Clinical News

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Expanded Delivery Platform Under Investigation for Long-Acting Injectable Antipsychotics

The development of long-acting formulations of second-generation antipsychotic (SGA) drugs has been technically challenging, especially with respect to the drug delivery systems. Risperidone microspheres, the first long-acting SGA, was delivered in a dissolvable base system so that the drug can be administered every two weeks. Olanzapine palmitate—the results of registration studies for this drug were described in an earlier issue of ***CS***—is an oily-based preparation given monthly. It has been associated with an uncommon but distressing post-injection sedation effect that is due to leakage of the drug directly into the vascular system. Paliperidone palmitate is another oily-based preparation that is given as a monthly injection.

The company Alkermes, Inc. is currently developing a long-acting injectable form of olanzapine—currently known as ALKS 7921—that hopefully will not result in the leakage effect of the present long-acting form of olanzapine. Alkermes was also responsible for developing the drug delivery platform for risperidone microspheres. The company also is currently developing an oral opiod modulator that might be of benefit in the treatment of substance abuse disorders and in binge eating disorder. Long-acting and other formulations expand the therapeutic options in schizophrenia.

Novel Neuroprotective Agent Examined for Cognitive Impairment in Schizophrenia

Previous issues of ***CS*** have detailed the development of novel cognitive enhancing agents as putative treatments for schizophrenia. These studies have been conducted under the NIMH-funded TURNS (Treatment Units for Research on Neurocognition and Schizophrenia) research program. In a twelve-week study of a putative neuroprotective drug called daucenetide, patients receiving this drug showed a significant increase in n-acetylaspartate (NAA) in the dorsolateral prefrontal cortex compared with patients who received placebo. These data—which were reported at the recent 2010 Schizophrenia International Research Society (SIRS) conference held in Florence, Italy—are of interest, in part because of daucenetide's action of microtubules. Additionally, NAA has been considered a marker of neuronal integrity. NAA has been reported as low in various stages of schizophrenia. This imaging study was part of a larger, multicenter study through the TURNS mechanism that showed some, albeit limited, effect of this drug on functional performance in schizophrenia.

New Study Shows that Estrogen Augmentation is Effective for Schizophrenia

Several aspects of schizophrenia are thought to point to a role for estrogen. The marked gender differences—later age of onset in females, higher proportion of females in later life that develop schizophrenia, overall more favorable illness course in females—have been variously attributed to the neuromodulatory effects of estrogen. This mechanism has previously been covered in an earlier ***CS*** article by Dr. Mary Seeman. A recent study from Jayashri Kulkarni has provided provocative results for the use of the selective estrogen receptor raloxifene (a drug currently used for treating osteoporosis) as an add-on treatment for schizophrenia. Twenty-six patients with schizophrenia—all female—were randomized to receive raloxifene at 120 mg/day or placebo and they were evaluated for four weeks. Data from another pilot study of 60 mg/day of raloxifene were also included. Although the analysis is still of relatively small sample size and did not include male patients, the researchers found improvements in psychotic symptoms and in memory. This study builds on prior studies of estrogen augmentation by Dr. Kulkarni's group, including earlier work showing benefit in both male and female patients. The present study of raloxifene has additional interest because this more selective agent does not appear to confer the risk of uterine and breast cancer that has been associated with other estrogen therapies.

Kulkarni J, Gurvich C, Lee SJ, Gilbert H, Gavrilidis E, de Castella A, et al. Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia. Psychoneuroendocrinology 2010 Feb 18.

New Genetic Findings in Schizophrenia

Several important findings in schizophrenia genetics have recently been published. Some of these are highlighted here. In earlier issues of ***CS*** we have highlighted the promising findings of an excess of copy number variants (CNVs) in large international studies of schizophrenia. These duplications or microdeletions of key DNA sequences have now been replicated, and they show an increased incidence in patients with schizophrenia. In a recent study of 1,735 schizophrenia patients and 3,485 normal subjects, Glessner and colleagues reported CNVs among the genes (CACNA1B and DOC2A) located on chromosome 16 that regulate calcium-related neurotransmitter release. This is of interest in pointing to a selective effect on a brain signaling pathway. Additionally, this group had previously found similar microdeletions on chromosome 16 in autism.

Another group of investigators from Columbia University in New York have developed a unique mouse model for schizophrenia, based upon genetic engineering to create "knockout mouse" that has a genetic deletion on chromosome 22q11.2. These mice have prepulse and memory defects. In a recent study, Sigurdsson and colleagues examined working memory in these knockout mice compared to healthy mice. The genetically deficient mice showed memory and behavioral difficulties. They also showed reduced neural firing and a dysynchrony between the hippocampus and frontal cortex in these mice. Given the inherent problems in creating a mouse model for schizophrenia, these findings are noteworthy.

Neuregulin and its receptor ErbB4 have been a focus of schizophrenia research, with abnormalities being reported in previous candidate gene association studies in schizophrenia. Wen and colleagues at the Medical College of Georgia—led by Dr. Lin Mei—recently reported behavioral and memory disturbances in genetically engineered mice that lacked ErbB4 parvalbumin containing interneurons. These findings are compatible with post mortem studies that show fundamental deficits in the number of interneurons that connect pyramidal cells in the brains of patients with schizophrenia. This is another heuristic genetic/animal model for examining neurobiology relevant to schizophrenia.

A Canadian study by Gauthier and colleagues, recently published in *Proceedings of the National Academy of Sciences of the United States of America*, found a mutation in the SHANK3 gene. This gene has been previously linked to autism. SHANK3 is a neurodevelopmental gene of particular interest because it promotes the integrity and development of synaptic spines. Four patients in the study carried this mutation. It is noteworthy that all four exhibited some features of developmental delay/mental retardation prior to the onset of their schizophrenia illness.

Glessner JT, Reilly MP, Kim CE, Takahashi N, Albano A, Hou C, et al. Strong synaptic transmission impact by copy number variations in schizophrenia. Proc Natl Acad Sci U S A 2010 May 20.

Sigurdsson T, Stark KL, Karayiorgou M, Gogos JA, Gordon JA. Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. Nature 2010;464(7289):763-767.

Wen L, Lu YS, Zhu XH, Li XM, Woo RS, Chen YJ, et al. Neuregulin 1 regulates pyramidal neuron activity via ErbB4 in parvalbumin-positive interneurons. Proc Natl Acad Sci U S A 2010;107(3):1211-1216.

Gauthier J, Champagne N, Lafreniere RG, Xiong L, Spiegelman D, Brustein E, et al.; S2D Team. De novo mutations in the gene encoding the synaptic scaffolding protein SHANK3 in patients ascertained for schizophrenia. Proc Natl Acad Sci U S A 2010;107(17):7863-7868.

NAMI Asserts its Voice

The National Alliance on Mental Illness (NAMI) is advocating for a 12% increase in funding to reach a total of $36 billion in funding for the National Institutes of Health, with $1.7 billion specifically for the National Institute of Mental Health. NAMI also called for a $100 million increase in "block grants" from the Substance Abuse and Mental Health Services Administration (SAMHSA) federal agency. These block grants, which have been a core of SAMHSA's funding programs, support mental health clinical services and programs in communities throughout the United States.

New CDC Stigma Survey Results Released

The Centers for Disease Control and Prevention (CDC) just released interesting findings from a 2007 nationwide survey on stigma and mental illness. The vast majority of the public surveyed—the evaluation included 202,063 respondents from across the United States in 35 states—felt that people with mental illness can function well in society. However, only just over half of respondents (57.3%) concurred with the statement that the general public cares about people with mental illness. Among this epidemiologically derived sample, 14% of respondents reported significant emotional distress and 10.8% reported being/having received mental health treatment. Those individuals with mental problems were less in agreement with the statement that the general public cares about people with mental illness. Several analyses—including a state-by-state breakdown—are tabulated in the report which can be accessed at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a3.htm

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.*