Clinical News

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News from the National Institute of Mental Health

The National Institute of Mental Health (NIMH) is nearing completion of a new strategic plan that will provide direction to the Institute, investigators and our field. Dr. Tom Insel, NIMH Director, and colleagues have articulated an exciting vision for clinical research (see www.nimh.nih.gov/about/strategic-planning-reports/index.shtml). They recommend a shift in focus toward the "four Ps:"

- Prediction—increase the capacity to Predict who is at risk for developing disease;
- Preemption—develop interventions that Preempt the disease process;
- Personalize—use knowledge about individual biological, environment, and social factors to better Personalize interventions; and,
- Participation—ensures that clinical research involves Participation from the diversity of people and settings involved in healthcare.

The NIMH is committed to advancing an integrative approach to research on brain and behavior that will translate into new understandings of mental disorders and their treatments. A key aspect of this understanding is in achieving more reliable, valid diagnostic tests, as well as biomarkers for mental disorders. Dr. Insel stresses that knowledge of the fundamental genetic and environmental risk architecture for mental disorders is a priority. Such information will help inform the design, and speed up the development of interventions to prevent occurrence and/or reduce relapse of mental disorders. Dr. Insel also emphasizes the need to develop more effective, safer and equitable treatments, as well as see psychiatry move quickly toward effective personalized care. In addition, Dr. Insel has highlighted the need to achieve rapid dissemination of science to mental healthcare and service efforts. There are also impressive continued efficiencies in NIMH peer-review processes for grant review. The NIMH is committed to innovation, and the electronic submission of grants is going well. Additionally, the NIMH is piloting the use of camcorder and web-based technologies to support grant reviewing by committees. This facilitates high-quality scientific review without the expense, logistics and efforts of travel to a central meeting place. This pilot is being led by the Interventions Committee for Disorders Related to Schizophrenia, Late Life, or Personality (ITSP). Dr. Insel recently addressed the Committee using this technology. There are lots of exciting and innovative developments going on at NIMH these days. Stay tuned!

New Information on Long-Acting Injectable Formulations of Second-Generation Antipsychotics

There is new information concerning the currently approved long-acting formulation of a second-generation antipsychotic: the long-acting injectable formulation of risperidone, risperidone microspheres, which is FDA-approved for the treatment of schizophrenia. Recently, data from a new study of risperidone microspheres in 139 bipolar patients found a relapse rate of 22.2% with risperidone microspheres and 47.8% with placebo. The time-to-relapse was also significantly longer in the microspheres-treated group. An elegant aspect of this study was the use of an independent relapse monitoring board to determine (blind to each subject's treatment assignment) whether relapses occurred during the study. Treatment-emergent side effects, as well as serious side effects, occurred more frequently in the group that received placebo and standard treatment than in the group that received risperidone and standard treatment. Tremor (23.6% in risperidone group, 16.4% in placebo group), muscle rigidity (11.1% risperidone, 6% placebo), weight gain (6.9% risperidone, 1.5% placebo), and hypokinesia (6.9% risperidone, 6% placebo) were more common side effects associated with risperidone. Risperidone microspheres therapy is not FDA approved for treating bipolar patients.

The U.S. Food and Drug Administration (FDA) recently reviewed a new formulation of Eli Lilly's olanzapine. The FDA did not approve the New Drug Application (NDA) at its final review recently. The long-acting injection of olanzapine (olanzapine LAI) combines the second-generation antipsychotic medication olanzapine with a palmoate salt, which enables an extended delivery of the drug up to four weeks. Results that were reviewed from the clinical trials showed greater symptom improvement in olazapine LAI-treated patients, compared with those on placebo. In clinical trials, olazapine LAI had a safety profile similar to oral olazapine, with the exception of post-injection excessive sedation events.

Continued Interest in Potential Cognitive Enhancing Agents in Schizophrenia

In accordance with the fundamental impact of cognitive dysfunction in contributing to schizophrenia patients' ability to function, there is continued interest and development of drugs targeting the cholinergic system. Memory

Pharmaceuticals Corporation is conducting a double-blind, placebo-controlled Phase 2a clinical trial in patients with schizophrenia of a new compound, MEM 3454. The agent is a nicotine alpha-7 receptor partial agonist. The primary objective of this study is to evaluate the effectiveness of MEM 3454 for cognitive impairment in schizophrenia. The study is using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (see below). The study will also evaluate, as secondary measures, other symptoms of schizophrenia and functional performance. It is anticipated that 160 patients will be involved in this study.

AstraZeneca is also conducting a study of another new compound, AZD3480, that is a nicotinic alpha-7 receptor agonist. Dr. Rob Conley described details of this trial in the October, 2007 issue of ***Clinical Schizophrenia & Related Psychoses.***

In addition, Lexicon Pharmaceuticals, Inc. plans to conduct a Phase 2a clinical trial of an oral suspension formulation of a new compound, LX6171. The initial study will test the bioavailability of the drug in an elderly, healthy sample, and then the study will evaluate the safety and tolerability in subjects who have age-associated memory impairment. LX6171 is a small molecule whose proposed mechanism of action is to inhibit a CNS membrane protein found in synapses and in presynaptic membranes of glutamatergic neurons. In earlier preclinical tests in mice, the agent was found to enhance memory and learning in tests performed in rodents. The study will be conducted in Europe.

These studies are in addition to a National Institute of Mental Health (NIMH) TURNS (Treatment Units for Research on Neurocognition and Schizophrenia) study network. TURNS is a major initiative to study novel compounds that may enhance cognition in schizophrenia. Details of this exciting research program can be found at: www.turns.ucla.edu.

TURNS is led by an outstanding team of investigators, with Stephen R. Marder, MD as Principal Investigator. This group, and a larger consortium, first developed the NIMH MATRICS Battery (Nuechterlein et al., 2008). This comprises measures of verbal, visual, and working memory, speed, problem solving, attention/vigilance, and social cognition. This was an important effort to standardize cognitive assessment. The Battery typically takes approximately seventy minutes to complete. Nuechterlein and colleagues have recently reported good reliability findings for the Battery.

Although it is, of course, less clear where all this will end up, and especially how much developments may ultimately impact clinical care for patients with schizophrenia, it is encouraging that cognitive dysfunction is being targeted (Harvey and Cornblatt, 2008). Harvey and Cornblatt give a good account of this potential.

Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS Consensus Cognitive Battery, Part 1: test selection, reliability, and validity. Am J Psychiatry 2008;165(2):203-213.

Harvey PD, Cornblatt BA. Pharmacological treatment of cognition in schizophrenia: an idea whose method has come. Am J Psychiatry 2008;165(2):163-165.

Continued Development of Glutamate Agonists for Treating Schizophrenia

Recently, Patil and colleagues (2007) published the results of an exciting compound, LY2140023. This is an mGluR (metabotropic glutamate receptor) agonist. The data showed evidence of antipsychotic efficacy with a low propensity for weight gain and metabolic side effects. Separately, Pfizer has just entered into an agreement to research, develop and commercialize TS-032, another novel mGluR agonist discovered by the Japanese company Taisho Pharmaceutical Co., Ltd. It will be of interest to watch the development over the coming years of these candidate schizophrenia drugs and, thereupon, the clinical testing of the glutamate hypothesis of schizophrenia.

Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nat Med 2007;13(9):1102-1107.

Anti-Smoking Drug May Have Psychiatric Side Effects?

It is estimated that almost 45% of cigarettes smoked in the U.S. are by patients with mental illness. Rates of smoking among patients with schizophrenia are inordinately high, with upwards upon 80% of patients smoking daily. Although The Joint Commission has promoted smoke-free psychiatric facilities, it is hard for patients to stop smoking and they often relapse and they can't quit for long. The use of nicotine replacement therapies and/or bupropion has been studied with mixed results (Evins et al., 2007; Goff et al., 1992). The advent of varenicline is welcome as it has a new mechanism of action and has proved to be an effective agent in smoking cessation studies of nonpsychiatric populations (Rollema et al., 2007). Its mechanism of action is appealing in view of the growing evidence for cholinergic dysfunction in schizophrenia. However, postmarketing surveillance and case reports (Freedman, 2007) have been reviewed by the FDA, and they have noted new onset psychiatric symptoms including anxiety, depression, worsening psychosis, and even suicidality.

These observations prompted the FDA to request a recent change in product label, incorporating a warning about possible psychiatric adverse effects. To date, there are no published studies examining the efficacy of varenicline in

patients with schizophrenia. Information about risk-benefit profile of this agent in patients with schizophrenia is needed.

Evins AE, Cather C, Culhane MA, Birnbaum A, Horowitz J, Hsieh E, et al. A 12-week double-blind, placebo-controlled study of bupropion sr added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. J Clin Psychopharmacol 2007;27(4):380-386.

Goff DC, Henderson DC, Amico E. Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. Am J Psychiatry 1992;149(9):1189-1194.

Rollema H, Chambers LK, Coe JW, Glowa J, Hurst RS, Lebel LA, et al. Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. Neuropharmacology 2007;52(3):985-994.

Freedman R. Exacerbation of schizophrenia by varenicline. Am J Psychiatry 2007;164(8):1269.

A New Study of a Weight-Reducing Agent for Antipsychotic-Induced Weight Gain in Schizophrenia

Check out the article by Wu and colleagues that appeared in the *Journal of the American Medical Association (JAMA)* recently! This very elegant study, which was conducted in China, evaluated both a behavioral modification strategy and an antiobesity medication intervention in 128 patients with schizophrenia who had already experienced more than 10% of weight gain during antipsychotic therapy. Patients continued on their antipsychotic (olanzapine, risperidone, or sulpiride) and were randomized to receive metformin and continued antipsychotic treatment, metformin plus a behavioral modification, placebo alone, or a behavioral modification only. The study found that those who just were given placebo (i.e., those who got "standard therapy" without either a pharmacological or nonpharmacological intervention for weight gain) continued to gain weight over the course of the twelve-week study. In contrast, significant reductions in weight (mean weight and body mass index), as well as in measures of insulin functioning, were seen in the other three groups—i.e., those that received some intervention, pharmacologic, nonpharmacologic, or combined medication and behavioral treatments. Importantly, the study also found that the combination of both antiobesity medication and a targeted lifestyle intervention to reduce weight yielded the best results. The study was in a Chinese population and so it remains to be seen how generalizable this might be for a Western (and more overweight) population.

Nevertheless, readers will recall a thorough recent review by Strassnig and Ganguli, which appeared in ***Clinical Schizophrenia & Related Psychoses*** (April, 2007) that strongly suggested that such behavioral interventions work in patients with schizophrenia. The Chinese study was also in a first-episode patient sample that was less obese than typically seen in U.S. first-episode studies. Nevertheless, this is good news. It demonstrates that targeted, combined treatment for antipsychotic-induced weight gain may be beneficial, and it offers another alternative to (simply) switching the patient to another agent. We also eagerly await the results of the ongoing NIMH Comparison of Antipsychotics for Metabolic Problems (CAMP) study. This important study is evaluating whether behavioral intervention plus staying on your present medication is any more or less effective than switching to aripiprazole. Details about CAMP also appeared in the April, 2007 issue of ***Clinical Schizophrenia & Related Psychoses.***

Wu RR, Zhao JP, Jin H, Shao P, Fang MS, Guo XF, et al. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. JAMA 2008;299(2):185-193.

New British Study Casts Doubt on Role of Antipsychotics in Agitated, Developmentally Disabled Population

Remember the Geddes and colleagues study from England suggesting that the benefits of second-generation antipsychotics (SGAs) were overemphasized? This important and influential metaanalysis provided the explanation that higher doses of the first-generation antipsychotics (FGAs) in SGA-FGA comparator studies contributed to this more favorable outlook. Then, there was the CUTLASS study showing no difference between SGAs and FGAs for treating patients with chronic schizophrenia. Now *The Lancet* has just published another important and provocative study suggesting that risperidone and haloperidol are not effective for managing aggressive behavior in patients with developmental disabilities. The multicenter study, led by senior investigator Dr. Peter Tyrer, evaluated risperidone and haloperidol in comparison to placebo in eighty-six adults with developmental disabilities in community residential centers in England, Wales and Australia. The study reported a 79% reduction in aggressive behavior in the patients receiving placebo, compared with a 65% reduction in the treatment groups. This is an important study and has implications for treatment, especially since antipsychotic medications are often prescribed off-label for the management of aggression in a host of psychiatric circumstances. In addition, the study drug in this study, risperidone, was FDA approved in 2007 for the treatment of irritability associated with autism. There is also a federally funded research network on pediatric psychopharmacology that has previously shown positive effects of risperidone in this population (McDougle et al., 2005).

Tyrer P, Oliver-Africano PC, Ahmed Z, Bouras N, Cooray S, Deb S, et al. Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disabil-

ity: a randomized controlled trial. The Lancet 2008;371(9606):57-63.

McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, et al. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. Am J Psychiatry 2005;162(6):1142-1148.

Antenatal Stress Exposure and Later Risk of Schizophrenia

A consortium of researchers from England, Ireland and Denmark has just published an important and provocative study in *Archives of General Psychiatry*. The investigators examined whether maternal exposure to stress during the first trimester of pregnancy was associated with a higher rate of schizophrenia (later on) in the offspring. And what they found was that mothers who were exposed to the death of a relative during the first trimester of their pregnancy were 1.67 times more likely to have offspring who later developed schizophrenia or related psychoses. Interestingly, they did not find any higher risk of schizophrenia if the death of the relative occurred in the six months before conception or even after the first trimester. Thus, the temporal selectivity of this effect is intriguing. The study adds weight to several other studies showing associations between maternal influenza or rubella exposure, hunger, and other in-utero stressors, and the later development of schizophrenia. There are several lines of evidence that point to the vulnerability of the fetal brain to the physiological impact of stress, especially the effects of glucocorticoids that occur early in brain development. There is a confluence of evidence that these risk factors (in-utero stress, infection, malnutrition, and vitamin D) may play a role in the etiology of schizophrenia. These risk factors also point to aberrant neurodevelopment as a major etiopathological trajectory in schizophrenia. The capacity of this study to capture such detail on the stressful life event of the death of a relative is impressive. This study is particularly interesting because of both the timing of the proposed "insult," and the observation that stress itself could be causative.

Khashan AS, Abel KM, McNamee R, Pedersen MG, Webb RT, Baker PN, et al. Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. Arch Gen Psychiatry 2008;65(2):146-152.