Clinical News … Congress awards … new antipsychotic drug developments and new clinical trials … RAISE … IOM and clinical trials data … precision medicine … double trouble … early detection …

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International Congress on Schizophrenia Research Co-Founders Honored

On March 31, 2015, Dr. Carol Tamminga and Dr. Chuck Schulz were honored for their lifetime contributions and commitment as co-leaders of the International Congress on Schizophrenia Research (ICOSR). Through their selfless leadership since 1987, ICOSR has grown to be the major conference for our field, attracting research clinicians and scientists. Drs. Schulz and Tamminga founded ICOSR in 1987. They have nurtured the field and their support of ICOSR—including its Young Investigator Awardees—has enabled a whole new generation of schizophrenia researchers to come through and contribute to our field. Our patients, their relatives, and ourselves as clinicians and researchers collectively owe Chuck and Carol a great debt of gratitude.

William K. Warren Awardee

ICOSR presents an award to a prominent schizophrenia researcher. This year's recipient was ***CS*** Editorial Board Member Dr. Anthony Grace, Distinguished Professor of Neuroscience, University of Pittsburgh. Dr. Grace has had a remarkably productive career studying the physiology of neurons, especially dopaminergic neurons and the effects of various psychotropic drugs. He gave an outstanding presentation and even included new data on the effects of synthetic cannabis that are relevant to the broader public debate on medical marijuana.

Update on Putative Antipsychotic Medications

Several of the putative antipsychotic drugs under development were covered in previous issues of ***CS***. Cariprazine was recently studied in a 26-week trial in comparison to risperidone in 461 patients with predominantly negative symptoms of schizophrenia. There were modestly better reductions in negative symptoms in the cariprazine group. In a 6-month, randomized, dose ranging, efficacy and tolerability study, ALKS 3831 was comparable to olanzapine in efficacy with less weight gain. Another putative antipsychotic—ITI-007—was shown in a Phase 2, placebo-controlled study in comparison with risperidone to demonstrate efficacy along with an encouraging adverse effect profile.

New Information on Brexpiprazole

Correll and colleagues (2015) provide an important study on brexpiprazole, a novel putative antipsychotic that has modulation at both serotonin and dopamine receptors. This pivotal placebo-controlled, 6-week study evaluated three doses of brexpiprazole. The study shows efficacy for the 2 mg/day and 4 mg/day doses of brexpiprazole. Side effect profile was quite favorable, especially for metabolic disturbance although only just over one third of patients enrolled were from the U.S. and most patients were from Eastern Europe or India, where baseline rates of obesity and metabolic disturbances are low. The 4 mg/day dose of brexpiprazole had more side effects. It will be of interest to better understand how this putative antipsychotic might fare with respect to other clinically available antipsychotics. Dosing profile and relapse prevention potential of this agent are other important considerations to determine in future trials.

Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. JAMA Psychiatry 2015 Apr 16: doi:10.1176/appi.ajp.2015.14101275. [Epub ahead of print]

New Information on Paliperidone Palmitate

Two recent trials (Fu et al., 2015; Berwaerts et al., 2015) provide complementary information on the one-month and three-month formulations of paliperidone palmitate. Among 334 patients with schizoaffective disorder who were initially stabilized and then randomized to a 15-month, double-blind, placebo-controlled, relapse-prevention phase, the once monthly version of paliperidone palmitate was associated with over 2 to 3 times lower risk of relapse than placebo and with improvements in functioning. Among over 500 patients with schizophrenia who had a 12-week, open-

label trial and then a double-blind, placebo-controlled phase of the 3-month formulation of paliperidone palmitate, there was significant effect of the 3-month injection on reducing relapse—such that an independent data safety monitoring board recommended stopping the study early. The U.S. Food and Drug Administration has reviewed the data as part of a New Drug Application and has approved this new drug for use in clinical practice. This approval was under a new "priority review" process aimed at speeding potential breakthroughs to clinical practice. Patients must first demonstrate tolerability to the one-month injection of paliperidone palmitate. Future head-to-head comparisons among injectable formulations of antipsychotics are warranted.

Fu DJ, Turkoz I, Simonson B, Walling DP, Schooler NR, Lindenmayer JP, et al. Paliperidone palmitate once-monthly reduces risk of relapse of psychotic, depressive, and manic symptoms and maintains functioning in a double-blind, randomized study of schizoaffective disorder. J Clin Psychiatry 2015;76(3):253-262.

Berwaerts J, Liu Y, Gopal S, Nuamah I, Xu H, Savutz A, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. JAMA Psychiatry 2015 Mar 29. doi: 10.1001/jamapsychiatry.2014.0241. [Epub ahead of print]

RAISE: New Treatment Information from Important Pragmatic Trial

Two of our ***CS*** Editorial Board members, Drs. Kane and Schooler, have now published some initial information on the RAISE ("Recovery After an Initial Schizophrenia Episode") study, a large pragmatic study of both medications and psychological treatment for patients in their first episode of psychosis (Kane et al., 2015; Correll et al., 2014). This important study was a large program conducted over 314 clinical sites in 21 U.S. states and involved over 400 first-episode psychosis patients (NCT01321177). The rationale and basic methodology is described by Kane and colleagues (Kane et al., 2015). In a related paper that focuses on the prevalence of metabolic problems in these patients, Correll and colleagues (2014) report that 48% of patients were obese, 15.4% were prediabetic (based upon hemoglobin A1c), with 2.9% of patients being diabetic. There were medicated-related differences, in that olanzapine treatment was associated with greater insulin resistance while quetiapine-treated patients had a higher triglyceride/high-density cholesterol ratio. The findings of early metabolic disturbances are consonant with earlier studies, although the greater extent of obesity and prediabetes is noteworthy.

Kane JM, Schooler NR, Marcy P, Correll CU, Brunette MF, Mueser KT, et al. The RAISE early treatment program for first-episode psychosis: background, rationale, and study design. J Clin Psychiatry 2015;76(3):240-246.

Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP Study. JAMA Psychiatry 2014;71(12):1350-1363.

Sharing Clinical Trials Data: New Institute of Medicine Report

The Institute of Medicine (IOM) recently released an important and provocative report (www.iom.edu/datasharing) on the status and desirability of sharing clinical trials data. Challenges identified include the infrastructure and platform(s) to support data sharing, technology related to such efforts, the need for an adequate and competent workforce, and the sustainability of effort to share data … with money inevitably being a consideration. The IOM Committee also opined on "the ground rules" for the appropriate interface and timing between primary investigations and secondary—post hoc—investigators. This report is a valuable read.

"Precision Medicine" Comes of Age?

Schizophrenia research—just like all other areas of medicine—needs to take stock of the potential (and future needs to realize that potential) of pharmacogenetics and preventative genetics to improve detection and treatment of illness on a broad, societal scale. This is the challenge set by President Barack Obama's declaration earlier this year that "precision medicine" has come of age. A provocative review by Ms. Rubin (2015) highlights the opportunities and challenges that lie ahead for precision medicine.

Rubin R. Precision medicine: the future or simply politics? JAMA 2015;313(11):1089-1091.

"Double Trouble" and Recovery Needs

Green and colleagues (2015) conducted a very interesting thematic analysis of recovery from comorbid substance abuse in 177 people with serious mental illness, most of whom suffered from either schizophrenia or related bipolar mood disorders. Patients sought recovery from their addiction through a variety of self-help/group addiction approaches as well as more formal programs. The authors identified three overall themes that included the need for education about drugs and alcohol, sobriety also having additional benefit in advancing the person's recovery from his underlying psychotic or mood disorder, and the effect of sobriety in building self-confidence and overall resilience. Flexibility in treatment approaches—including some tolerance of partial abstinence rather than an "all-or-nothing" philosophy—was also expressed. Peer support also takes on a particular relevance for this "double trouble" treatment group, wherein adherence to medication is foundational to recovery as opposed to primary addictions where medications are often received as a "crutch" or even a cop-out.

Green CA, Yarborough MT, Polen MR, Janoff SL, Yarborough BJ. Dual recovery among people with serious mental illnesses and substance problems: a qualitative analysis. J Dual Diagn 2015;11(1):33-41.

Early Detection and Intervention for People with Psychosis

For readers who are interested in learning more about the rapidly evolving areas of prodromal research, there is a terrific issue of *The Journal of Nervous and Mental Disease* (May 2015, Volume 203, Number 5) that is dedicated to this topic. Included here are superb overview articles on conversion to psychosis and on the development of prodromal services, as well as biomarker developments. The issue also includes formative personal accounts by Dr. Patrick McGorry and by Dr. Thomas McGlashan, two pioneers in the field of early intervention for psychosis.

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.*