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Editor-in-Chief

Update on Putative and New Antipsychotic Medications

Jointly, two international pharmaceutical companies—Otsuka and Lundbeck—have submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for putative antipsychotic brexpiprazole. This agent has an interesting pharmacodynamic serotonin-dopamine modulator profile with partial agonism at both 5HT_{1A} and D₂ receptors. The clinical trials program submitted with this NDA included drug exposure among over 5,000 individuals. More to follow.

Another pharmaceutical company—Alkermes plc—also submitted an NDA to the FDA for another putative antipsychotic agent. This drug is a long-acting putative antipsychotic called aripiprazole lauroxil, which is administered as a once-monthly intramuscular formulation. The drug converts in vivo to aripiprazole and the NDA data include a placebo, double-blind, controlled trial that demonstrated efficacy in patients with schizophrenia.

New Study Further Confirms Role of Long-Acting Injectable Antipsychotic Medications

Two CS Board Members—Joseph McEvoy and Peter Buckley—along with other colleagues in schizophrenia research recently published a 24-month comparative study (McEvoy et al., 2014) of paliperidone palmitate versus haloperidol decanoate in just over 310 patients with schizophrenia/schizoaffective disorder. The results were sobering and showed no difference in relapse rate between patients receiving new or old long-acting injectable antipsychotic medication. Side effect profile differed, with hyperprolactinemia more associated with paliperidone palmitate while extrapyramidal symptoms were higher in patients receiving haloperidol decanoate.

McEvoy JP, Byerly M, Hamer RM, Dominik R, Swartz MS, Rosenheck RA, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA* 2014;311(19):1978-1987.

More is More ... New Genetics Study Excites Public and our Field

The Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014), as part of the large Psychiatric GWAS Consortium (PGC), has produced great interest across our field with findings from a large genetics study—a whole genome-wide scan association (GCVA) study of almost 37,000 patients and 114,000 normal subjects—which highlighted 108 potential risk loci implicated in schizophrenia. These findings—highlighting dopamine receptor genes, glutamate-related genes, and calcium-channel related genes—replicated a previous study by the PGC (2013) that emphasized developmental gene associations which were common across schizophrenia, autism, bipolar disorder and ADHD. This suggests at least some convergence in recent genetics findings in schizophrenia. In a prior issue of *CS*, we reported on this important 2013 PGC study published in *The Lancet* that highlighted genetic abnormalities and overlap between schizophrenia and other developmental disorders, most notably autism. The 2014 PGC study replicates and extends these “genetic hits” and also finds several immune gene associations in schizophrenia. It is likely that this vital study will stimulate broader research in the genetics of schizophrenia. Lead author Stephan Ripke and his colleagues from the Broad Institute received a \$650 million grant from the Stanley Foundation to continue their productive research.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014;511(7510):421-427.

Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 2013;381(9875):1371-1379.

Other Genetic Findings in Schizophrenia Focus on Glutamate System

In another important paper, Fromer and colleagues (2014), in a pooled analysis of international genetic data sets,

report disruptions in genes related to N-methyl-d-aspartate receptor (NMDAR) and cytoskeleton-associated protein (ARC) complexes. These findings of specific genetic mutations affecting neurodevelopment are also shared with other disorders.

Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, et al. De novo mutations in schizophrenia implicate synaptic networks. *Nature* 2014;506(7487):179-184.

Marijuana and “Societal” Health ... Just the Facts ...

Dr. Nora Volkow, director of the National Institute on Drug Abuse (NIDA), authored an authoritative review of the societal and mental health consequences of marijuana use. Dr. Volkow highlights the increase in use of marijuana among adolescents, with concomitant declines in scholastic performance and increased road traffic accidents. Regarding schizophrenia, Dr. Volkow affirms the growing literature that marijuana use both increases the risk of developing schizophrenia and worsens its symptoms.

Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med* 2014;370:2219-2227. doi: 10.1056/NEJM-ra1402309.

Antipsychotics and Pregnancy

A recent article in *PLoS One* (Kulkarni et al., 2014) highlights the “high-risk state” of pregnant mothers who have serious mental illnesses requiring antipsychotic medications. The bottom line is that 45% of neonates end up in the NICU. It is, of course, difficult to disentangle whether the effects are antipsychotic drug related or related to the overall higher risk associated with women who have serious mental illnesses who become pregnant.

Kulkarni J, Worsley R, Gilbert H, Gavrilidis E, Van Rheenen TE, Wang W, et al. A prospective cohort study of antipsychotic medications in pregnancy: the first 147 pregnancies and 100 one year old babies. *PLoS One* 2014;9(5):e94788. doi: 10.1371/journal.pone.0094788.

NIH BRAIN Initiative Gathering Momentum

The National Institutes of Health’s (NIH) BRAIN—Brain Research through Advancing Innovative Neurotechnologies—initiative is moving along, with a recent NIH report endorsing \$4.5 billion in funding over the next 12 years, beginning with \$40 million of initial funds in fiscal year 2014 and an additional \$100 million intended for fiscal year 2015. The proposal (available at www.nih.gov/science/brain) addresses seven principles: advance both animal and human studies; advance interdisciplinary collaborations; advance data sharing; advance technology; integrate spatial

and temporal scales; be sensitive to ethical concerns; and, ensure accountability. The psychiatric community is represented on the advising committee. More information to follow.

Swedish Study Emphasizes Lower Risk of Violence when Patients with Major Mental Illnesses are on Medications

Fazel and colleagues (2014) examined—through psychiatric, medication, and criminal database linkage in Sweden—the trajectory of violence and criminal behavior in relation to prescribed medication among almost 83,000 patients. Between 2006–2009, violent crime was reduced 45% in patients on antipsychotics and 24% in patients receiving mood stabilizing medications. A dose effect was also noted, as was a benefit for depot antipsychotic medications.

Fazel S, Zetterqvist J, Larsson H, Langstrom N, Lichtenstein P. Antipsychotics, mood stabilisers, and risk of violent crime. *The Lancet* 7 May 2014. doi: 10.1016/S0140-6736(14)60379-2. [E-pub ahead of print.]

Bereavement as a Risk Factor for Schizophrenia?

In an earlier issue of *CS*, we noted an important study showing that maternal bereavement during the first trimester was associated with a higher risk (relative risk of 1.67) of the offspring later developing schizophrenia. More recently, the same team of investigators (Abel et al., 2014) did not replicate their initial findings. Rather, in this study of over one million births between 1973–1985, they observed a modestly high risk of psychoses overall (relative risk of 1.17) for offspring who were themselves exposed to death of a relative at an early time (between 2–13 years) in their life. This is a provocative finding, although it did not reach statistical significance.

Abel KM, Heuvelman HP, Jorgensen L, Magnusson C, Wicks S, Susser E, et al. Severe bereavement stress during the prenatal and childhood periods and risk of psychosis in later life: population based cohort study. *BMJ* 2014;348:f7679. doi: 10.1136/bmj.f7679.

Virtual Reality Training Improves Social Skills in Schizophrenia: Interesting Model and Findings

A pilot study by Rus-Calafell and colleagues (2014) demonstrates the application of virtual reality techniques to enhance the social skills among patients with schizophrenia. The authors adapted to a computer-based virtual reality program the original psychosocial skills training approach of Robert Liberman that focused on seven domains: social perception, processing social information, responding and sending social skills, affiliative skills, assertive communica-

tion, instrumental role skills, and conversational skills. The study, while limited by a small sample, demonstrated improvements across these domains upon 16 virtual reality 1-hour sessions and after a 4-month follow-up evaluation. Such approaches are gaining in treating PTSD and anxiety

disorders. This is an important approach in the emergent area of social cognition in schizophrenia.

Rus-Calafell M, Gutierrez-Maldonado J, Ribas-Sabate J. A virtual reality-integrated program for improving social skills in patients with schizophrenia: a pilot study. *J Behav Ther Exp Psychiatry* 2014;45(1):81-89.

*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, or go directly to the journal that published this work.*

