Clinical News

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Updates on Long-Acting Injectable Antipsychotics

There have been several recent developments in the area of long-acting injectable antipsychotics. A Phase I study of a four-week long-acting injectable (LAI) formulation of risperidone has been commenced. The study will test the efficacy and tolerability of this four-week LAI formulation in twenty-six patients who have chronic schizophrenia. Risperidone microspheres, administered every two weeks, has been FDA-approved since 2003.

The LAI formulation of olanzapine is still under review by the FDA. The concern raised has been the uncommon (apparently in approximately 1% of patients) occurrence of post-injection confusional syndrome. While the FDA has not required any additional studies, it has requested a detailed management plan for this adverse event. Oral olanzapine has been FDA approved since 1996.

Paliperidone palmitate, an investigational LAI formulation of oral paliperidone (available as extended release [ER]), was shown to have statistically significant improvements in symptoms in a thirteen-week, placebo-controlled, treatment study in schizophrenia. Efficacy was demonstrated among all three doses (25 mg, 100 mg, 150 mg, equivalent doses given every four weeks) of paliperidone palmitate. The drug was started at a 150 mg initiation dose. Paliperidone palmitate was well tolerated, with an adverse effect profile similar to ER. A dosing initiation study is currently in progress to evaluate the efficacy and tolerability of paliperidone given at an initial dose of 150 mg followed by another injection of 100 mg one week later. In another 53-week study, paliperidone palmitate did not show "non inferiority" to risperidone microspheres. Both patient groups showed similar improvements in symptoms. Paliperidone palmitate was administered in the gluteal muscle and in the deltoid muscle. Paliperidone ER has been FDA approved for clinical use since 2007.

Update on Putative Cognitive-Enhancing Drugs

The results have become available from a multicenter, double-blind, placebo-controlled trial of an investigation drug (AZD3480) added to second-generation antipsychotics in the treatment of cognitive dysfunction in schizophrenia. The twelve-week study evaluated cognitive performance using a sophisticated computerized battery of tests in almost 450 patients with schizophrenia. Although AZD3480 was well tolerated, the drug did not achieve statistical superiority over placebo on the cognitive measures. As a result, it seems unlikely that there will be any further studies of this drug in schizophrenia. The drug is being studied in Alzheimer's disease and in adult attention deficit hyperactivity disorder.

Another putative cognitive-enhancing agent has been studied. In a four-week, placebo-controlled study of the investigational compound MK-0777, patients with schizophrenia showed improvements in memory functioning. The drug is of interest because it acts to boost GABA receptor activity at a distinct type of receptors that contain alpha 2 subunits. This putative agent was shown to have selective memory effects. It did not, however, influence overall cognition or symptoms among patients in this pilot study (Lewis et al., 2008).

Lewis DA, Cho RY, Carter CS, Eklund K, Forster S, Kelly MA, et al. Subunit-selective modulation of GABA type A receptor neurotransmission and cognition in schizophrenia. Am J Psychiatry 2008;165(12):1585-1593.

Novel Approach to Antipsychotic-Induced Weight Gain Shows Benefits in Early Clinical Trials

The use of a novel compound called mifepristone, a progesterone and glucocorticoid antagonist, was shown to reduce weight in a preliminary study. A four-week, double-blind controlled study was conducted in which normal subjects received either risperidone alone, risperidone and mifepristone, or mifepristone alone. A statistically significant difference was observed between the risperidone alone group (who gained 9.2 lbs) and the risperidone mifepristone group (who gained 5.1 lbs). The drug had previously been shown to reduce weight gain associated with olanzapine therapy. Mifepristone is also currently under investigation for the treatment of psychotic depression and for Cushing's syndrome (Nihalani and Schwartz, 2007).

Nihalani ND, Schwartz TL. Mifepristone, a glucocorticoid antagonist for the potential treatment of psychotic major depression. Curr Opin Investig Drugs 2007;8(7):563-569.

Phosphodiesterase Inhibitors and Schizophrenia Treatment

The Stanley Medical Research Institute—a major source of support for cutting edge research in schizophrenia—has increased its funding support for candidate drugs that inhibit the phosphodiesterase 10 (PDE 10) system. This has been a focus of earlier research. There is a confluence of evidence for abnormalities of phospholipid metabolism in schizophrenia (Keshavan et al., 2008). Abnormalities have been reported in blood samples, in tissue, in cerebral spinal fluid, and in functional brain imaging studies—even in patients who are in their first psychotic episode and who have not been exposed to antipsychotic medications. The "phospholipid hypothesis" of schizophrenia is appealing because it offers a potentially unifying theory to explain the wide variety of manifestations observed in schizophrenia.

Keshavan MS, Tandon R, Boutros NN, Nasrallah HA. Schizophrenia, "just the facts": what we know in 2008 Part 3: neurobiology. Schizophr Res 2008;106(2-3):89-107.

Continued Concern about Risks of Sudden Death in Patients Receiving Antipsychotic Medications

A new analysis of Medicaid data for over 250,000 patients observed a higher risk of sudden death among the one-third of patients who had received either a first-generation antipsychotic (FGA) or a second-generation antipsychotic (SGA) (Ray et al., 2009). Patients with a prior history of cardiac problems were excluded from the study. The risk of death did not differ between patients receiving FGAs or SGAs. However, for each class the incident rates of sudden cardiac death did increase from patients receiving a low dose of antipsychotics (rates for FGAs at low dose=1.31; for SGAs=1.59) to patients of high doses of medication (rates for FGAs=2.42; for SGAs=2.86). This is a comprehensive analysis of a large database. The results resonate with earlier findings of a heightened risk of sudden death and cardiac mortality in schizophrenia, as well as studies that have implicated medications (Waddington et al., 1998; Michelsen and Myer, 2007).

Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009;360(3):225-235.

Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. Br J Psychiatry 1998;173:325-329.

Michelsen JW, Meyer JM. Cardiovascular effects of antipsychotics. Expert Rev Neurother 2007;7(7):829-839.

New Meta-Analysis of SGAs

The debate as to whether one SGA is "better" than another (Heres et al., 2006) continues. In a recently published meta-analysis of SGA comparative studies published before 2007 (Leucht et al., 2009), seventy-eight studies were identified and analyzed. Olanzapine proved to have a more robust antipsychotic response than risperidone, quetiapine, ziprasidone, or aripiprazole. Risperidone was more effective than quetiapine or ziprasidone. While the authors concluded that these observations were meaningful and not attributable to commercial support, the issue of refinements in dosing of SGAs remains to be clarified.

Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 2006;163(2):185-194.

Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry 2009;166(2):152-163.

Perceptual Disturbances Evident Even in First-Episode Schizophrenia

A recently published study from Israel shows that people with schizophrenia can have substantial difficulties in perception and in recognition of emotional stimuli—even early on in their illness. Bleich-Cohen and colleagues (2009) examined the responses—as well as the brain imaging pattern on MRI—of ten patients with first-episode schizophrenia and ten control subjects when they were shown distorted faces during an MRI examination. Patients were less responsive—both emotionally and in neural activation—to the presence of these disturbing faces. The neural activity appeared to be reduced in the fusiform gurus. This is an elegant and interesting study that provides valuable insights into the neurobiology of affectivity responsivity in schizophrenia (Bleich-Cohen et al., 2009).

Bleich-Cohen M, Strous RD, Even R, Rotshtein P, Yovel G, Iancu I, et al. Diminished neural sensitivity to irregular facial expression in first-episode schizophrenia. Hum Brain Mapp. In press 2009.

What's the Overlap between Schizophrenia and Bipolar: Swedish Study Provides Clues

We appreciate that schizophrenia and bipolar disorder are genetic disorders (some would conclude, with a high genetic loading). Two common questions are: firstly, are these disorders genetically related?; secondly, what are the roles of genes versus environment in each disorder? A

recently published study based upon analysis from a longitudinal Swedish population database addressed these two vexing questions (Lichtenstein et al., 2009). The heritability of schizophrenia and bipolar disorder was estimated at 64% and 59%, respectively, and first-degree relatives of people with either condition had an increased risk for these disorders. Environmental influences were estimated at 4.5% for schizophrenia and 3.4% for bipolar disorder. The authors concluded that the substantial overlap between these disorders was not artifactual or phenomenologically based and that it was attributable to shared genetic effects rather than environmental influences (Lichtenstein et al., 2009).

Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 2009;373(9659):234-239.

Stigma Still the Biggest Problem

A recently published study asserting discrimination against people with schizophrenia confirms that stigma remains a pervasive problem (Thornicroft et al., 2009). The INDIGO Study (International Study of Discrimination and Stigma Outcomes) evaluated "potential discriminatory experiences" among 732 people with schizophrenia in twenty-seven countries (Thornicroft et al., 2009). Positive discrimination was rarely noted, and the majority of patients had experienced some form of negative discrimination. Over 70% of patients did not wish to reveal their mental illness in public. Patients felt they were discriminated against in getting (29% of patients) and keeping (29%) a job, and most patients (64%) said they would decline to even apply for a job because of the certainty of discrimination. People (27% of patients) also felt discriminated against in personal relationships. These results are salutary and are consistent with the survey from NAMI that was described in an earlier issue of ***Clinical Schizophrenia & Related Psychoses***.

Thornicroft G, Brohan E, Rose D, Sartorius N, Leese M; INDIGO Study Group. Global pattern of experienced and anticipated discrimination against people with schizophrenia: a cross-sectional survey. Lancet 2009;373(9661):408-415.

Readers wishing to know more about the details of individual studies cited in ***Clinical News*** *should consult directly the pharmaceutical company who sponsored the study and/or www.clinicaltrials.gov.*