Clinical News

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Antipsychotic Drug Development Continues Along Innovative Paths

Intra-Cellular Therapies, Inc. recently announced the results of a Phase IB/II study of a putative antipsychotic, ITI-007. The study was a double-blind, placebo-controlled trial to clarify dose, tolerability and safety profiles of ITI-007. Forty-five patients with schizophrenia received active drug or placebo over five days. Doses of ITI-007 up to 140 mg/day were tested, and the drug was well tolerated, even at the highest dose range. Improvements were also observed in symptoms, including noteworthy gains in improving depressive symptoms and sleep disturbance. ITI-007 possesses a unique pharmacological profile with high potency antagonism of serotonin 5HT2A receptors and modulator activity of the dopamine system. The latter property—as a dopamine receptor phosphoprotein modulator (DPPM)—combines postsynaptic dopamine (D2) receptor antagonism along with presynaptic partial agonism. These DPPM effects also appear to have some relative selectivity for mesocortico-mesolimbic dopaminergic innervations.

Dr. Robbie Schwarcz and colleagues at the University of Maryland are studying the potential of kynurenic acid as a putative agent to improve cognition in schizophrenia. In a study of knockout mice that were genetically engineered to have low expression of kynurenic acid, these mice outperformed normal comparison mice on selective tests of memory and cognition. These results are provocative and open the way for examining other compounds that influence kynurenic acid levels as a potential therapeutic strategy to enhance cognition in schizophrenia.

The U.S. Food and Drug Administration (FDA) has just approved the use of second-generation antipsychotic asenapine beyond its initial regulatory indications. The FDA has now also approved asenapine for ongoing treatment of schizophrenia, and for monotherapy in the treatment of acute mania and for mixed episodes in adult patients with bipolar I disorder. The FDA has approved, as well, asenapine's use as an adjunctive therapy with either lithium or valproate in the acute treatment of adult patients with bipolar I disorder.

New Lieber Institute for Brain Development Announced

Our field owes a great depth of gratitude to our remarkable advocates and philanthropists, the Lieber family (of New York) and the Maltz family (of Cleveland). Together, they are funding an exciting new neuroscience program—the Lieber Institute for Brain Development—that will be affiliated with Johns Hopkins University. The program will be led by our brilliant schizophrenia researcher, Dr. Daniel Weinberger. Dr. Weinberger is a cofounder of this exciting project along with two other luminary scientists—Drs. Ronald McKay and Solomon Snyder. This project has immense potential to enhance our understanding of the neurobiology of mental illness. We wish Danny and his collaborators every success.

Important British Governmental Enquiry Registers Declining Rates of Suicide and Homicide among the Mentally Ill

In response to governmental review several years ago, the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness has recently reported a decline in homicides and suicides between 1997 and 2006. The report also notes that suicides and homicides have particularly fallen among inpatients, likely reflecting closer observation and appreciation of the high risk of harm in this setting. The report shows, as well, a decrease in homicide attributable to people with schizophrenia. This finding reverses the increase rate that this group had reported in its earlier evaluation.

Genetics Impetus in Schizophrenia Research Sustained

The National Institute of Mental Health (NIMH) has recently approved continued funding for a major genetics initiative in schizophrenia research. The six-site Consortium on the Genetics of Schizophrenia (COGS) was originally funded by NIMH in 2003. During the initial funding period, well over 2,000 patients and their family members have undergone a comprehensive battery of assessments, aimed at evaluating heritable neurophysiological and neurocognitive deficits. This large and very important research effort seeks to define "endophenotypes" of schizophrenia, in this instance exploring proposed "genetic" and "nongenetic" forms of schizophrenia. The investigators' systematic approach is powerful, and it builds upon the already well-appreciated observation that, for many patients, schizophrenia runs in families. This study will help delineate the

neurobiological signatures of this widely known association. The sites included in COGS are UC San Diego (with Dr. David Braff as overall project Principal Investigator), Johns Hopkins University, University of Washington, University of Pennsylvania, UC Los Angeles, and Mount Sinai School of Medicine. The COGS team has now received an additional $10 million to continue their work over the next four years. We wish them every success!

The copy number variant (CNV) "story" in schizophrenia—described in several prior issues of ***CS***—continues to unfold. Recently, Emory University investigators (led by Stephen Warren, PhD) teamed up with Johns Hopkins University investigators (led by Anne Pulver, PhD) to examine the extent of CNVs in a large sample of Ashkenazi Jewish patients with schizophrenia that Dr. Pulver has been studying for years. Interestingly, in patient control comparisons, they observed an excess of large, rare CNVs: an odds ratio of 16.98 was reported for the identified CNV microdeletion at chromosome 3q29 site. This finding may have particular significance, since two genes within that region are already known to be associated with mental retardation. The study was recently published in *The American Journal of Human Genetics*.

In another study, the genetics consortium from Ireland and Wales published a paper in *Archives of General Psychiatry* that reports on the impact of a variation in specific gene ZNF804A. The authors found, perhaps counterintuitively, in this large, genome-wide association study analysis that the single-nucleotide polymorphism in the ZNF804A was actually associated with enhanced performance in selective cognitive tests in patients with schizophrenia. These results are exciting and may have implications for the design of future cognitive enhancement strategies in the treatment of schizophrenia.

Mulle JG, Dodd AF, McGrath JA, Wolyniec PS, Mitchell AA, Shetty AC, et al. Microdeletions of 3q29 confer high risk for schizophrenia. Am J Hum Genet 2010;87(2):229-236.

Walters JT, Corvin A, Owen MJ, Williams H, Dragovic M, Quinn EM, et al. Psychosis susceptibility gene ZNF804A and cognitive performance in schizophrenia. Arch Gen Psychiatry 2010;67(7):692-700.

Babies at Risk for Schizophrenia have Larger Brains at Birth?

Dr. John Gilmore and colleagues at the University of North Carolina have recently observed prenatal ultrasound evaluations in mothers whose children later developed schizophrenia. In an elegant and meticulously conducted study, they showed larger fetal brain size overall in this "at risk in utero" sample compared with the fetal brains of normal children. This effect was predominantly observed in male rather than female brains in utero. This is an interesting and stimulating finding, especially since prior studies of children who are at high risk for psychosis have shown smaller brains in these children. Brain size in utero has not been studied before in relation to schizophrenia. Larger brain size is typically seen in adults/adolescents with autism. The Gilmore et al. study is likely to attract a lot of attention. Additionally, since these children are being followed prospectively, this study will generate further important observation on the timing and trajectory of neurodevelopmental dysfunction in schizophrenia.

Gilmore JH, Kang C, Evans DD, Wolfe HM, Smith MD, Lieberman JA, et al. Prenatal and neonatal brain structure and white matter maturation in children at high risk for schizophrenia. Am J Psychiatry 2010 Jun 1. Epub ahead of print.

New Mental Illness Social Media Site Supports Relative Needs

The Mental Health America organization (www.mha.org) has just launched an internet support community that will facilitate online discussions among groups, posting of personal stories, and be a resource to the relatives of people with mental illness. Registration is free and people can communicate with one another—under privacy directives—about mental illness concerns. The community is located at www.mentalhealthamerica.net/community. This is an example of the increasing use of websites and chat rooms to support people with mental illness and their relatives. Another noteworthy website is Headspace (www.headspace.org.au), which was created by Dr. Patrick McGorry—who incidentally (actually, not so incidentally!) was awarded Australian of the Year for his pioneering work—to support discussion about mental illness among Australia's youth and to facilitate early access into care for those in need. These approaches will likely, overtime, transform our ability to educate the public about mental illness. Such efforts may also influence our clinical care, including our ability to evaluate functioning of patients over the course of their lives.

Does Catatonia Still Exist?

Whether catatonia still exists as a distinct form of schizophrenia has been a subject of great debate. Our phenomenology texts have described the motoric and expansive features of catatonia at great length. However, clinicians nowadays see fewer patients with catatonia. Patients with catatonia today appear often to have some underlying organic pathology, such as a brain tumor or encephalitis. Some people also consider catatonic and neuroleptic malignant syndrome to be related in some way. Either way, the diagnosis of catatonia schizophrenia is less frequently used. Dr. Delores Malaspina and colleagues at New York University have recently studied this topic, drawing from their large

Israeli sample of over 90,000 offspring who have been followed prospectively. Among just over 500 people who went on to develop schizophrenia, 7.6% of them were diagnosed with catatonic schizophrenia. The genetic risk for schizophrenia was similar between patients with a diagnosis of catatonia and those with other schizophrenia diagnoses. Catatonic patients tended to have older mothers. Male and female gender representation was similar. Patients with catatonia were more likely to engage in suicidal behavior. This latter finding is surprising and is not intuitive. Depression is the primary risk factor for suicide in schizophrenia and catatonic patients are less likely than other patients with schizophrenia to have comorbid depression.

Kleinhaus K, Harlap S, Perrin MC, Manor O, Weiser M, Harkavy-Friedman JM, et al. Catatonic schizophrenia: A cohort prospective study. Schizophr Bull 2010. 2010 Aug 6. Epub ahead of print.

*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.*