s more than 2 million individuals in the US, there’s a huge number of people who will find this drug as effective as anything else they can receive and certainly more tolerable.”

Bifeprunox Mesilate and Placebo

Presenter: Michel Bourin, MD, Professor, Université de Nantes, Nantes Cedex, France

Another trial, comparing bifeprunox 30 or 40 mg with placebo, resulted in similarly favorable findings. The six-month trial was conducted among approximately 500 stable patients with schizophrenia. Time to deterioration, the primary endpoint, was significantly prolonged with both bifeprunox doses. The risk of deterioration was 1.5 times higher with placebo. Significantly more placebo patients experienced deterioration (59%) than the bifeprunox patients, 41% of whom received 20 mg and 38% of whom received 30 mg.

Weight loss was significantly greater with bifeprunox 30 mg, compared with placebo; the prevalence of metabolic syndrome showed a downward trend with bifeprunox therapy and an upward trend with placebo.

Substance Abuse: The OPUS Project

Presenter: Merete Nordentoft, MD, Associate Professor, Copenhagen University Hospital, Copenhagen, Denmark

In a two-year study comparing standard treatment with integrated mental health care plus substance abuse treatment, the integrated approach improved clinical outcomes and reduced substance abuse.

Dr. Nordentoft was the lead investigator in a study that enrolled 547 first-episode patients with psychosis from the Danish OPUS Project. Many of these patients were also substance abusers. OPUS is a clinical treatment and research project funded by the Danish Ministries of Health and Social Affairs with the aim of reducing substance abuse and improving outcomes. Intensive treatment included home visits, invitations to families to participate in both individual and group family sessions, and interventions. Standard treatment offered

contact with a community mental health center. The main outcome measure was a reduction in comorbid substance abuse.

First-episode patients with schizophrenia spectrum disorders were randomly assigned, in a 1:1 fashion, to OPUS or standard treatment. Among 36% of males with substance abuse, cannabis was the most frequently abused substance (in 18%); alcohol was second (in 7%). Dr. Nordentoft’s other presentation at this meeting showed poorer outcomes in this schizophrenia-spectrum disorder population in the presence of comorbid cannabis abuse. Among 14% of females with substance abuse, alcohol abuse was most common (in 6%), with cannabis second (in 4%).

After two years of follow-up, the integrated approach resulted in a reduction in the number of patients with substance abuse: 17% with OPUS and 21% with standard treatment meeting criteria for substance abuse (OR = 0.5). OPUS treatment significantly reduced negative and disorganized symptoms in the substance abuse group. The number of bed days was also significantly lower in the OPUS group (109 vs. 167 days at two years), both during the two years of treatment and in the subsequent three years.

Dr. Nordentoft stated, “This is an effective, cost-saving kind of treatment. We could have done even better—our treatment was not specialized for substance abuse.”

He is proceeding with a trial that includes focused therapy for substance abuse. ■