Clinical News

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New Antipsychotic Drug Submitted to FDA

Forest Laboratories, Inc. and Gedeon Richter Plc. have submitted a New Drug Application to the U.S. Food and Drug Administration (FDA) for cariprazine, a potent dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors. Cariprazine was discovered by Gedeon Richter Plc. and is licensed to Forest Laboratories, Inc. in the U.S. and Canada.

The application for the treatment of schizophrenia includes results from three positive trials in over 1,700 patients: two fixed-dose studies with active controls and one fixed-flexible, placebo-controlled dose study using the change from baseline in PANSS total score as the primary efficacy endpoint.

The application for the acute treatment of manic or mixed episodes associated with bipolar I disorder includes results from three positive placebo-controlled trials in over 1,000 patients: two flexible-dose studies and one fixed-flexible dose study using the change from baseline in the YMRS total score as the primary efficacy endpoint.

In the schizophrenia and bipolar mania pivotal trials, cariprazine was generally well tolerated. The most commonly reported adverse reactions (≥5% and twice placebo), which were predominantly mild to moderate in severity, were akathisia, extrapyramidal disorder, dyspepsia, restlessness, tremor, fatigue and vomiting.

Update on Long-Acting Injectable Antipsychotic Formulations

Janssen Pharmaceuticals confirmed that the FDA approved the change in administration of paliperidone palmitate so that the titration and initial dosing is more flexible in supporting the monthly injection regimen.

Lundbeck and Otsuka Pharmaceuticals have confirmed that the FDA has favorably reviewed its New Drug Application for the long-acting injectable formulation of aripiprazole. Information on this drug was given in an earlier issue of ***CS***.

Two New Studies of Long-Acting Injectable Antipsychotic Medications Inform Clinical Practice

Two recent studies—one in patients with chronic schizophrenia, the other in a first-episode psychosis population—give additional insights into the potential clinical role of long-acting injectable antipsychotic medications. Covell and colleagues (2012) conducted an important six-month, open-label, randomized, comparative trial of either staying on a first-generation antipsychotic (FGA) in long-acting injectable formulation (haloperidol decanoate or fluphenazine decanoate) or switching to risperidone microspheres—the second-generation antipsychotic (SGA) that was available at the time of this study.

In detailed analyses, they report similar relapse rates as well as comparability between groups on psychopathology and hospitalizations over the six-month duration of the naturalistic trial. However, study discontinuation was less (10% versus 31%) among those who did not switch medications, and they also had less weight gain and prolactin elevation. Another ongoing study (ACLAIMS) will add further information to the comparative merits of FGA and SGA long-acting formulations.

Weiden and colleagues (2012) report 1-year outcomes on 37 first-episode patients who were randomized to either risperidone microspheres or to continue on their oral antipsychotic medication. Surprisingly, the advantage in medication adherence that was seen with risperidone microspheres-treated patients early on in the study was not sustained. In fact, 81% of patients discontinued medications. Additionally, there were no between-group differences in symptoms or re-hospitalization during this prolonged follow-up period. The authors concluded that while the long-acting injectable formulation is a feasible treatment strategy in first-episode patients and may heighten awareness and opportunity to detect medication nonadherence earlier in the course of illness, it does not adequately mitigate the pernicious and pervasive impact of nonadherence to treatment itself.

Covell NH, McEvoy JP, Schooler NR, Stroup TS, Jackson CT, Rojas IA, et al.; Schizophrenia Trials Network. Effectiveness of switching from long-acting injectable fluphenazine or haloperidol decanoate to long-acting injectable risperidone microspheres: an open-label, randomized controlled trial. J Clin Psychiatry 2012;73(5):669-675.

Weiden PJ, Schooler NR, Weedon JC, Elmouchtari A, Sunakawa-McMillan A. Maintenance treatment with long-acting injectable risperidone in first-episode schizophrenia: a randomized effectiveness study. J Clin Psychiatry 2012;73(9):1224-1233.

Inhibitors of Histone Deacetylases Might Provide New Avenue of Inquiry in Schizophrenia Therapeutics Research

A complicated yet fascinating recent paper by Kurita and colleagues (2012) that appeared in *Nature Neuroscience* shows how drugs that are inhibitors of a gene regulator—

histone deacetylases (HDACs)—might be of therapeutic advantage through a complex cascade of effects that modulate the expression of metabotropic glutamate 2 (mGlu2) receptors. In previous issues of ***CS*** we have highlighted the role of glutamate in the pathophysiology of schizophrenia as well as the therapeutic potential of mGlu2 agonists. In this series of studies using a mouse model and also drawing upon post mortem human brains, the authors report how second-generation antipsychotics cause a selective upregulation of HDAC in the frontal cortex and this effect may cause mGlu2 receptor changes which, thereupon, contribute to the development of treatment resistance. If replicated and extended, this approach could explain the development of treatment refractoriness among patients with schizophrenia.

Kurita M, Holloway T, Garcia-Bea A, Kozlenkov A, Friedman AK, Moreno JL, et al. HDAC2 regulates atypical antipsychotic responses through the modulation of mGlu2 promoter activity. Nature Neurosci 2012;15(9):1245-1254.

Important Study Affirms Presynaptic Dopamine Receptors Hypersensitivity in Schizophrenia

Howes and colleagues (2012) at the Institute of Psychiatry in London have conducted a very useful meta-analysis to synthesize available data on the vexing and persistent issue as to whether a fundamental deficit in dopamine receptor functioning exists in schizophrenia. In combining neuroimaging studies from two major functional modalities—positron emission tomography, single photon emission tomography—they examined measures of dopamine function derived from 44 studies that included over 600 patients with schizophrenia. They reported no abnormality in the dopamine transporter function and, perhaps surprisingly, only a modest increase in dopamine D2/3 receptors availability. The most pronounced effect was seen in the presynaptic dopamine receptors which showed heightened sensitivity. The importance of this analysis lies in the observation that the dopamine abnormality in schizophrenia is not (just) a simple excess of dopamine in the receptor and/or an overabundance of dopamine receptors. Rather, the pathology in schizophrenia seems more circumscribed.

Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Arch Gen Psychiatry 2012;69(8):776-786.

Primer for Schizophrenia Genetics

Dr. Michael Owen, a preeminent psychiatric geneticist at Cardiff University, Wales, was recently honored by the Brain and Behavior Research Foundation (formerly known as NARSAD) with the Lieber Prize for contributions to schizophrenia research. His recent publication in our "sister" journal *Schizophrenia Bulletin* provides an authoritative overview of the genetics of schizophrenia. Many years ago, another leading British psychiatrist—Sir Robin Murray—said that "the genetics of schizophrenia are the genetics of neurodevelopment." This overview by Dr. Owens resonates with that viewpoint. We have highlighted genetic findings in multiple issues of ***CS*** to keep readers abreast of a complex area of schizophrenia research and this review nicely synthesizes current concepts as well as recent findings in the genetics of schizophrenia … well worth a read … and it's brief!

Owen MJ. Implications of genetic findings for understanding schizophrenia. Schizophr Bull 2012;38(5):904-907.

Update on Genetic Mutations in Schizophrenia

In contrast to the "easy-to-read" genetic primer by Dr. Owen, Xu and colleagues (2012) from Columbia University, New York, provide a complex appraisal of de novo genetic mutations evaluated in two separate populations that in total comprised a sample of 231 parent-proband trios and 34 unaffected trios. They found de novo mutations in 4 genes that are well known to influence neurodevelopment. The affected chromosomes were chromosomes 1, 6, 7, and 15. This is a complicated yet exciting paper to read from another leading genetics team.

Xu B, Ionita-Laza I, Roos JL, Boone B, Woodrick S, Sun Y, et al. De novo gene mutations highlight patterns of genetic and neural complexity in schizophrenia. Nature Genetics 2012;44:1365-1369.

How Good are Your Schizophrenia Treatment Services? Some Pointers for Evaluations

This interesting paper by Don Addington (a leading Canadian schizophrenia researcher) and his colleagues (2012) provides a framework and rationale for evaluating a schizophrenia treatment program. Core measures are described across domains of safety, acceptability, effectiveness, efficiency, access, continuity, and appropriateness of care as well as the competency of providers. These measures were distilled from an exhaustive list that was generated by a review of the literature and then narrowed down through a "Delphi model" review process. These measures might be useful in evaluating the quality-of-care in your program.

Addington DE, Mckenzie E, Wang J, Smith HP, Adams B, Ismail Z. Development of a core set of performance measures for evaluating schizophrenia treatment services. Psychiatr Serv 2012;63(6):584-591.

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.*