Clinical News … prodrome conversion to psychosis over time, immunological and neuroimaging putative biomarkers, metabolic syndrome and appropriate "best practices" with antipsychotic medications, compulsory treatment, mental health parity "comes of age" …

Peter F. Buckley, MD
Editor-in-Chief

Update on Putative New Antipsychotics

In previous issues of ***CS*** we have highlighted research on RP5063, a dopamine-serotonin system stabilizer with partial agonist effects at both receptor systems. The research is now moving from a Phase 2 to a Phase 3 clinical trial program. Research to date shows that RP5063 has a favorable adverse effect profile.

A 12-week, placebo-controlled trial has been completed on a long-acting form of aripiprazole—aripiprazole lauroxil (previously cited as ALKS 9070 in earlier ***CS*** reports). This formulation is a once-monthly injectable form of aripiprazole. Results of this study are expected during 2014.

A new putative drug that inhibits phosphodiesterase 10 (OMS824, being developed by Omeros Corporation) is now being studied in a Phase 2 clinical trial in patients with schizophrenia. This is an innovative approach that is consonant with evidence of phospholipid abnormalities in schizophrenia.

In an earlier issue of ***CS***, Dr. Leslie Citrome provided us with a comprehensive review of lurasidone for schizophrenia, including synthesis of data explaining number-needed-to-treat and number-needed-to-harm with this new antipsychotic. Two other recent studies by Loebel and colleagues (2013) describe pivotal studies of lurasidone for bipolar disorder. Lurasidone is now approved by the FDA for bipolar disorder.

Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J, Calabrese JR. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of Bipolar I Depression: A randomized, double-blind, placebo-controlled study. Am J Psychiatry 2013 Oct 30; doi:10.1176/appi.ajp.2013.13070985. [Epub ahead of print.]

Loebel A, Cucchiaro J, Silva R, Kroger H, Hsu J, Sarma K, et al. Lurasidone monotherapy in the treatment of Bipolar I Depression: A randomized, double-blind, placebo-controlled study. Am J Psychiatry 2013 Oct 30; doi:10.1176/appi.ajp.2013.13070984. [Epub ahead of print.]

Two-Year Outcomes of People at High Risk of Psychosis

After much debate (Fusar-Poli et al., 2012), attenuated psychosis syndrome made its way into *DSM-5*. In a recent issue of ***CS*** we reviewed an important Fusar-Poli et al. review (**Clinical News**, Volume 7, No. 2) of high-risk populations that showed transition to psychosis risks of 18% at 6 months, 22% at 1 year, 29% at 2 years, 32% at 3 years, and 36% thereafter. In this new meta-analysis of 23 studies (Fusar-Poli et al., 2013), among the patients who became psychotic over time, 73% developed schizophrenia psychoses, while only 11% developed affective psychoses. Symptoms at baseline strongly predicted subsequent transition to a schizophrenia psychosis. These results are not surprising, but they add substance and actual data points to explaining the relationship between high-risk states for psychosis and later schizophrenia.

Fusar-Poli P, Yung AR. Should attenuated psychosis syndrome be included in the DSM-5? Lancet 2012;379(9816):591-592.

Fusar-Poli P, Bechdolf A, Taylor J, Bonoldi I, Carpenter WT, Yung AR, et al. At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. Schizophr Bull 2013;39(4):923-932.

Australian High-Risk Prodrome Study: 10-Year Conversion Rate to Psychosis

In previous issues of ***CS*** we have highlighted important studies of prodrome individuals, as well as the conversion rate to psychosis over various time points, including a recent major meta-analysis by Fusar-Poli and colleagues (2013) cited above. Nelson and colleagues (2013) present 10-year outcomes from the Australian high-risk samples, wherein 114 of 416 subjects developed a florid psychotic illness. The cumulative conversion rate at 10 years was 34.9%. This is important, as this study best exemplified that the risk of conversion is highest in the first two years following presentation to healthcare services.

Nelson B, Yuen HP, Wood SJ, Lin A, Spiliotacopoulos D, Burxner A, et al. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the Pace 400 study. JAMA Psychiatry 2013;70(8):793-802.

Elevated Cortisol in High-Risk Psychosis Individuals

Walker and colleagues (2013) present baseline cortisol levels and psychopathology associations from the longitudinal collaborative study involving eight institutions, the North American Prodrome Longitudinal Study (NAPLS). In this initial analysis of NAPLS data involving 256 high-risk subjects and 141 control subjects, the high-risk subjects had elevated cortisol, and this was most pronounced among individuals who went on to exhibit florid psychotic symptoms. These results replicated—and now extend to the very earliest stages of illness—findings of raised cortisol in first-episode psychosis and glucocorticoid receptor downregulation.

These effects appear independent of antipsychotic medications, an important observation since these drugs are well known to exert powerful effects upon the hypothalamic-pituitary-adrenal function.

Walker EF, Trotman HD, Pearce BD, Addington J, Cadenhead KS, Cornblatt BA, et al. Cortisol levels and risk for psychosis: initial findings from the North American Prodrome Longitudinal Study. Biol Psychiatry 2013:74(6):410-417.

Immunological Dysfunction and Schizophrenia: New Danish Data

We have highlighted in previous issues of ***CS*** a conference of new data suggesting a robust relationship between immunological disorders, heightened risk for prenatal infections, and risk of schizophrenia. Benrós and colleagues (2013) provide interesting additional perspectives, drawn from a Danish database comprised of over 39,000 patients with schizophrenia/schizophrenia-like psychoses and some 142,000 patients with established autoimmune diseases. Autoimmune diseases were present in 3.6% of patients with schizophrenia, and 3.1% of patients with autoimmune diseases had a positive family history of schizophrenia. While this study cannot directly address causative or mediating factors (e.g., health status, infections, sociocultural environment), it nevertheless points to a robust association between immune dysfunction and schizophrenia.

Benrós ME, Pedersen MG, Rasmussen H, Eaton WW, Nordentoft M, Mortensen PB. A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. Am J Psychiatry 2013 Oct 16. doi: 10.1176/appi.ajp.2013.13010086. [Epub ahead of print.]

Is C-Reactive Protein a Kind of "ESR" for Schizophrenia?

In previous issues of ***CS*** we have highlighted a range of immunological abnormalities that are associated with schizophrenia. In this Danish national use registry study, Wium-Andersen and colleagues (2013) report a 6- to 11-fold rise in C-reactive protein (CRP) among patients with schizophrenia. Elevated CRP is a common and nonspecific marker of inflammation, perhaps much in the same way as elevated "ESR" is a nonspecific indicator of ill health. CRP is raised in a host of conditions, including common comorbidities in schizophrenia such as alcoholism and hypercholesterolemia. This study took these confounds into account; however, the study focused on patients whose illness began after 20 years of age.

Wium-Andersen MK, Orsted DD, Nordestgaard BG. Elevated C-reactive protein associated with late- and very-late-onset schizophrenia in the general population: a prospective study. Schizophr Bull 2013 Aug 31. [Epub ahead of print.]

Brain Imaging Analysis Does *Not* Affirm Clinical Utility of Imaging Screening for Schizophrenia

This is an interesting analysis from the Dutch first episode of psychosis study among 656 patients and over 700 healthy control subjects. Radiological reports were assessed as normal, not clinically relevant, clinically insignificant abnormality, or clinically relevant abnormality. Essentially, the main extent of scans—74%—was recorded as normal between patients and controls. Similarly, 11% of both groups showed clinically relevant abnormalities: atrophy, benign tumors, corpus callosum agenesis, and pituitary abnormalities, but these did not alter the clinical scenario. These findings are provocative and do not endorse the routine use of brain imaging as a screening tool in patients presenting with first-episode psychosis; nevertheless, a negative scan gives reassurance to patients and especially family members at a key time of great concern.

Sommer IE, de Kort GA, Meijering AL, Dazzan P, Hulshoff Pol HE, Kahn RS, et al. How frequent are radiological abnormalities in patients with psychosis? A review of 1379 MRI scans. Schizophr Bull 2013;39(4):815-819.

Similar Rates and Progression of Metabolic Syndrome over Time Between Patients with Bipolar Disorder and Schizophrenia

Dr. McEvoy and several of our other ***CS*** editorial board members have reported high rates of metabolic syndrome (MS)—with an average cross-sectional evaluation rate in studies of 40 to 50%—among patients with schizophrenia. Subsequent research seeks to determine the host vulnerability of MS. In this interesting longitudinal study from India assessing MS cross-sectionally and thereafter at 6 months (Malhotra et al., 2013), 46% of patients with bipolar disorder and 32% of patients with schizophrenia met criteria for MS. Interestingly, both groups showed a modest increase in MS over a 6-month period: 8% for bipolar patients and 9.4% among schizophrenia patients.

Malhotra N, Kulhara P, Chakrabarti S, Grover S. A prospective, longitudinal study of metabolic syndrome in patients with bipolar disorder and schizophrenia. J Affect Disord 2013;150(2):653-658.

Metformin Used for Weight Loss in Patients with Schizophrenia

The Schizophrenia Clinical Trials Network (STN) published an important study evaluating the impact of 16 weeks of metformin (versus placebo) add-on to antipsychotic therapy alongside diet and exercise counseling involving 148 patients with chronic schizophrenia or schizoaffective

disorder. The effects were modest, with a mean 3 kg weight loss in the metformin patients compared with a 1 kg loss in the placebo-controlled patients. There were no significant side effects associated with metformin. This study follows on another earlier Chinese study of metformin in first-episode psychosis patients, which showed a more pronounced benefit in that patient group.

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.

Wu RR, Jin H, Gao K, Twamley EW, Ou JJ, Shao P, et al. Metformin for treatment of antipsychotic-induced amenorrhea and weight gain in women with first-episode schizophrenia: a double-blind, randomized, placebo-controlled study. Am J Psychiatry 2012;169(8):813-821.

Two Major British Studies on Compulsory Treatments for People with Schizophrenia

Two important papers appeared recently in the *Lancet*. In a study of what appears to be the British equivalent of "Advanced Directions," Thornicroft and colleagues (2013) reported on a randomized, effectiveness clinical trial—CRIMSON (CRisis plan IMpact: Subjective and Objective coercion and eNgagement)—of Joint Crisis Plans (JCP) and treatment-as-usual among 569 patients with schizophrenia. Sixty-four mental health teams at four public systems of care ("Trusts") participated. Contrary to two earlier studies of JCP and to the study hypotheses, there was no reduction in the use of compulsory hospitalizations over the 18 months of follow-up.

In another study, Burns and colleagues (2013) conducted a randomized trial of outpatient commitment versus routine care in 336 patients with schizophrenia. The number of patients readmitted over the 12-month follow-up did not differ between the two groups. This is an important and likely contentious finding given the introduction of community treatment orders in England in 2008.

Thornicroft G, Farrelly S, Szmukler G, Birchwood M, Waheed W, Flach C, et al. Clinical outcomes of Joint Crisis Plans to reduce compulsory treatment for people with psychosis: a randomised controlled trial. Lancet 2013;381:1634-1641.

Burns T, Rugkasa J, Molodynski A, Dawson J, Yeeles K, Vazquez-Montes M, et al. Community treatment orders for patients with psychosis (OCTET): a randomised controlled trial. Lancet 2013;381(9878):1627-1633.

American Psychiatric Association "Weighs In" on Appropriate Use of Antipsychotic Medications

In a laudable effort to advance best practices for the use of antipsychotic medications, the American Psychiatric Association has highlighted five key aspects of prescribing these drugs. The report highlights the need for ongoing monitoring of adverse effect, the judicious use of antipsychotics in combination, and avoiding the use of antipsychotics as first-time treatment for behavioral symptoms of dementia, for insomnia, or for nonpsychotic childhood conditions.

A Clever Way to Try to Enhance Medication Adherence

Dr. Velligan and colleagues (2013) present a very nice study comparing treatment-as-usual with electronic monitoring of medication adherence and with a specific home-based adherence intensive program called PharmCAT. Medication adherence was better in both active interventions than in treatment-as-usual although, surprisingly, this was not associated with improvements in symptoms over the treatment-as-usual group. There were some baseline differences between the two groups, as well as perceived relatively high rates of medication adherence that may have mitigated finding an advantage from PharmCAT, which sounds—at least instinctively—as a great clinical approach.

Velligan D, Mintz J, Maples N, Xueying L, Gajewski S, Carr H, et al. A randomized trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia. Schizophr Bull 2013;39(5):999-1007.

U.S. Mental Health Parity Emphasized in Healthcare Reform

The U.S. Department of Health & Human Services Director, Ms. Kathleen Sebelius, recently announced specific efforts as part of healthcare reform to implement and realize mental health parity. This is an important development in federal policy. It also applies to both mental health and addiction disorders. Given the high prevalence of both physical and psychiatric (especially substance abuse) comorbidities among people with schizophrenia, this is a development of keen interest to clinicians who work within the public mental health system … more later …

*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.*