Clinical News

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FDA Provides New Guidance on Antipsychotic Usage during Pregnancy

The U.S. Food and Drug Administration (FDA), taking stock of all available and new pharmacoepidemiological information on antipsychotic medication use, has provided updated guidance on prescribing antipsychotics during and immediately after pregnancy. Firstly, the FDA report affirms the long-held clinical message that untreated psychosis in the expectant mother is associated with (far) greater risk than the risks associated with continued use of antipsychotics. Nevertheless, the report cautions about risks of antipsychotic medications for extrapyramidal side effects (EPS) and withdrawal side effects in the newborn. The report cites outcomes for 69 instances of EPS and withdrawal side effects that were reported to the FDA up until the fall of 2008. The data affirm the occurrence and anticipated profile of these adverse effects, although, interestingly, a number of confounding effects (e.g., prematurity, polypharmacy) is also noted. In addition to identifying these risks, the FDA also cautions the abrupt discontinuation of antipsychotic medications, and the need for clinicians to continue reporting serious side effects from the use of antipsychotic drugs to the FDA MedWatch program. For clinicians who are interested in additional information, it is worthwhile to consult the FDA website at www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm.

Antipsychotics and Long-Term Brain Changes

Another provocative brain imaging report by colleagues from the University of Iowa—with the senior author being our ***CS*** Editorial Board member, Dr. Nancy Andreasen—addresses the vexing issue of whether long-term use of antipsychotic medication is helpful, or harmful, over the course of illness. The article appeared in the February '11 issue of *Archives of General Psychiatry*. This topic of antipsychotic-related brain changes has been featured in previous issues of ***CS***, and there are studies for and against the proposition that these drugs might cause brain changes in people with schizophrenia. The most notable effect has been enlargement of the caudate nucleus, which appears to be at least in part related to the dopaminergic receptor affinity across first- and second-generation antipsychotic medications. In this study, which followed up over 211 patients after their first episode of psychosis, the authors documented an impact of prolonged exposure to antipsychotic medications upon total brain volume, as well as both gray matter and caudate-putamen volumes. Modest volumetric reductions were observed. There appeared to be a dose effect of antipsychotics as well. Although the effects were not independent of other factors that are known to influence potential brain changes—namely, duration of follow-up, illness severity, and comorbid substance abuse—the effect of medications persisted even when these other influences were taken into account statistically. This is a noteworthy observation.

While the results are still open to other interpretations, the observations for this study are sobering. They are also in line with earlier preclinical studies from the University of Pittsburgh that have demonstrated potential neurotoxic effects of antipsychotic medication upon selective neurons. Nevertheless, the "jury is still out" on this contentious topic, especially since other imaging studies have highlighted neurodegenerative changes that appear to be intrinsic to the illness and, in particular, changes that are aggravated by repeated relapse. Accordingly, the benefit of long-term antipsychotic therapy remains a complex consideration of risk. Additionally, this study was undertaken across a period (1991–2009) of substantial change in the use of first- and second-generation antipsychotic medications. The authors also highlight the relevance of their findings as another cautionary observation concerning off-label use of antipsychotic medications.

Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 2011;68(2):128-137.

Cannabis and Schizophrenia

The role of cannabis as a risk factor for schizophrenia has been highlighted in prior issues of ***CS***. A recent meta-analysis (Large et al.) confirms a powerful effect of cannabis in at least bringing on schizophrenia earlier than might otherwise have occurred. In a meta-analysis of 43 studies, the age of onset of psychosis was 2.7 years earlier among cannabis abusers than in patients who did not abuse cannabis. The analysis was—as is often the case—complicated by the concomitant use of other illicit drugs and of alcohol. However, alcohol use did not appear to impact age of onset, and the effect of "all drug abuse" was considerably less powerful than that of cannabis upon age of onset. The findings are salutary and add to the further growing weight of evidence that cannabis is an important risk factor for developing schizophrenia.

Although the recent commentary by Drs. Csernansky and Smith in the February '11 issue of *The American Journal of Psychiatry* pertains to another study and is (seemingly) unrelated to the meta-analysis described above, the commentary is well worth a read, as it calls for greater attention to the deleterious effects of illicit drugs upon mental health and specifically upon psychotic symptoms. This is important both from the causal risk perspective and from the capacity of drugs of abuse to worsen illness—attributes that are often ill-informed among our patients and among the community at large.

Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic metaanalysis. Arch Gen Psychiatry 2011.

Csernansky JG, Smith MJ. Thought, feeling, and action in real-time—monitoring of drug use in schizophrenia. Am J Psychiatry 2011;168(2):120-122.

Largest Ever Prospective Schizophrenia Treatment Study Examines Mortality

The results of the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) Trial showed comparable nonsuicide mortality rates among 18,154 patients with schizophrenia who were randomized to treatment with ziprasidone or olanzapine. This is an enormous study spanning 18 countries following, prospectively, a large cohort over one year inclusive of whether the patient remained on the chosen treatment or not. The rate of all cause mortality was 1.13% in ziprasidone-treated patients and 1.12% in olanzapine-treated patients. The rate of nonsuicide mortality was 0.91% and 0.90% respectively for ziprasidone-treated and olanzapine-treated patients. The results suggest a low—and comparable—risk of serious cardiac events among patients who are treated with either ziprasidone or olanzapine. While these findings are encouraging and potentially "debunk" the cardiac concerns originally attributable to ziprasidone, it is nevertheless important to remember that patients with schizophrenia have a higher rate of sudden death. This robust, epidemiological-clinical observation still remains unexplained.

Strom BL, Eng SM, Faich G, Reynolds RF, D'Agostino RB, Ruskin J, et al. Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). Am J Psychiatry 2011;168(2):193-201.

Two Important Issues of *Biological Psychiatry* that Inform Schizophrenia Research

We are fortunate that our outstanding schizophrenia researcher, Dr. John Krystal, is serving as Editor of *Biological Psychiatry*. He has done a terrific job. Recently, he supported the publication of several key articles that inform key areas of neurobiological research in schizophrenia. In the January 1, 2011 issue of *Biological Psychiatry*, papers report new findings on two key areas of research: 7 nicotinic receptors and novel pharmacological approaches to cognitive deficits in schizophrenia. Additionally, the same issue has several key papers on cognition and glutamate dysfunction in schizophrenia. These articles are complemented by three papers illustrating aspects of neural dysconnectivity in schizophrenia.

The January 15th issue of *Biological Psychiatry* has a collection of key papers addressing postmortem research in schizophrenia. The commentary by Paul Harrison is particularly noteworthy and he lauds the greater use of "omics" (proteomics, epigenomics) technologies in postmortem research. Both of these issues of *Biological Psychiatry* provide very nice overviews of complex areas of neurobiological research in schizophrenia, and I highly recommend these to you.

N-Methyl-D-Aspartate receptor function and cortical connectivity in schizophrenia. Biol Psychiatry 2011 Jan 1;69(1):A1-A12, 1-100.

Postmortem studies of psychosis: status, opportunities, and challenges. Biol Psychiatry 2011 Jan 15;69(2):A1-A10, 101-194.

New Information on Lurasidone

Results from the PEARL (Program to Evaluate the Antipsychotic Response to Lurasidone) Study 3 were presented at the recent 49th Annual Meeting of the American College of Neuropsychopharmacology. PEARL 3 comprised 488 patients with schizophrenia in a 6-week, double-blind study evaluating 80 mg/day and 160 mg/day of lurasidone. A priori response criteria were achieved by 65% of patients receiving 80 mg/day of lurasidone and by 79% of patients being treated at the higher dose of 160 mg/day. The adverse effect profile on EPS, weight and metabolic measures was generally comparable between the two doses. However, it is important to recognize the FDA has approved lurasidone for use up to 80 mg/day. It is important that clinicians follow these FDA recommendations.

British Study Provides New Findings on Suicide in Schizophrenia

A study following 3,000 British patients with schizophrenia who were followed up for over eleven years found that these patients were twelve times more likely to commit suicide than the general population. Of particular note from this study is the observation that the risk remains high over this ten-year course of illness. The historical perception of suicide risk in schizophrenia has posited that the risk is highest earlier on in the illness, proposed as a depressive reaction to demoralization and insight at the beginning of

illness in recognizing the anticipated poor later outcome of schizophrenia. The British study also reports the rate of suicide to be lower than in several previous studies.

Dutta R, Murray RM, Hotopf M, Allardyce J, Jones PB, Boydell J. Resassessing the long-term risk of suicide after a first episode of psychosis. Arch Gen Psychiatry 2010;67(12):1230-1237.

Expanded Clinical Trials Program for New Putative Antipsychotic Zicronapine

Zicronapine is a novel, putative antipsychotic that is currently under investigation and development by H. Lundbeck A/S, the makers of the antipsychotic sertindole. This drug has a pharmacological receptor affinity profile that bears similarity to that of clozapine, especially with respect to its low binding to dopamine (D2) receptors. In early trials, which have a primary emphasis on evaluating tolerability and safety, zicronapine was statistically superior to placebo in treating symptoms of schizophrenia over 8 or 12 weeks. The side effect profile also held up well, especially in comparison to olanzapine in a Phase 2 clinical trial. A Phase 3 trial comparing zicronapine and risperidone over 6 months of treatment in 160 patients with schizophrenia is now under consideration.

Update on Staccato Loxapine

We have provided information on staccato loxapine—a rapid-acting nasal preparation of loxapine—in previous issues of ***CS***. The results of a Phase 3, placebo-controlled trial of inhaled loxapine (5 mg or 10 mg doses) were recently published in *The British Journal of Psychiatry*. In a study of 344 acutely agitated psychotic patients, both doses of loxapine proved effective for the treatment of agitation. The side effect profile was comparable to that seen with the regular oral tablet formulation of loxapine. The FDA is reviewing data from several trials in consideration of loxapine as a treatment for agitation associated with psychosis.

Lesem MD, Tran-Johnson TK, Reisenberg RA, Feifel D, Allen MH, Fishman R, et al. Rapid acute treatment of agitation in individuals with schizophrenia: multicentre, randomised, placebo-controlled study of inhaled loxapine. Br J Psychiatry 2011;198:51-58.

Update on Genetics and Schizophrenia

We have been committed to keeping our ***CS*** readership informed about developments on the genetics research in schizophrenia. We have previously described the findings on microdeletions and duplications on several chromosomes. Another important study was recently reported from the Molecular Genetics of Schizophrenia (MGS) study. This large collaborative group found in a combined sample of almost 4,000 schizophrenia patients new and confirmatory evidence of microdeletions on chromosomes 1, 15, and 22. The group also observed a duplication in the gene for vasoactive intestinal peptide receptor 2, a gene that has pre-viously been associated with other neurodevelopmental disorders

Levinson DF, Duan J, Oh S, Wang K, Sanders AR, Shi J, et al. Copy number variants in schizophrenia: confirmation of five previous findings and new evidence for 3q29 microdeletions and VIPR2 duplications. Am J Psychiatry 2011;168(3):302-316.

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.*