Clinical News

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Update on NIMH Strategic Plan

In an earlier issue of ***Clinical Schizophrenia & Related Psychoses*** (***CS***, **April 2008**), we told you about the National Institute of Mental Health's (NIMH) future plans for research. Consistent with its long-term vision and strategic mission, Dr. Thomas R. Insel, NIMH Director, has recently announced the agency's strategic plan. This ambitious yet appropriate plan supports the NIMH mission of transforming the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery and cure. It also supports the strategic directives ("4 Ps" of research) of the NIMH that we highlighted in our April '08 issue: increasing the capacity to Predict who is at risk for developing disease; developing interventions that Preempt (or interrupt) the disease process; using knowledge about individual biological, environmental and social factors for Personalized interventions; and, ensuring that clinical research involves Participation from the diversity of people and settings involved in healthcare.

The NIMH's new strategic plan has four overall objectives:

- promote discovery in the brain and behavioral sciences to fuel research on the causes of mental disorders;
- chart mental illness trajectories to determine when, where, and how to intervene;
- develop new and better interventions that incorporate the diverse needs and circumstances of people with mental illnesses;
- strengthen the public health impact of NIMH-supported research.

Additionally, NIMH has undertaken a comprehensive evaluation of the peer-review process for federal grant application. We will provide further information on this in a subsequent issue of ***CS***.

Further details of this strategic plan can be obtained from the NIMH web site (www.nimh.nih.gov).

New NAMI Survey on Schizophrenia

The National Alliance on Mental Illness (NAMI) has recently released the results of a nationwide survey that reveal continued public misinformation and misperceptions about schizophrenia. The survey shows that, in spite of new medical information and ongoing media attention, the general public is still both confused and scared about schizophrenia. The study also highlights the gaps in service and inadequate access, with a reported 8.5 years in delay between onset of symptoms and initiation of treatment. The results of the survey are available at www.nami.org. We are delighted that Dr. Ken Duckworth, Medical Director, NAMI, will consider submitting a summary report on the survey results for publication in a future issue of ***CS.***

Update on New Antipsychotics that are under Consideration by the U.S. Food and Drug Administration

In previous issues of ***CS***, we told you about putative antipsychotics that were being considered by the U.S. Food and Drug Administration (FDA). Here is an update.

Bifuprenox, a dopamine-receptor partial agonist, was reviewed by the FDA, and it requested additional information on short-term use and tolerability. Although a long-term maintenance study showed a favorable profile on weight, the results of short-term studies suggested difficulties with tolerability due to nausea and vomiting.

Iloperidone, a drug with a complex pharmacology, was recently reviewed by the FDA. The FDA expressed concern about iloperidone's efficacy, and the agency has requested additional data on iloperidone's efficacy in comparison with a placebo and including another active comparator such as olanzapine.

There is no further news yet from the FDA on either of the two long-acting injectable antipsychotics—olanzapine palmitate and paliperidone palmitate—that are under FDA review. Olanzapine palmitate was reviewed earlier this year. The manufacturer received a non-approvable letter from the FDA due to concern over sedative effects, now called post-injection delirium/sedation syndrome (PDSS) during these studies. PDSS is characterized by sedation, delirium, dizziness, confusion, disorientation, slurred speech, or altered gait. It appears to be an uncommon occurrence following an injection. While of obvious concern, PDSS appears transient in nature. A summary of the clinical trials program for olanzapine long-acting injectable formulation was presented at the inaugural meeting of the Schizophrenia International Research Society (SIRS) in Venice, June 2008.

Information on paliperidone palmitate was submitted to the FDA in October 2007. Data on its efficacy and toler-

ability, based upon presentations at the Annual Meeting of the American Psychiatric Association, in Washington, May 2008, were reviewed in the July 2008 issue of ***CS***. The FDA has just requested additional information from the manufacturer.

Results of Study on ACADIA Compound Available

In an earlier issue of ***CS***, we told you about another putative antipsychotic that is under investigation—ACADIA Pharmaceuticals' ACP-104. The results of a six-week, multicenter, double-blind, placebo-controlled trial of ACP-104 in almost 250 patients with schizophrenia, unfortunately, were disappointing. Neither dose of ACP-104 demonstrated improved efficacy in comparison to placebo. The most common adverse events in the treatment arm were salivation, tachycardia and mild indigestion. Time will tell whether the clinical trials program of ACP-104 to support a potential indication for the treatment of psychosis goes forward.

Use of Antipsychotic Medications in Older Adults with Dementia

In June 2008, the FDA requested boxed warnings for first-generation antipsychotics (FGAs) related to their use in dementia. These are similar to the boxed warnings for second-generation antipsychotics (SGAs) that occurred in 2005. These label changes now also extend warnings to FGAs concerning an increased risk of death associated with the off-label use of these drugs to treat behavioral problems in older adults with dementia. Neither FGAs nor SGAs are FDA-approved for use in the treatment of dementia-related symptoms. However, clinicians do prescribe these agents for patients with dementia.

While published studies have shown benefits in treating agitation in patients with dementia, there have been several studies recently showing either no benefit and/or harmful effects in the elderly. Most recently, a study has appeared in *Archives of Internal Medicine* by Rochon and colleagues (2008) that adds to this concern. This group studied older adults with dementia living in the community or in nursing homes between 1997 and 2004. Among 20,682 older adults with dementia living in the community, 6,894 did not receive antipsychotics, 6,894 were prescribed SGAs, and 6,894 were prescribed FGAs. Among 20,559 older adults with dementia living in nursing homes, 6,853 received no antipsychotics, 6,853 received SGAs, and 6,853 received FGAs. The authors found that, in comparison to community-dwelling older adults with dementia who did not receive antipsychotics, senior adults who received SGAs were three times more likely, and those who received FGAs were almost four times more likely, to experience a serious adverse event (hospitalization or death) within thirty days of starting drug treatment. While the study sample is substantial, there are several other considerations including the short length of follow-up and the outcome measure itself (not all serious events in nursing homes result in hospital admission).

This concern about use of antipsychotics in dementia has also reached public and parliamentary scrutiny in England, where family doctors regularly prescribe SGAs for patients with dementia. The management of agitation and dementia-related behavioral disturbances in older adults remains a complex clinical conundrum.

Rochon PA, Normand SL, Gomes T, Gill SS, Anderson GM, Melo M, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. Arch Intern Med 2008;168(10):1090-1096.

New Study on Statins

In response to the extent of metabolic-related side effects during the long-term pharmacotherapy for patients with schizophrenia, clinicians are now increasingly prescribing statins. Clinicians, therefore, may be particularly interested in a recently published (reanalysis) study, which suggests that people at high risk for dementia who were prescribed cholesterol-lowering statin agents were half as likely to go on to develop dementia as those people who did not receive statins. This longitudinal study by Cramer and colleagues was just published in the journal *Neurology*. The original longitudinal study was funded in 1997 to look at metabolic and vascular conditions such as hypertension and diabetes and their effect on the risk of dementia and Alzheimer's disease. The authors reported initially that metabolic and vascular disorders predicted Alzheimer's and dementia. For instance, they found that people with Type 2 diabetes are up to three times more likely to develop Alzheimer's disease. In this current study, of 1,674 participants who were free of dementia at the start of the study, 452 people (27%) took statins at some point in the study. Over the five-year follow-up period, 130 participants developed dementia or cognitive impairment. The study is provocative as it suggests that if a patient takes statins over a course of about five to seven years the risk of dementia might be reduced in half. Also, while statins lowered the risk of dementia in all participants, they had more impact on the group at high risk due to metabolic syndrome. Researchers adjusted for factors such as education, smoking status, the presence of an APO-E allele and history of stroke or diabetes. How this effect might occur is unknown, although statins may reduce high insulin levels in the brain.

Cramer C, Haan MN, Galea S, Langa KM, Kalbfleisch JD. Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. Neurology 2008;71(5):344-350.

New Treatment Study on Oxidative Stress and Schizophrenia

Oxidative stress has been proposed as one mechanism to understand how schizophrenia occurs and how the disease has such a broad constellation of effects. It is proposed that, through vulnerability to oxidative damage, there are free radical effects that impact cellular processes, especially mitochondrial, prostaglandin, and cell membrane functioning. This hypothesis has been studied in a variety of ways including plasma and cerebrospinal fluid assays for breakdown products of oxidative stress, brain imaging of neurochemistry using magnetic resonance spectroscopy, and treatment studies using vitamin E and/or fish oil products. Most recently, an Australian group has come up with another approach of giving n-acetyl cysteine in addition to antipsychotic medications. N-acetyl cysteine is a precursor of glutathione, a key element in the phospholipid pathway. In their study, Berk and colleagues (2008) gave n-acetyl cysteine (2 grams a day) under placebo-controlled, double-blinded conditions to patients with schizophrenia for twenty-four weeks. The results suggested some (but not dramatic) benefit in overall symptoms and the compound was well tolerated. This is an interesting avenue of research, now taking practical observations into the treatment arena.

Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine as a glutathione precursor for schizophrenia: a double-blind, randomized, placebo-controlled trial. Biol Psychiatry 2008;64(5):361-368.

Genetic Breakthrough for Schizophrenia?

A large international schizophrenia genetics consortium has provided exciting new data on an important new genetics study appearing in the major journal *Nature*. Until recently, the usual way to examine for genetic abnormalities was to test for single mutations using genome-wide scanning. These approaches also sought out candidate regions based upon prior studies and for known pathophysiological links. This new approach also applies genome-wide single nucleotide polymorphism arrays, but this technique is being used now to explore for rare copy number variants (CNVs). A group, led by Pamela Sklar from the Broad Institute at Harvard Medical School, found evidence for rare genetic variants in an extremely large patient sample (3,391 patients with schizophrenia) compared with matched control (n=3,181) subjects. In addition to the anticipated deletions in the region on chromosome 13 that have already been implicated in velo-cardio-facial syndrome (a genetic condition in which 30% of patients develop a psychosis that is indistinguishable from schizophrenia), the group also found small deletions on chromosomes 1 and 15 that had not been previously reported.

A separate consortium of Icelandic, Finnish, Dutch and German investigators (Stefansson et al., 2008) also studied CNVs in a different sample. Their results appear as a companion paper in *Nature*. They also found small deletions in the exact same areas on chromosomes 1 and 15, as well as on another part of chromosome 15. While these variants are rare and represent deletion of sections of DNA, they substantially increase the risk of schizophrenia. Nevertheless, they still only account for a small amount of the total number of cases of schizophrenia. Collectively, these results are exciting because this approach may be more sensitive and informative in teasing out the genetic pathways that are involved in schizophrenia.

The International Schizophrenia Consortium; Stone JL, O' Donovan MC, Gurling H, Kirov GK, Blackwood DH, Corvin A, et al. Rare chromosomal deletions and duplications increase the risk of schizophrenia. Nature. In press 2008.

Stefansson H, Rujescu D, Cichon S, Pietilainen OP, Ingason A, Steinberg S, et al. Large recurrent microdeletions associated with schizophrenia. Nature. In press 2008.