Clinical News

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Lurasidone Approved as New Antipsychotic in the Treatment of Schizophrenia

The U.S. Food and Drug Administration (FDA) has approved the new antipsychotic lurasidone. The drug is anticipated to become available early in 2011, and it will be distributed under the brand name of Latuda. It will be marketed by Sunovion Pharmaceuticals, Inc., a U.S. subsidiary of Dainippon Sumitomo Pharma Co. Ltd., for the treatment of adult forms of schizophrenia. The FDA approval was forthcoming on the basis of the comprehensive review of four large clinical trials, each of which were of six-week duration. These studies established the favorable efficacy and tolerability profile of lurasidone over placebo. The recommended dosing of lurasidone is between 40 mg and 120 mg/day. Lurasidone is an antagonist at both dopamine (especially D1) and serotonin (especially 5HT2A and 5HT) receptors. It also has a partial agonist effect at 5HT1A receptors. A thorough and timely review of this new drug and its clinical profile is provided in this issue by Dr. Leslie Citrome.

FDA Provides Company with Feedback on AZ-004 (Staccato Loxapine)

In a previous issue of ***CS*** we provided information on a novel preparation of loxapine, an intranasal formulation AZ-004 (staccato loxapine). The makers of this formulation, Alexza Pharmaceuticals, earlier submitted a New Drug Application (NDA) for consideration by the FDA. Feedback from the FDA has focused on clarifying the impact of this formulation on respiratory function, specifically on the standard measure of pulmonary performance called forced expiratory volume in one second (FEV1). The FDA has also requested additional information on the delivery system for staccato loxapine. Alexza Pharmaceuticals is responding to these issues.

Progress on the Development of an Intramuscular (IM) Depot Preparation

Oral aripiprazole is an established antipsychotic available for the treatment of schizophrenia and mood disorders. It is also available in an acute intramuscular (IM) formulation for treatment of acute agitation associated with psychosis. As alluded to in a previous issue of ***CS***, Otsuka Pharmaceutical Co., Ltd. is developing a long-acting IM formulation of aripiprazole. This putative antipsychotic is already being tested in a Phase 3 clinical trial. Recently, results became available from an interim analysis of a 52-week, multicenter, randomized, placebo-controlled trial of depot aripiprazole. The study of the depot formulation achieved the a priori efficacy criteria ahead of time, such that the independent data monitoring committee recommended that the study cease early. It is now anticipated that the NDA for depot aripiprazole will be filed with the FDA in 2011.

Injectable Antipsychotic Reported to Reduce Hospitalization

Data that were recently presented at the 2010 U.S. Psychiatric and Mental Health Congress suggest that paliperidone palmitate—the newly available long-acting injectable antipsychotic—may reduce relapses/rehospitalization in patients with chronic schizophrenia. In an analysis that combined data from two long-term studies involving a total of 213 patients with schizophrenia, the number of hospitalizations per year was reduced with active treatment compared to placebo. The sample in these two Janssen-supported studies comprised patients predominantly with chronic schizophrenia, almost one-third of whom had been ill for five years or longer. Comparisons with, and between, other long-acting antipsychotics are certainly warranted to inform the utility of this and all other depot antipsychotics in clinical practice.

New Research Alliance Formed to Develop Drugs for Schizophrenia

Takeda Pharmaceutical Company Ltd. and Envoy Therapeutics Inc. have entered into a three-year research drug development alliance. This collaborative venture will focus on innovative drug discovery for the treatment of schizophrenia. This collaboration will use genetic engineering capacity alongside new molecular biology techniques for identifying proteins to examine for potential new drugs for schizophrenia. The use of transgenic mice is a key strategy here.

New Test Developed to Potentially Assist in the Initial Diagnosis of Schizophrenia

A company called Rules-Based Medicine has announced that it has developed, and will now make available, a novel test for schizophrenia. This putative biomarker test—called VeriPsych—is a blood test that comprises 51 immunoassays tapping key components of the biochemical pathways of cell signaling, metabolism, and inflammation. It has been developed with input from Professor Sabine Bahn and colleagues

based in Cambridge, U.K. (Schwarz et al., 2010). In an evaluation of these 51 immune-base analytes between 577 patients with schizophrenia and 229 control subjects, this group determined that the assay had a sensitivity of 83% and a specificity of 83% for the initial diagnosis of schizophrenia. It is apparently not intended to be a definitive diagnostic test for schizophrenia. It will be of interest to see how this develops over time, and to evaluate research data to critically inform the potential utility of this test.

Schwarz E, Izmailov R, Spain M, Barnes A, Mapes JP, Guest PC, et al. Validation of a blood-based laboratory test to aid in the confirmation of a diagnosis of schizophrenia. Biomark Insights 2010;12(5):39-47.

Update on Recent Genetic Studies in Schizophrenia

In several prior issues of ***CS***, we have highlighted many of the recent important advances in the genetics of schizophrenia, especially the growing story of copy number variants (CNVs) and the neurobiology of schizophrenia. Recently, Drs. Chen, Kendler and colleagues have examined a pooled analysis of genome-wide association studies, and they identified a significant association with a gene called cardiomyopathy-associated 5 (CMYA5). This association was internally replicated in a meta-analysis of 23 samples that make up this genetics network and also the CATIE schizophrenia trial study sample. The results are reported in a recent paper (Chen et al., 2010).

Dr. Moreno-De-Luca and colleagues (Moreno-De-Luca et al., 2010) have also studied the overlap in genetic risk between schizophrenia and autism. They examined 23,000 patients with either autism and related spectrum disorders and schizophrenia and they found a deletion located on chromosome 17 in 24 patients that included these diagnoses. They have proposed that this particular CNV is associated with neurodevelopmental delay and confers a high risk for both schizophrenia and autism.

Chen X, Lee G, Maher BS, Fanous AH, Chen J, Zhao Z, et al. GWA study data mining and independent replication identify cardiomyopathy-associated 5 (CMYA5) as a risk gene for schizophrenia. Mol Psychiatry 2010. doi: 10.1038/mp.2010.96.

Moreno-De-Luca D; SGENE Consortium, Mulle JG, Simons Simplex Collection Genetics Consortium, Kaminsky EB, Sander SJ, et al. Deletion 17q12 is a recurrent copy number variant that confers high risk of autism and schizophrenia. Am J Hum Genet 2010;87(5):618-630.

New Findings on Glutamate and Schizophrenia

We have highlighted in a previous issue of ***CS***—including an excellent recent article by Kantrowitz and Javitt—the role of glutamate in the pathophysiology of schizophrenia. An elegant neuroimaging study from England by Dr. Stone and colleagues (Stone et al., 2010) now provides new evidence of a fundamentally abnormal relationship between glutamate and dopamine in "patients" who are in the prodrome of schizophrenia. Sixteen people with prodromal features and 12 normal control subjects underwent the dual imaging procedures of MR spectroscopy and positron emission tomography. While the control subjects showed no association between striatal dopamine (on PET) and hippocampal glutamate levels (on MRIs), the prodromal subjects as a group showed an inverse correlation between dopamine (high in striatum) and glutamate (low in hippocampus). Of note, this was most pronounced among those individuals who later became frankly psychotic. It is known from preclinical studies that glutamatergic cells can modulate the activity of dopaminergic cells. These findings are consonant with this proposition at clinical level and they also point to fundamental neurochemical perturbations that are observed very early on in the course of schizophrenia.

Dr. Mullasseril and colleagues (2010) have described an agent—CIQ—that selectively interacts with selective NMDA receptor subtypes (NR2C and NR2D) that can enhance glutamatergic function. This agent may have a modulation effect. Although this work is still in its infancy, clearly the potential now to design drugs that selectively enhance subtypes of the NMDA receptor might have therapeutic value for schizophrenia.

Readers might also want to check out an excellent topic issue of *Nature* (November 11, 2010) that is dedicated to schizophrenia research. This is an excellent synopsis of the etiology and treatment of schizophrenia.

Stone JR, Howes OD, Egerton A, Kambeitz J, Allen P, Lythgoe DJ, et al. Altered relationship between hippocampal glutamate levels and striatal dopamine function in subjects at ultra high risk of psychosis. Biol Psychiatry 2010;68(7):599-602.

Mullasseril P, Hansen KB, Vance KM, Ogden KK, Yuan H, Kurtkaya NL, et al. A subunit-selective potentiator of NR2C- and NR2D-containing NMDA receptors. Nat Commun 2010;1(7):1-8.

Dr. Ming Tsuang Receives Lieber Award from NARSAD

We were delighted that our very own Ming Tsuang, MD, PhD, DSc—a preeminent schizophrenia researcher and member of the ***CS*** editorial board—was recently honored as this year's recipient of the prestigious Lieber Award from the National Alliance for Research on Schizophrenia and Depression (NARSAD). Dr. Tsuang is at the forefront of schizophrenia research. Throughout a distinguished and highly productive career, he has made seminal contributions—especially in the areas of nosology and schizophrenia genetics—to our understanding of the boundaries and neurobiology of schizophrenia. Congratulations to Dr. Tsuang and we look forward to his continued contributions to our field.

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.*