Clinical News … SIRS, antipsychotics for refractory schizophrenia, the trajectory of cognitive decline in schizophrenia, head injury and psychosis risk, marijuana and psychosis risk …

Peter F. Buckley, MD
Editor-in-Chief

Another Successful SIRS (Schizophrenia International Research Society) Meeting

Congratulations to ***CS*** Board Member John Kane, MD, program co-chairs Anissa Abi-Dargham, MD and Jonathan Rabinowitz, PhD, and the entire program committee on a successful international schizophrenia meeting held April 5–9, 2014 in Florence, Italy. There were over 300 oral presentations and over 800 poster presentations spanning virtually every aspect of schizophrenia research. Congratulations also to ***CS*** board members Dr. Lynn DeLisi and Dr. Henry Nasrallah who both received Distinguished Service Awards. More information on presentations is available at www.schizophreniaconference.org, and more meeting coverage can be found later in this issue.

Update on Putative Novel Antipsychotics

Several of the putative antipsychotic drugs currently in development have been covered in prior issues of ***CS***. Cariprazine, a selective dopamine partial agonist under development by Forest Laboratories, Inc. and Gedeon Richter Plc, has also been studied in bipolar depression. In a 6-week Phase 2b trial, cariprazine was effective for treating depressive symptoms.

Another putative antipsychotic—ITI-007, under development by Intra-Cellular Therapies, Inc.—was shown to reduce psychotic symptoms with good tolerability during a recent 28-day study.

A trial of a novel formulation of paliperidone palmitate, which is a 3-month formulation, was terminated before conclusion due to a strong effect seen in reducing relapse. Johnson and Johnson is likely to submit, over the coming months, a New Drug Application (NDA) to the FDA.

A one-month formulation of injectable aripiprazole (Aripiprazole Lauroxil) was shown to be effective for psychosis in a placebo-controlled 30-month study. Alkermes is also likely to submit an NDA to the FDA over the coming months.

Lundbeck and Otsuka have also submitted a supplemental NDA to the FDA for acute use of Abilify Maintena®.

Long-Acting Antipsychotics have a Role in Treatment-Refractory Schizophrenia?

Long-acting injectable antipsychotics (LAIs) are considered by many to be underutilized and are most often confined to patients with recalcitrant nonadherence to medication. Their use in patients who are actually refractory to oral antipsychotic medications is less well understood and is addressed in a study by Meltzer and colleagues (2014). Over six months of treatment, patients with documented treatment-refractory schizophrenia received either 50 mg or 100 mg of LAI risperidone. Perhaps surprisingly, there was no difference between the high-dose LAI risperidone and the 50 mg dose. Overall, ≥20% of patients responded. These are interesting observations.

Meltzer HY, Lindenmayer JP, Kwentus J, Share DB, Johnson R, Jayathilake K. A six month randomized controlled trial of long acting injectable risperidone 50 and 100mg in treatment resistant schizophrenia. Schizophr Res 2014;154(1-3):14-22.

Naturalistic Study of Medications for Acute Agitation in Schizophrenia

The inpatient management of acute agitation in patients with schizophrenia is complicated and of recurrent concern to clinicians, especially now given ever-increasing federal focus on inappropriate "chemical restraint" and polypharmacy. This 5-day Swiss study compared the efficacy of haloperidol (10 mg/daily), risperidone (2 mg), and olanzapine (15 mg). Although the study had limitations, especially relatively small sample (43 patients completed the study), it found that all three drugs worked in reducing agitation … essentially to a similar extent among each drug.

Walther S, Moggi F, Horn H, Moskvitin K, Abderhalden C, Maier N, et al. Rapid tranquilization of severely agitated patients with schizophrenia spectrum disorders: a naturalistic, rater-blinded, randomized, controlled study with oral haloperidol, risperidone, and olanzapine. J Clin Psychopharmacol 2014;34(1):124-128.

Cannabis and Legalization of Medical Marijuana Use in U.S.—Implications for Addictions and Schizophrenia

Several U.S. states have passed legislation allowing the medical use of marijuana—most often in its cannabinoid deriva-

tive—to treat intractable forms of childhood epilepsy, some form of neurological spasticity, and cancer-related nausea. This direction is occurring while it is known from various epidemiological studies that cannabis use increases the risk of schizophrenia by about 4.5 times. A drug vigilance study by Wang and colleagues (2014) showed that the rate of exposure to marijuana in children aged 9 years and younger increased disproportionately between 2005 and 2011 in those states that had legalized marijuana. It remains to be determined how this legislative role will affect the rate and course of schizophrenia.

Wang GS, Roosevelt G, Le Lait MC, Martinez EM, Bucher-Bartelson B, Bronstein AC, et al. Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. Ann Emerg Med 2014;63(6):684-689.

Head Injury and Psychosis

As previously highlighted in ***CS***, head injury might account for about 1–2% of schizophrenia as a risk factor, although under current nosology such presentations are excluded from the diagnosis of schizophrenia and are viewed accordingly as "organic phenocopies." A Danish register study by Orlovska and colleagues (2014) showed a higher rate of schizophrenia (1.65 incidence rate) following head injury. This increase was seen more in people without a family history of schizophrenia too—interesting observations.

Orlovska S, Pedersen MS, Benros ME, Mortensen PB, Agerbo E, Nordentoft M. Head injury as risk factor for psychiatric disorders: a nationwide register-based follow-up study of 113,906 persons with head injury. Am J Psychiatry 2014;171(4):463-469.

The Trajectory of Cognitive Impairment in Schizophrenia: A "Growth Charting" Approach

In our last issue of ***CS***, we highlighted two articles (Kahn and Keefe, 2013; Heckers, 2013) debating the fundamental significance of cognitive impairment in people with schizophrenia. Additionally, "high-risk" prodromal and first-episode psychosis population studies complement and confirm the presence of cognitive deficits early on in the illness. Gur and colleagues (2014) bring another unique perspective to this issue by examining cognitive "growth chart" trajectories in a large cohort (n=18,344) of young adolescents between 18–21 years old, 9,138 of whom later had psychotic symptoms. Examining the prediction of cognitive performance egressed to chronological age across five aspects of cognition (social cognition, motor agility, executive function, memory, and "complex" cognition), the authors report that adolescents who had broader psychotic symptoms exhibited a greater lag in chronological-based cognitive performance compared to adolescents who had "milder" psychotic symptoms. The authors suggest that strategies that are targeted to detect this neurocognitive delay as early as possible might aid in the identification and care of people who are at risk for later florid psychoses.

Gur RC, Calkins ME, Satterthwaite TD, Ruparel K, Bilker WB, Moore TM, et al. Neurocognitive growth charting in psychosis spectrum youths. JAMA Psychiatry 2014;71(4):366-374.

Cognitive Decline Antedates Psychotic Symptoms in Schizophrenia?

In previous issues of ***CS***, we highlighted the controversy as to whether cognitive impairments are the most core characteristic of schizophrenia—an assumption first made by Emil Kraepelin. Another recent study addresses this topic. Meier and colleagues (2014) studied the cognitive trajectory from ages 7, 9, 11, 13, and 38 among healthy subjects, and individuals with either schizophrenia, depression, or mild cognitive impairments who were originally observed neuropsychologically in Dunedin, New Zealand. Individuals who later developed schizophrenia had more marked cognitive impairments which—for IQ, executive and motor functions—declined further over the subsequent assessments. Although this is an important observation from the seminal Dunedin study (that has yielded other excellent contributions to schizophrenia research), the cognitive signature is neither robust nor specific enough to be of any predictive value.

Meier MH, Caspi A, Reichenberg A, Keefe RS, Fisher HL, Harrington H, et al. Neuropsychological decline in schizophrenia from the premorbid to the postmorbid period: evidence from a population-representative longitudinal study. Am J Psychiatry 2014;171(11):91-101.

Cognitive Remediation Selectively Boosts Supported Employment Outcomes in Schizophrenia

Bell and colleagues (2014) provide an interesting one-year long analysis of the impact of cognitive remediation given in adjunctive mode among 175 patients with schizophrenia who were (already) enrolled in two individual and placement support (IPS) studies of supportive employment. Patients who had low functioning booster therapy through cognitive remediation were 2.5 times more likely to find employment, and they achieved 1.5 times more hours of work than patients who were receiving IPS alone. Beyond the obvious reasons why this study is provocative and important, a basic early concern about cognitive remediation was whether it would impact "real world outcomes" and not just result in better computer test scores (without functional gains). As previously highlighted in ***CS***, there is growing interest in cognitive remediation as a potential treatment modality for people with schizophrenia. More later.

Bell MD, Choi KH, Dyer C, Wexler BE. Benefits of cognitive remediation and supported employment for schizophrenia patients with poor community functioning. Psychiatr Serv 2014;65(4):469-475.

Adjunctive Ziprasidone in Clozapine Therapy

The known and burdensome side effect profile of clozapine—coupled with the now broader recognition that an appreciable number of patients (perhaps as high as 30%) might prove refractory to clozapine therapy—has fueled efforts to examine whether adding another antipsychotic might boost efficacy and/or alleviate side effects during clozapine therapy. Muscatello and colleagues (2014) tested this hypothesis in a 16-week placebo controlled trial of adjunctive ziprasidone in 40 patients whose clozapine therapy was already optimized. Ziprasidone-treated patients improved more in symptoms and cognitive performance. The combination was well tolerated and with no difference between both groups with respect to qtc prolongation.

Muscatello MR, Pandolfo G, Mico U, Lamberti Castronuovo E, Abenavoli E, Spina E, et al. Augmentation of clozapine with ziprasidone in refractory schizophrenia: a double-blind, placebo-controlled study. J Clin Psychopharmacol 2014;34(1):129-133.

*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.*