Clinical News … new treatments under development, stigma, genetics and nosology, genetic counseling coming of age …

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The American College of Psychiatrists Honors Schizophrenia Researcher … One of Our Own

Dr. Robert Buchanan, ***CS*** Editorial Board Member and Professor of Psychiatry at the University of Maryland School of Medicine and Deputy Director of the Maryland Psychiatric Research Center, was the recipient of the 2012 Stanley Dean Award for Research in Schizophrenia. This distinguished award, given annually by the American College of Psychiatrists, recognizes a leader who has had a major impact on the understanding and treatment of schizophrenia disorders, especially through their research. Dr. Buchanan has made major contributions to our understanding of the neurobehavioral and neuroanatomical basis of the pathophysiology of schizophrenia. He also has led key investigations of novel pharmacological approaches to the treatment of cognitive impairments, negative symptoms, and treatment-resistant positive symptoms in people with schizophrenia. At the February 2013 College annual meeting, Dr. Buchanan delivered a remarkable presentation ("The Pharmacological Treatment of Cognitive Impairments in People with Schizophrenia"), a synthesis of his and other colleagues' important work. Congratulations, Bob.

FDA Approves Non-Injection Novel Formulation for Treatment of Agitation in Relation to Schizophrenia or Bipolar Disorder

In previous issues of ***CS*** we have detailed components of the clinical trials program for Staccato loxapine, a novel inhalation delivery formulation that the U.S. FDA recently approved for the management of acute agitation associated with either schizophrenia or bipolar disorder. It is anticipated that this drug will be available shortly to clinicians under the trade name of Adasuve. It is recommended for use at 10 mg for agitated patients with schizophrenia or bipolar, although the risk of bronchospasm has led the FDA to approve its use in conjunction with the presence of registration and monitoring through the Adasuve Risk Evaluation and Mitigation Strategy. Details of the clinical efficacy and safety profile of Staccato loxapine are provided in a comprehensive review by Drs. Currier and Walsh in this issue of ***CS***.

FDA Approves Long-Acting Injectable Formulation of Aripiprazole

On February 28th, the FDA approved for the management of schizophrenia a long-acting injectable formulation of aripiprazole, an already well-established oral antipsychotic. This long-acting formulation of aripiprazole (which will be released under the name "Abilify Maintena") will be administered as a once monthly injection. Information about pivotal trials of this new injectable antipsychotic was provided in earlier issues of ***CS***.

Novel Putative Antipsychotics Progress in their Clinical Trials Development Programs

An Irish biopharmaceutical company—Alkermes plc—is advancing to a Phase 2 (in patients) study of a novel putative antipsychotic (ALKS 3831) that is a combination of olanzapine and an opioid (mu receptor) modulator. It is being developed in the hopes of delivering the robust clinical efficacy associated with olanzapine while ideally mitigating the adverse effect of weight gain. The findings in a safety Phase 1 trial have led the company to advance this agent into a Phase 2 clinical trial.

A California-based pharmaceutical company—Reviva Pharmaceuticals—anticipates results shortly from a Phase 2 clinical trial of a putative antipsychotic RP5063, a novel agent that has partial agonist activity at both several dopamine (D2, D3, D4) and serotonin (5HT6, 5HT7) receptors.

Another California-based pharmaceutical company—DURECT Corporation—completed a Phase 1 clinical trial of a putative antipsychotic Relday. This agent is a novel subcutaneous formulation of long-acting risperidone that is administered once a month. The results are broadly in line with the established efficacy and tolerability profile of long-acting injectable risperidone.

A Useful Overview of Where We Have Come with Schizophrenia

Silveira and colleagues (2012) present an interesting review of schizophrenia—euphemistically entitled "More than one century of schizophrenia: an evolving perspective." It is a useful review of the nosology of schizophrenia, and it

includes references to many seminal studies in our field. The article emphasizes how our field has evolved in its efforts to search out for a biomarker for schizophrenia. This is a nice companion article to an outstanding recent ***CS*** guest editorial ("Is it Time Schizophrenia Research Left the Museum?") by McGrath and Meyer-Lindenberg that also highlights the current state of play of schizophrenia research.

Silveira C, Marques-Teixeira J, de Bastos-Leite AJ. More than one century of schizophrenia: an evolving perspective. J Nervous Ment Dis 2012;200(12):1054-1057.

Using Knockout Mouse Model to Examine Putative Neurodevelopmentally Based Genetic Aberrations Influencing Neuronal Networks in Schizophrenia

Stachowiak and colleagues (2013) provide a terse yet interesting overview of transgenetic mouse strategies to tease out dopamine, serotonin, and nicotinic neuroreceptor dysfunction. Their focus is on a complex neurodevelopmental pathway—Integrative Nuclear FGFR1 Signaling (INFS). They draw from other candidate gene and pre-pulse inhibition studies in humans, as well as from their own work in transgenic mice … well worth a read.

Stachowiak MK, Kucinski A, Curl R, Syposs C, Yang Y, Narla S, et al. Schizophrenia: a neurodevelopmental disorder-integrative genomic hypothesis and therapeutic implications from a transgenic mouse model. Schizophr Res 2013;143(2-3):367-376.

Cannabis-Induced Psychosis or Primary Psychosis with Abuse of Cannabis? How Would You Know?

Rubio and colleagues (2012) from Madrid, Spain assessed patients who presented with psychosis in the context of recent cannabis use in order to determine future outcomes and the relationship of cannabis use and psychosis. They conducted a follow-up on 450 patients with—what was determined at the time of admission as—cannabis-induced psychotic disorder and 104 patients who had primary psychotic disorders with concomitant cannabis abuse. At 6-month follow-up, these diagnoses remained stable and it was estimated that the amalgam of anxiety and depressive symptoms were associated more with primary psychotic disorders, especially schizophrenia. This is somewhat counter-intuitive given the effects of cannabis on inducing anxiety and dysphoria.

Rubio G, Marin-Lozano J, Ferre F, Martinez-Gras I, Rodriguez-Jimenez R, Sanz J, et al. Psychopathologic differences between cannabis-induced psychoses and recent-onset primary psychoses with abuse of cannabis. Compr Psychiatry 2012;53(8):1063-1070.

Ecstasy and Psychosis: What's the Risk of Use?

We know that the risk of psychosis and schizophrenia is also not uniformly distributed across drugs of abuse. Cannabis is particularly associated with psychosis risk. Methamphetamine ("ecstasy") is another drug known to be associated with a heightened risk of psychosis. In a recent Australian study by McKetin and colleagues (2013), 278 methamphetamine-dependent patients were followed up over 4 months to evaluate the occurrence of psychotic symptoms. They found a 5-fold increase in psychotic symptoms among persistent ecstasy users. Not surprisingly, the timing of these symptoms was coincident with periods of abuse. There is also previous neuroimaging research that supports this work and shows direct neurotoxicity of ecstasy (Panenka et al., 2012). The extent to which acute or chronic ecstasy abuse can lead to schizophrenia (as opposed to acute psychosis or a chronic drug-induced psychosis) is less clear. Either way, this is a particularly toxic agent for the brain.

McKetin R, Lubman DI, Baker AL, Dawe S, Ali RL. Dose-related psychotic symptoms in chronic methamphetamine users: evidence from a prospective longitudinal study. JAMA Psychiatry 2013 Jan 9:1-6. [Epub ahead of print]

Panenka WJ, Prodychyn RM, Lecomte T, Macewan GW, Flynn SW, Honer WG, et al. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Depend 2012 Dec 26. [Epub ahead of print]

Genetic Counseling for Schizophrenia —Ready for Primetime?

In ***Clinical News***, we have made a real effort to highlight state-of-the-art findings in genetics schizophrenia research. Here is an interesting study "taking the temperature" regarding genetic counseling, which is based upon both qualitative and quantitative data assessing knowledge and readiness to receive genetic information about schizophrenia. This study-focus group qualitative research from the University of Toronto exemplifies a new area in schizophrenia genetics: the opportunity and challenges of genetic counseling. It appears that this approach clarifies information and needs of patients. The study also highlights guilt and low self-esteem related to blame for having (and potentially transmitting) this illness. Not surprisingly to those who look after patients with schizophrenia over time, patients and their relatives cited stigma as a barrier to genetic counseling—the concern that understanding the genetic risks of schizophrenia fuels demoralization that unaffected family members might be "doomed from the womb." This is an interesting article to stimulate consideration of how genetic advice, information, and counseling might make its way into clinical practice and family support.

Costain G, Esplen MJ, Toner B, Scherer SW, Meschino WA, Hodgkinson KA, et al. Evaluating genetic counseling for individuals with schizophrenia in the molecular age. Schizophr Bull 2012 Dec 12. [Epub ahead of print]

Major New Genetics Study Suggests More Overlap across Diagnoses Including Schizophrenia

Given the imminent publication of *DSM-5* and the continued (actually incessant!) debate about psychiatric nosology, an important study from the Psychiatric Genomics Consortium (PGC) has been published. PGC was established in 2007 and draws genetic data from 19 countries. In this formative analysis of data from over 33,000 patients across five diagnostic groups (schizophrenia, bipolar disorder, major depression, ADHD, and autism spectrum disorder) and almost 28,000 control subjects, this "mega genome-wide association study" showed that single-nucleotide polymorphism (SNPs) at 4 loci were overrepresented from chromosomes 3, 10, and 12 *across* these (apparently) distinct phenomenologically based disorders. Moreover, two of these SNPs are at gene loci related to calcium-channel pathophysiology that may suggest a final neurobiological pathway for these ostensibly disparate disorders.

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 Feb 28. [Epub ahead of print]

Awareness of Schizophrenia by the Lay Public: "Psychosis" is a Poorly Understood Term

Don Addington, a leading Canadian psychiatrist, and colleagues report on a large telephone survey (n=1,685) of the Canadian lay public showing a reasonable extent of understanding about schizophrenia and its assessment (Addington et al., 2012). However, when the lens was broadened to the concept of psychosis, efforts to understand access and pathways to care were highlighted. The study is worth a read to appreciate what degree of basic information and promotion of awareness is needed to implement early psychosis/prodromal assessment and treatment programs for young people who are at risk/in early stages of developing schizophrenia.

Addington D, Berzins S, Yeo M. Psychosis literacy in a Canadian health region: results from a general population sample. Can J Psychiatry 2012;57(6):381-388.

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.*