# Clinical News

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## *DSM-5* Posting and Commentaries

Recently, a preliminary draft of recommendations for *DSM-5* has been posted. The reader can access these at www.dsm5.org. Dr. Will Carpenter from the University of Maryland School of Medicine and the Maryland Psychiatric Research Center led the psychosis workgroup. The major proposals are to include an "at risk" or "prodromal" section, and to exclude schizoaffective disorder as a distinct entity. Other less pronounced changes are outlined in the draft.

The whole process, while rigorous and involving outstanding leaders in psychiatry, has drawn considerable criticism. The potential inclusion of an "at risk" state for psychosis and the potential exclusion of schizoaffective disorder are points of contention in the psychosis section. Other points of contention include the broadening of autism (which would now "fold in" Asperger's Syndrome), and changes to the criteria for bipolar disorder, which would also adopt a new term in kids called "temper dysregulation disorder with dysphoria." These proposed changes walk the tightrope of identifying and treating (early) conditions that are associated with distress and impairment, while increasing the risk of stigma and also the risk of excessive treatment. Accordingly, these proposed changes might also influence the use of antipsychotics, which is of considerable concern in view of the already substantial off-label use of the drugs for conditions beyond their FDA-approved indications.

## Novel Technology Approach to Long-Acting Injectable Antipsychotics

Alkermes Inc., the company which pioneered risperidone microspheres and other drug delivery formulations among CNS agents, is developing a long-acting preparation of aripiprazole. This formulation is currently in the preclinical phase of drug development with clinical studies planned. If proven effective and safe, and if it receives FDA approval—obviously all of these outcomes are presently uncertain and a long way off—this may expand the treatment options for patients and clinicians who might consider a long-acting injectable formulation of an antipsychotic.

## FDA Approves Olanzapine Use in Adolescents

The FDA, while approving the use of olanzapine in adolescents with schizophrenia or bipolar I disorder, has requested that additional cautionary information be included in the prescribing information. It now highlights the lack of efficacy and safety data for olanzapine in pediatric patients under thirteen years of age, the need for careful evaluation of the potential risks of weight gain and metabolic disturbances in this adolescent population, and the need to consider medication use within the context of a comprehensive treatment program for pediatric patients. A recent article on the use of second-generation antipsychotics (SGAs) in children and adolescents also drew sharp attention to these concerns (Correll et al., 2009). These are all important considerations for the use of antipsychotics in pediatric patients.

Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA 2009;302(16):1765-1773.

## New Drug Application (NDA) for Two Putative Antipsychotic Agents

Staccato loxapine, manufactured by the company Alexza Pharmaceuticals, has been filed as a New Drug Application (NDA) to the FDA. Although oral loxapine has been available to clinicians for decades, this formulation of loxapine—staccato loxapine—is an inhalation agent that is being developed and evaluated for the rapid treatment of agitation in schizophrenia and in bipolar disorder. Initial results, which looked promising, were presented at the 2009 International Congress on Schizophrenia Research meeting.

Lurasidone, developed by the company Dainippon Sumitomo Pharma, has also been submitted to the FDA for consideration under an NDA. The NDA was submitted in December 2009 and has just been accepted for review by the FDA. Studies that were part of this NDA include the PEARL I and PEARL II (Program to Evaluate the Antipsychotic Response to Lurasidone) global clinical trials. The entire data for this NDA involves some 2,500 patients who have received

lurasidone. Lurasidone has high affinity for dopamine (D2), serotonin 5-HT(2A) and serotonin 5HT(7) receptors where it has antagonist effects. In addition, lurasidone is a partial agonist at the serotonin 5HT(14) receptor. lt has no appreciable affinity for histamine or muscarinic receptors.

## Early Investigations for Three Putative Antipsychotic/Cognitive Agents under Development

EVP-6124, a selective alpha-7 nicotinic agonist developed by EnVivo Pharmaceuticals, will now be evaluated in a clinical trial to determine whether it can enhance cognitive performance in patients with schizophrenia. The potential of agents that focus on the nicotinic system has been described in earlier issues of ***CS***. The three-month study of EVP-6124 will be conducted at four sites: two in the United States, and two in Europe. It is hoped that results from this study, when complete, will become available in 2011.

ITI-007, a putative antipsychotic under development by the biopharmaceutical company Intra-Cellular Therapies, Inc., is currently being studied in preclinical studies and, most recently, also in a positron emission tomography imaging study in healthy volunteers. The drug has a potentially unique pharmacological profile of 5-HT2A antagonism and dopamine receptor phosphoprotein modulation (DPPM) and serotonin reuptake inhibition. It is unclear at present how this complex profile might translate into clinical advantages for patients with schizophrenia.

TC-5619, a novel compound that is being developed by Targacept, Inc. in conjunction with AstraZeneca, is an alpha-7 nicotinic receptor agonist that is soon to be tested in a phase II double-blind trial. This will evaluate the impact of TC-5619 among 200 patients with schizophrenia.

## New Large Academic-Pharma Consortium

King's College, London, as a part of its portfolio as a premiere British academic center, is heading up an academic-pharma consortium that involves the Karolinska Institute, University of Cambridge, University of Manchester, CSIC in Spain, the Bar-Ilan University in Israel, and the Central Institute of Mental Health in Germany. The collaboration also involves Lundbeck Pharmaceuticals and two other smaller pharmaceutical companies. It is also likely to involve partnerships with other CNS companies. The aims of this consortium are to develop and test animal models for drug discovery, to advance the early study of drugs in humans, and to incorporate potential imaging and genetic putative biomarkers into drug discovery. The group is known as NEWMEDS (Novel Methods Leading to New Medications in Depression and Schizophrenia).

## Global Findings from SOHO Study

The three-year observational study called Worldwide-Schizophrenia Outpatient Health Outcomes Study (W-SOHO) examined medication affects among 17,000 people with schizophrenia in 37 countries across the world. The study was funded by Eli Lilly and Company. Seventy-four percent were taking more than one psychotropic (beyond their antipsychotic), and 24% of patients were being treated with two or more antipsychotic medications. Patients were moderately ill, with a CGI severity of illness score of 4.4. Sixty-two percent were living in some form of supported housing. Only 19% of patients were in any type of paid job.

*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.*