Clinical News … national awards for *CS* Editorial Board Members, neuroinflammation, putative antipsychotics, dopamine imbalance, metabolic dysfunction, cognitive deficits at the core of schizophrenia, recovery …

Peter F. Buckley, MD
Editor-in-Chief

CS Editorial Board Members Receive Prestigious Honors

Two of our Editorial Board members were recently honored for their lifetime accomplishments in schizophrenia research. William Carpenter received the 2013 Rhoda and Bernard Sarnat International Prize in Mental Health from the Institute of Medicine (www.iom.awards). This prestigious award acknowledges remarkable leadership contributions to mental health—and, wow, what a leader Will is for schizophrenia research. Congratulations, Will, and thank you for all you do!

Chuck Schulz received the 2014 Stanley Dean Award for outstanding accomplishments in schizophrenia research from the American College of Psychiatrists (ACP). Chuck gave a terrific presentation at the recent ACP annual meeting, highlighting the field of early-onset (adolescent) schizophrenia as well as the magnitude of impact that the International Congress on Schizophrenia Research has had for our field. Congratulations, Chuck, and we greatly appreciate your leadership!

Update on Putative Novel Antipsychotics

We are well aware of how recalcitrant negative symptoms of schizophrenia are to current treatments. We have previously highlighted RG1678 (bitopertin), a novel Roche compound that is a glycine reuptake inhibitor at N-methyl-D-aspartate receptors. A recent analysis from two Phase III studies of patients with prominent negative symptoms of schizophrenia did not demonstrate superiority of RG1678 over placebo as an add-on therapy over 24 weeks of treatment. The results of other studies are awaited.

A phosphodiesterase (PDE) 10 inhibitor (Omeros Corporation's OMS824) was found in a Phase I trial to show 70% binding to PDE 10, and it may be a candidate drug for schizophrenia. A Phase II clinical trial is presently underway.

We have previously reported in ***CS*** on cariprazine, a putative antipsychotic. The U.S. Food and Drug Administration (FDA) reviewed the New Drug Application from Forest Laboratories and Gedeon Richter, comprised of study information on over 2,700 patients. Additional clinical trials and pharmacokinetic data were recommended by the FDA. More later on this agent.

Intra-Cellular Therapies, Inc. released results of a Phase II trial of ITI-007 in over 310 patients with schizophrenia. Over the 4-week study, ITI-007 showed statistically significant efficacy at a dose of 60 mg/day and it was well tolerated. More research is planned on this putative antipsychotic.

Targacept, Inc. reported on a 24-week, placebo-controlled trial of its putative antipsychotic—TC-5619—in over 470 patients with schizophrenia. While the drug was well tolerated, it did not show the expected improvements in cognition or negative symptoms.

Jazz Pharmaceuticals plc is releasing an oral suspension of clozapine called Versacloz. It will be accompanied by a registration program.

Teva Pharmaceutical is releasing Adasuve (loxapine) inhalation powder 10 mg, an orally inhaled medicine for the acute treatment of agitation associated with schizophrenia and bipolar I disorder in adults. The drug is only available through a restricted program called the Adasuve Risk Evaluation and Mitigation Strategy (REMS).

New Genetic Study Offers Provocative Interpretation of Copy Number Variants in Schizophrenia

We have highlighted the research findings on copy number variants (CNVs)—aberrant microdeletions and/or microduplications of genetic material—in previous issues of ***CS***. In a provocative multinational collaborative study, Rees and colleagues (2014) conduct an analysis of CNVs among 47,000 people. Interestingly, and with some provocation, they find that larger duplications in chromosome 22 occurred more in healthy controls (0.085%) than in patients with schizophrenia (0.014%). Chromosome 22 aberrancy is characteristic of the neurodevelopmental condition called velocardiofacial syndrome, which is associated with a higher rate of (schizophrenia-like) psychosis. Thus, the findings of this study, favoring a potentially protective CNV on this chromosome, are provocative and, to some extent, counter-intuitive to current perceptions of the role and impact of CNVs and schizophrenia.

Rees E, Kirov G, Sanders A, Walters JT, Chambert KD, Shi J, et al. Evidence that duplications of 22q11.2 protect against schizophrenia. Mol Psychiatry 2014;19(1):37-40.

Dopamine and Schizophrenia: Addressing an Imbalance

Amidst a constellation of theories—including the hypoglutamatergic hypothesis previously well described by Kantrowitz and Javitt in an earlier issue of ***CS***—the notion that schizophrenia's pathophysiology resides in dopamine overactivity has been an enduring and remarkably helpful construct. A recent elegant review by Drs. Mary and Philip Seeman provides an historical and scientific aggregation of findings that unify around the notion of dopamine receptor supersensitivity in schizophrenia. It is an excellent review that highlights the impact of dopamine cell pruning, dopamine synoptic release and activation, dopamine (D2) receptor activation, and induction of D2 receptors. Very interesting.

Seeman MV, Seeman P. Is schizophrenia a dopamine supersensitivity psychotic reaction? Prog Neuropsychopharmacol Biol Psychiatry 2014;48:155-160.

Cells and Schizophrenia: Neuroscience Potential to Disentangle Relative Neurodegenerative and/or Neurodevelopmental Pathobiologies

Neuroimaging and cognitive neuroscience studies have yielded divergent findings on the relative impact of neurodegenerative and neurodevelopmental processes in schizophrenia. Two recent, more basic science reports further illuminate these trajectories. In a Spanish study (Gasso et al., 2014) of cultured fibroblasts that were extracted from antipsychotic-naive, first-episode schizophrenia patients, fibroblasts exhibited more apoptotic (cell degeneration) changes as exemplified by heightened caspase-3 activity than healthy controls.

In a broad overview from leaders at the Salk Institute for Biological Studies (Wright et al., 2014), the emergent neuroscience of stem cells and application to schizophrenia research are presented in a provocative and exciting manner. This is a burgeoning aspect of research in other areas of medicine, with the potential and promise of regenerative medicine. This is still at a nascent state in schizophrenia research, though gladly this approach is being applied to our field.

Gasso P, Mas S, Molina O, Lafuente A, Bernardo M, Parellada E. Increased susceptibility to apoptosis in cultured fibroblasts from antipsychotic-naive first-episode schizophrenia patients. J Psychiatr Res 2014;48(1):94-101.

Wright R, Rethelyi JM, Gage FH. Enhancing induced pluripotent stem cell models of schizophrenia. JAMA Psychiatry 2014;71(3):334-335.

Inflammation and Schizophrenia

Our ***CS*** Associate Editor, Dr. Brian Kirkpatrick, and Editorial Board Member, Dr. Brian Miller, provide a thoughtful synthesis of the current literature on inflammation and schizophrenia (Kirkpatrick and Miller, 2013). They reach the following conclusions: prodromal studies are required; anti-inflammatory and immunotherapy drugs offer some therapeutic potential; inflammation marker studies in treatment-refractory schizophrenia are needed; peripheral indices of inflammation on their own are insufficient; inflammatory markers need to be studied longitudinally over the course of illness; and, other key and longstanding relationships (e.g., inflammation and toxoplasmosis) should be studied further.

Kirkpatrick B, Miller BJ. Inflammation and schizophrenia. Schizophr Bull 2013;39(6):1174-1179.

Immune Dysfunction and Metabolic Disturbances in Schizophrenia: Chance "Bedfellows" or Not?

We have reported on studies of immune dysfunction in schizophrenia in prior issues of ***CS***. This comprehensive review by Steiner and colleagues (2014) from Germany summarizes a large and disparate literature at the interface of immunology, endocrinology, and schizophrenia. The authors evaluate whether impaired glucose metabolism drives both the pathobiology of schizophrenia and, thereupon, immune dysfunction as a reactionary response to illness, whether immune dysfunction contributes to both the pathobiology of schizophrenia and the expression of metabolic disturbances, or whether some other pathogenic processes underlie both immune dysfunction and metabolic disturbances in schizophrenia. Both endpoint disturbances contribute to premature death in schizophrenia. The strength and direction of these inter-relationships are still poorly understood. This is an excellent review in summarizing a clinically meaningful pathophysiological debate in schizophrenia research.

Steiner J, Bernstein HG, Schiltz K, Muller UJ, Westphal S, Drexhage HA, et al. Immune system and glucose metabolism interaction in schizophrenia: a chicken-egg dilemma. Prog Neuropsychopharmacol Biol Psychiatry 2014;48:287-294.

METS Trial Shows Modest Weight Loss Effect in Outpatients with Schizophrenia

Jarskog and colleagues (2013) report on a 16-week, placebo-controlled trial of metformin (1,000 mg b.i.d.) among 148 patients who were obese (with body mass index [BMI] greater than or equal to 27). Body weight reduced by 3 kg in one metformin-treated group, compared with a 1 kg reduction in the placebo group. Similarly, metformin-treated patients had a reduction in BMI of 0.7 compared to the control group. Metformin was generally well tolerated. The anti-obesity and metabolic effects were less than one

might have anticipated, although it remains unclear how to choose one anti-obesity drug over another for antipsychotic-related obesity and metabolic disturbances.

Jarskog LF, Hamer RM, Catellier DJ, Stewart DD, Lavange L, Ray N, et al.; METS Investigators. Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder. Am J Psychiatry 2013;170(9):1032-1040.

Adolescent Study Confirms Association between Trauma and Psychosis

An Irish cohort of adolescents (n=1,112)—drawn from a larger European suicide prevention study called "Saving and Empowering Young Lives in Europe (SEYLE)"—was evaluated at 3 and 12 months for psychotic symptoms, childhood trauma and bullying (Kelleher et al., 2013). Childhood trauma and bullying predicted—in a dose-dependent manner—the emergence of psychotic symptoms. Additionally, when these traumatic experiences lessened, similarly the psychotic symptoms lessened. While it is less clear that these features presage schizophrenia itself, the strength of these relationships are noteworthy.

Zammit and colleagues (2013) also examine—retrospectively—the relationship of childhood psychotic symptoms to more florid psychosis at age 18 years. In their sample of 4,724 young adults with psychotic experiences, 1.7% met criteria for a psychotic disorder and only 5% of these individuals received any treatment. Additionally, there was a low positive predictive value (ranging from 5.5 to 22.8%) for psychotic symptoms at age 12 years to predict psychotic symptoms at age 18 years. Taking both studies (Kelleher and Zammit) together, it is clear that psychotic symptoms can occur in early childhood, especially in relation to childhood trauma. However, their predictive value—and thereupon the potential to intervene early to avert subsequent schizophrenia—seems too small to be clinically useful. Others (McGorry, 2013) hold a different opinion and they advance a staging concept of psychosis, much like in cervical and other cancers.

Kelleher I, Keeley H, Corcoran P, Ramsay H, Wasserman C, Carli V, et al. Childhood trauma and psychosis in a prospective cohort study: cause, effect, and directionality. Am J Psychiatry 2013;170(7):734-741.

Zammit S, Kounali D, Cannon M, David AS, Gunnell D, Heron J, et al. Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. Am J Psychiatry 2013;170(7):742-750.

McGorry PD. The next stage for diagnosis: validity through utility. World Psychiatry 2013;12(3):213-214.

Cognitive Dysfunction at the Core of Schizophrenia

Drs. Kahn and Keefe (2013) provide a provocative rationale for considering cognitive underperformance as the most fundamental feature of schizophrenia. They highlight that focusing on cognition would lead to earlier diagnosis and intervention, arguing that it is this feature (rather than positive or negative symptoms) that predicts transition to psychosis among prodromal patients. They also draw attention to the lack of effective treatments for cognitive assessments, which are somewhat crude and nonspecific, being derived ultimately from tests on brain-injured patients decades ago. This is a thoughtful and provocative synthesis of this literature. In an accompanying editorial piece, Heckers (2013) asserts that these claims are overstated. His rebuttal is equally persuasive.

Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 2013;70(10):1107-1112.

Heckers S. What is the core of schizophrenia? JAMA Psychiatry 2013;70(10):1009-1010.

Recovery and Schizophrenia: We are Making Progress?

Jääskeläinen and colleagues (2013) conducted a meta-analysis of studies of recovery and schizophrenia. They identified 50 studies meeting inclusion criteria, ranging in years of publication from 1921 up until 2012. Some noteworthy studies—including the Vermont study and the Chicago longitudinal study—are missing from this analysis. The authors report that 13.5% of patients with schizophrenia met recovery criteria. This proportion did not appear to alter substantially over time.

Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull 2013;39(6):1296-1306.

*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.*