Clinical News

Peter F. Buckley, MD
Editor-in-Chief

NAMI Releases Second "State of the States" Audit

The National Alliance for Mental Illness (NAMI) recently released its second national evaluation of the United States mental health system. In 2006, the U.S. mental health-care system received an overall "D" grade in a comprehensive state-by-state evaluation. At that time, only 5 states received B grades and 8 states received an F grade. This time around, the national average was again a D, indicating little global change since 2006. Also, since the information was gathered during 2008, it is possible that mental health services have deteriorated further in 2009 given the global economic recession, which disproportionately burdens mental health services. In a state-by-state analysis now for 2009, 14 states improved their grades while 12 states fell backwards. Essentially, half of the states had similar grades on both reviews. The distribution of grades was 6 B grades, 18 C grades, 21 D grades, and 6 F grades. The complete report can be accessed online at www.nami.org/grades09.

New Antipsychotic Approved: Iloperidone Receives FDA Approval

In May 2009, the U.S. Food and Drug Administration (FDA) approved iloperidone for the treatment of adults suffering from schizophrenia. Iloperidone has a profile of being a mixed dopamine D2/serotonin 5HT2A antagonist. As has been detailed in an earlier issue of ***Clinical Schizophrenia & Related Psychoses*** (***CS***), iloperidone was found to be efficacious in two short-term (4 week and 6 week), placebo-controlled trials that were presented to the FDA. The drug was well tolerated, with the most commonly observed adverse reactions (those equal or greater than 5% incidence and twice that of placebo) were orthostatic hypotension, tachycardia, weight gain, and sedation. Iloperidone was compared to risperidone in these studies. The recommended target dose of iloperidone is between 12 mg–24 mg per day. It is recommended that the dose of 12 mg should be achieved over the first four days of treatment.

Sertindole Receives Favorable FDA Recommendation

The FDA also recommended sertindole for the treatment of a subgroup of patients suffering from schizophrenia. The drug had been presented to the FDA over ten years ago when concerns arose concerning cardiac side effects. Sertindole was subsequently available in a restricted capacity in Europe. Data presented to the FDA included a European study of 10,000 patients treated with either sertindole or risperidone. The study found a comparable "all-cause" mortality between sertindole and risperidone. The FDA will make a final ruling concerning the approval of sertindole shortly.

FDA Panel Considers Antipsychotic Use in Younger Patients

The FDA's Psychopharmacologic Drugs Advisory Committee has cleared three antipsychotics as treatments for schizophrenia and bipolar disorder in pediatric and adolescent populations. The panelists said the data provided by the companies showed that the atypical antipsychotics are effective and "reasonably safe" for younger patients.

For quetiapine, AstraZeneca is looking to market the drug for schizophrenia in patients aged 13 to 17, and for bipolar disorder in youngsters aged 10 to 17. The Committee voted pretty much unanimously in favor, despite a few abstentions, for both age groups and indications.

As for Lilly's olanzapine, for the proposed schizophrenia indication (13- to 17-year olds), the panel voted 11-5 (with two abstentions) that olanzapine effectiveness had been demonstrated, and voted 10-4 (with four abstentions) that these data demonstrated acceptable safety. For manic or mixed episodes associated with bipolar I disorder in the same age group, the panel voted 17-0 (with one abstention) on effectiveness and 11-4 (with three abstentions) on safety. The Committee expressed concerns about olanzapine's adverse reactions such as sedation, weight gain, increases in blood fats and sugars, and tardive dyskinesia.

The panelists were less enthusiastic about Pfizer's ziprasidone and voted 8-1 (with nine abstentions) that the drug is safe for 10- to 17-year olds with bipolar disorder. The abstaining members of the Committee were concerned that Pfizer had provided incomplete data.

The Committee noted that it is concerned about the lack of long-term studies on these three drugs, but its recommendations now make approvals from the FDA more likely. The FDA takes the advice of its Advisory Committees into consideration when deciding whether to approve new indica-

tions, but is not bound by their recommendations.

This is a topic of great concern. Using antipsychotics in young patients might have potential immediate endocrinal and metabolic effects, as well as potential untoward long-term effects. On the other hand, untreated and/or inadequately treated serious mental illness in youth can have immediate and long-term serious consequences. Advocacy groups are also weighing in on this complex issue.

FDA Approves Risperidone Long-Acting Injection as a Treatment as both Monotherapy and Adjunctive Therapy for Bipolar I Disorder

The FDA has approved long-acting risperidone either as monotherapy or in combination (with lithium or valproate) for the maintenance treatment on patients who have a diagnosis of bipolar mood disorder. This approval was based on two prospective, randomized, double-blind, placebo-controlled studies for the long-term treatment of bipolar I disorder. The first demonstrated that LAI risperidone, when used as a monotherapy, was significantly better than placebo at delaying the time to relapse of any mood episode. The second study demonstrated that, for patients already taking lithium or valproate, the addition of LAI risperidone significantly delayed the time to relapse compared to current treatments plus placebo.

Asenapine Continues Under FDA Review

The FDA requested additional information recently concerning asenapine, which is a novel antipsychotic that is being considered for approval as an acute treatment of schizophrenia and for the acute treatment of bipolar I disorder. The FDA requested information on proposed labeling as well as supplemental data from the existing clinical studies database. The FDA did not request any additional clinical trials. The clinical trials profile for asenapine was described in an earlier issue of ***CS.***

FDA Considers Quetiapine for Depression and Anxiety Disorders

In a previous issue of ***CS*** we highlighted the clinical trials program for quetiapine in anxiety disorders and depression. These data were recently considered by the FDA. The FDA considered that the use of quetiapine could be of benefit for refractory patients with either depression or anxiety disorders. However, the FDA stopped short of recommending quetiapine monotherapy for either condition. The FDA considered that the adverse effect profile of the antipsychotic quetiapine, coupled with the availability already of other drug classes to treat depression and anxiety, did not present a favorable enough advantage to warrant FDA approval for monotherapy.

New Study Information on Lurasidone

Lurasidone, discovered and under development by Dainippon Sumitomo Pharma Co., Ltd., is a novel putative antipsychotic with a high binding profile to dopamine (D2), serotonin (5HT2A, 5HT1A and 5HT7), and noradrenergic receptors. Results from a study called PEARL 1 (Program to Evaluate the Antipsychotic Response to Lurasidone) were recently presented at the 162nd Annual Meeting of the American Psychiatric Association. PEARL 1 is a multicenter and multinational, 6-week, placebo-controlled clinical trial of 40 mg, 80 mg, and 120 mg of lurasidone. In this study of 500 patients involving 51 trial sites worldwide, 80 mg of lurasidone was more effective than placebo on both PANSS and CG I-S study endpoints. The 40 mg and 120 mg doses of lurasidone were comparable to placebo. In terms of adverse effects, the median change of weight was 0.3 kg on lurasidone—similar to the 0 kg on placebo. Adverse events in the trial were overall mild. The most commonly reported adverse events (greater than 5% and at least twice the rate of placebo) were akathisia (17.6% versus 3.1% placebo), sedation (11.7% versus 5.5%), weight gain (5.9% versus 2.4%), and parkinsonism (6.8% versus 0%). The study sample was patients with schizophrenia/schizoaffective disorder, the majority of whom were male and with a mean age of 39 years.

Update on Long-Acting Injectable Olanzapine

Findings from ongoing trials of long-acting injectable (LAI) olanzapine were presented at the recent 162nd Annual Meeting of the American Psychiatric Association. Results from a 190-week interim analysis of a six-year, ongoing, open-label study reported a discontinuation rate of 46.3% in patients with schizophrenia/schizoaffective disorder being treated with LAI olanzapine. Patients were enrolled following one of three randomized, controlled studies of olanzapine LAI, in which patients had been randomly assigned to oral olanzapine, olanzapine LAI, or placebo. During the open-label extension, all patients received flexibly dosed olanzapine LAI at injection intervals of approximately two to four weeks. The most common reason for discontinuation was the patient's decision (23.4%) followed by adverse events (6.7%). Safety findings were consistent with those observed with oral olanzapine, with the exception of injection-related events, including post-injection delirium/sedation syndrome (PDSS), which are characterized by sedation- and/or delirium-related symptoms following injection. This was described in a previous issue of ***CS***.

Also presented at the APA Annual Meeting were eight-

month interim results from a two-year, ongoing, open-label study where patients with schizophrenia were switched to olanzapine LAI from a previous antipsychotic, either using a direct switch or while tapering their previous antipsychotic medication. Investigators, at their discretion, could either directly switch patients or taper their previous antipsychotic medication during the first two weeks of treatment. At the time of study entry, patients were either receiving typical antipsychotics (N=63), atypical antipsychotics (N=188) or not receiving any antipsychotics at all (N=34). Of those receiving atypical antipsychotics, 76 were taking oral olanzapine and 16 were on an injectable antipsychotic medication other than olanzapine LAI. No significant difference was found in overall rate of treatment discontinuation or mean change in PANSS score between patients who switched directly to olanzapine LAI and those who were tapered. Additionally, no significant differences were seen in the overall number of treatment-emergent adverse events, changes in laboratory measures or mean weight change.

Gene Identified for Schizophrenia Risk

An important study that was recently published in *The American Journal of Psychiatry* suggests overexpression of the gene NOS1AP in schizophrenia. This study was based on zeroing in on three single nucleotide polymorphisms from a total of 60 evaluated in a sample of 24 families with high amounts of schizophrenia. However, it must be recognized that a single-gene cause for schizophrenia is only likely to account for a very small effect, as it is well known that schizophrenia is not a single-gene disorder. Nevertheless, the findings in this important study echo findings of overexpression of the gene NOS1AP that were seen in earlier postmortem studies in schizophrenia.

Wratten NS, Memoli H, Huang Y, Dulencin AM, Matteson PG, Cornacchia MA, et al. Identification of a schizophrenia-associated functional noncoding variant in NOS1AP. Am J Psychiatry 2009;166(4):434-441.

Mistreated Children More Likely to Become Psychotic

A British epidemiological consortium published an interesting and indeed provocative study recently in the *Archives of General Psychiatry* (Schreier et al., 2009). The authors used a longitudinal, ongoing study to address correlates of childhood abuse among over 6,000 early adolescents. They found that between ages 8–10 over 46% of these adolescents had experienced some bullying. For those with bullying that was characterized as persistent and traumatic, there was a significant overrepresentation of psychotic-like symptoms. It is unclear that these symptoms are indicators of psychosis itself or whether these are PTSD related. There is also a growing literature indicating a baseline level of psychotic-like symptoms in the general population. The other point of note from this study is the importance of considering trauma in adults with schizophrenia. Some studies have suggested that as many as 40% of schizophrenia patients have experienced significant trauma during their lifetime.

Schreier A, Wolke D, Thomas K, Horwood J, Hollis C, Gunnell D, et al. Prospective study of peer victimization in childhood and psychotic symptoms in a nonclinical population at age 12 years. Arch Gen Psychiatry 2009;66(5):527-536.

New Psychosis Journal Launched

The International Society for the Psychological Treatments of Schizophrenia (www.isps.org) has launched a new journal entitled *Psychosis: Psychological, Social and Integrative Approaches*. The journal's editor is John Read, from the University of Auckland, New Zealand. Dr. Read published an outstanding review on psychological aspects of schizophrenia in the October 2008 issue of ***CS***.

Updated British Clinical Guideline for Schizophrenia

The National Institute for Health and Clinical Excellence (NICE), an independent organization which provides guidance on healthcare policy for the United Kingdom, has released a revised version of the guideline for schizophrenia. The schizophrenia guideline can be accessed at www.nice.org.uk/CG082. The updated guideline provides new recommendations on key aspects of care for people with schizophrenia. These recommendations include giving cognitive behavioral therapy to all patients and giving family interventions to all families who are close to the patient. The report also recommends art therapy for all patients, making the assertion that this may help improve the negative symptoms of schizophrenia. A collaborative approach to care is empha sized throughout this document.

Readers wishing to know more about the details of individual studies cited in ***Clinical News*** *should consult directly with the pharmaceutical company who sponsored the study and/or www.clinicaltrials.gov.*