Clinical News

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Paliperidone Tablets Approved for Treatment of Schizophrenia in Adolescents

Paliperidone extended release tablet formulation has recently been approved by the U.S. Food and Drug Administration (FDA) for use in adolescents (aged 12–17 years) with schizophrenia. The FDA approval was in support of findings from a 6-week, double-blind placebo-controlled trial of paliperidone (tablet dose range between 1.5 mg to 12 mg) in adolescents with schizophrenia aged between 12 and 17. The results of the study showed that paliperidone was effective for the treatment of schizophrenia in adolescents when used in the dose range between 3 mg–12 mg per day. The drug was generally well tolerated, with a similar profile of adverse effects to those observed in the registration trials of paliperidone that were conducted in adult populations with schizophrenia. Adverse effects were also dose related. The impact of the long-acting formulation of paliperidone—paliperidone palmitate—in this population is currently unknown.

Fascinating Artificial Neural Networks Study

Dr. Hoffman and colleagues (2011) at Yale University recently published a very cool and interesting computational study of disorganized and delusional thinking in schizophrenia. They tested a simulated model of narrative recall and understanding—an artificial neural network called DISCERN—in 20 healthy controls and 37 patients with schizophrenia or schizoaffective disorder. Patients had exaggerated neural activations—termed "hyperlearning"—and they also comingled and confused story elements toward delusional themes. These effects were more pronounced as the artificial system was set to higher amplitude. The study is a fascinating read, as well as opening the door to other types of applications of this approach to additional aspects of schizophrenia research.

Hoffman RE, Grasemann U, Gueorguieva R, Quinian D, Lane D, Mikkulainen R. Using computational patients to evaluate illness mechanisms in schizophrenia. Biol Psychiatry 2011; 69(10):997-1005.

Cultured Neurons from Patients with Schizophrenia Show Differences

A recent study from the Salk Institute by Dr. Brennand and colleagues (2011) showed that, in comparison with normal neurons, pluripotent stem cells induced from the fibroblasts of 4 patients with schizophrenia developed into neurons that had less dendritic spines and were less well connected together. Additionally, the authors of this very cool and meticulously conducted study found that growth of these cultured cells during exposure in loxapine enhanced their connectivity. These findings are very interesting. The apparent drug effect was only studied with loxapine and it is at variance with the findings of the human brain imaging study by Ho and colleagues that we reported in the last issue of ***CS***, which suggested that antipsychotic medications might be contributory to progressive neurodegeneration. We also don't know about the potential impact of other antipsychotic medications. The authors of this fibroblast-derived cell culture study also identified some 600 genes with misregulated activity in this sample. About a quarter of these genes are ones that have been found abnormal in earlier human genetics studies in schizophrenia. This is a very important study that represents the early stages of a new approach to understanding schizophrenia.

Brennand KJ, Simone A, Jou J, Gelboin-Burkhart C, Tran N, Sangar S, et al. Modelling schizophrenia using human induced pluripotent stem cells. Nature 2011;473(7346):221-225.

Metabolomics Study of Schizophrenia

Metabolomics is the study of metabolism at the global level. It involves systematic study of the metabolome, the complete repertoire of small molecules present in cells, tissues or organisms. Sophisticated metabolomic analytical platforms and informatic tools have recently been developed that are making it possible to begin the process of defining signatures for disease and pathways implicated in disease process. Oresic and colleagues (2011) in Finland studied glucose and lipid metabolism using a metabolomics platform in serum samples from almost 140 patients with psychotic disorders (45 with schizophrenia) and healthy subjects. Patients showed highly significant perturbations in 6 lipid clusters, with overexpression of proline metabolites being seen only in patients with schizophrenia. Although the influence of medications could not be entirely discounted here, the authors did report that, in adjusting for both medication status and for physical comorbidities, these abnormal findings prevailed and, therefore, may represent additional evidence of fundamental disturbances of glucose/lipid regulation in schizophrenia. Additionally, it suggests a perhaps less appreciated—and perhaps more specific—abnormality of the serum amino acid proline in patients with schizophrenia. The study also highlights the potential role

of metabolomics as a tool in the search for a biomarker for schizophrenia.

Oresic M, Tang J, Sappanen-Laakso T, Mattila I, Saarni SE, Scorni SI, et al. Metabolome in schizophrenia and other psychotic disorders: a general population-based study. Genome Med 2011;3(3):19.

Vasoactive Intestinal Peptide Receptor 2 (VIPR2) Genetic Abnormality in Schizophrenia

Another large collaborative genetics study has implicated the upper region of chromosome 7 in schizophrenia. In a study of 8,290 patients drawn from a combined Irish and U.S. multisite study, Vacic and colleagues (2011) reported an excess of copy number variants (CNVs) in chromosome 7. These CNVs, although small in absolute number, occurred overall 14 times more frequently in patients with schizophrenia than in normal control subjects. These findings build on previous studies reporting an excess of CNVs in schizophrenia. Several of these studies have been reported in previous issues of ***CS***. The focus here on VIPR2 is of interest because it resonates well with abnormalities in other disorders where VIPR2 is implicated. Additionally, since VIPR impacts cell signaling, this opens the door to consider how other similar peptides could potentially be developed and modified so that they could have a potential therapeutic benefit.

Vacic V, McCarthy S, Malhotra D, Murray F, Chou HH, Peoples A, et al. Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. Nature 2011;471(7339):499-503.

Comparing Relapse in Schizophrenia between Long-Acting Injectable and Oral Second-Generation Antipsychotic Medicine

Long-acting injectable (LAI) formulations of antipsychotic medications have been found in prior studies of first-generation antipsychotic (FGA) medications to reduce relapse rates in patients with schizophrenia. Based upon a recent meta-analysis by Leucht and colleagues (2011), relapse rates are reduced by 30% on LAI therapy. The extent to which this potential advantage also pertains to second-generation antipsychotic (SGAs) treatment is an important consideration. New information has just become available to begin to address this issue. In a large, multicenter study conducted in the U.S. Veterans Affairs system, Rosenheck and colleagues (2011) compared the effectiveness of LAI risperidone (risperidone microspheres) to physicians' choice SGA oral medications in 369 patients with schizophrenia. The extent of hospitalization was similar (37% versus 45%, a nonsignificant difference) between the group receiving LAI risperidone and the group being treated with oral SGAs. The result was surprising in view of prior studies with other FGA LAIs, as well as other studies showing a benefit of LAI risperidone microspheres in improving medication adherence, which is generally considered the mode of clinical advantage of LAI therapy (Weiden et al., 2010).

Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia: a critical systematic review and meta-analysis of randomised long-term trials. Schizophr Res 2011;127(1-3):83-92.

Rosenheck RA, Krystal JH, Lew R, Barnett PG, Fiore L, Valley D, et al.; CSP555 Research Group. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. N Engl J Med 2011;364(9):842-851.

Weiden PJ, Schooler NR, Weedon JC, Elmouchtari A, Sunakawa A, Goldfinger SM. A randomized control trial of long-acting injectable risperidone vs continuation on oral atypical antipsychotics for first-episode schizophrenia: initial adherence outcome. J Clin Psychiatry 2010;70(10):1397-1406.

Physical Comorbidity among People with Mental Illness

Previous articles in ***CS*** and, indeed, also the Ganguli et al. piece in this issue of ***CS*** draw attention to cardiometabolic comorbidity in patients with schizophrenia. As a field, we appear to have moved beyond the initial point of "it's all due to the drugs—no, it's got nothing to do with the drugs" to more complex appraisals that incorporate host-agent and host-environment interactions. With that in mind, a recent British study highlights the extent of physical comorbidity. Among 782 patients enrolled in a well-being support program delivered over a one-year period by some 212 mental health professionals in England, 66% of patients were obese with a body mass index (BMI) of above 25. At baseline, 19% of patients had an abnormal fasting glucose test. HDL cholesterol was abnormal in 29% of patients, while LDL cholesterol was abnormal in 52% of patients. The good news is that 80% of patients completed the well-being program (although, on average, only 2.10 of the 4 sessions were attended) and reductions in BMI were achieved. As Dr. Ganguli points out in his paper in this issue of ***CS***, managing cardiometabolic risk in our patients is a great challenge.

Eldridge D, Dawber N, Gray R. A well-being support program for patients with severe mental illness: a service evaluation. BMC Psychiatry 2011;11:46.

Valuable Mental Health "Stats" to Have at Your "Fingertips"

Two interesting reports have recently become available. A National Association of Psychiatric Health Systems (NAPHS) 2010 survey evaluated mental health service utilization trends during 2009 in comparison with 2008 data. The 2010 survey included 89.5% psychiatric hospitals and 10.5% general hospitals respondents with behavioral health services. The survey reported that Total Inpatient psychiatric admissions increased by 4.8%, while Total Inpatient Days increased by 5.9%. However, average inpatient hospital length

of stay (all programs combined for all ages trimmed at 30 days) remained steady at 9 days. There were, of course, variations in length of stay by age groups, as follows: Child programs (12 yrs. and below): 10.8 days; Adolescent programs (13–17 yrs. old): 9.4 days; Adult programs (18–64 yrs. old): 8 days; and, Older Adult programs (65 and older): 12.5 days. On the outpatient side of things, the average outpatient visits (defined as a clinic or practice setting) increased by 18.6%. Residential Care admissions also increased 6.4%, while Residential Care days of care increased by 2%, and the overall Residential Care length of stay decreased from 172 days to 169 days.

From a different vantage point, the National Institute of Mental Health reported that the life expectancy of people with a major mental illness is 56 years, compared with average life expectancy at 77.7 years. Moreover, each year there is nearly twice the number of suicides (33,000) as homicides (18,000) nationally. It is reliably estimated that mental disorders and substance abuse are the leading cause of disability in the U.S., with an estimated 26.2% of Americans over the age of 18 suffering from a diagnosable mental disorder in a given year. Furthermore, 17.6 million Americans (1 in 12) abuse alcohol or are alcohol dependent, and six of ten people with a substance abuse disorder also suffer from a form of mental illness. Thus, the extent of mental illness, addiction diseases, interrelated comorbidities and the service demands thereupon are staggering. We hope that these data are informative to our readers.

Excellent New NAMI Website on Schizophrenia

It is well worth checking out—and recommending to patients and their families—the new schizophrenia website developed by the National Alliance on Mental Illness (NAMI). Congratulations to Ken Duckworth, MD, and his colleagues on putting together such comprehensive and current information. New studies that are of relevance to patients and families are also covered on this website. It also provides guidance on additional information about medications. The website can be accessed at www.nami.org/schizophrenia.

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.*