Clinical News … new drug updates, *DSM-5*, brain initiative, urinary tract infections, prodromal research, stigma and global outreach …

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New Drug Updates

Phase 1 results have become available from a study of ALKS 3831, a novel compound previously described in ***CS*** that is under investigation for the treatment of schizophrenia. The compound is a combination of an opioid modulator and olanzapine. In a 3-week study comparing ALKS 3831 directly with olanzapine among 106 normal subjects, individuals had less weight gain on this investigational agent. This finding builds upon the proposition that this drug might be more favorable for the metabolic side effects of antipsychotics. Additionally, as a potent mu-opioid antagonist, it is considered that this compound may be beneficial in schizophrenia patients with comorbid substance abuse. This has not yet been tested. The next stage of investigation is a planned Phase 2 study.

Building upon the studies that led to the FDA-approved indication for psychosis, two studies (Prevail 1, an adjunctive therapy trial; and, Prevail 2, a monotherapy trial) recently presented show benefits for lurasidone in bipolar depression. This efficacy profile was complemented by a favorable metabolic profile. The FDA has now approved lurasidone as monotherapy and adjunctive therapy with either lithium or valproate to treat adult patients with major depressive episodes associated with bipolar I disorder (bipolar depression).

DSM-5 Launched: Implications for Schizophrenia

Dr. Rajiv Tandon did a masterful job in the prior issue of ***CS*** in describing for our readers the changes in the *DSM-5* that pertain to the diagnosing of schizophrenia. Major changes include the removal of schizophrenia subtypes, the inclusion of psychosis risk syndrome and further refinement and inclusion of schizoaffective disorder. Since these changes are more conceptually driven than based upon new neurobiologically driven perspectives, the arrival of *DSM-5* has already sparked off considerable debate regarding the "state-of-play" of psychiatry. The absence of biomarkers for mental illnesses—including most conspicuously for schizophrenia—is a real drawback in our current nosology. This has also drawn the distinctions between what is happening in the clinical world versus what is still very much "in the lab." For additional discussion of *DSM-5* and schizophrenia, see the ICOSR meeting highlights article on page 68.

BRAIN Initiative: Opportunity for Schizophrenia Research

President Obama and NIH Director Dr. Francis Collins announced a collective, federally led new scientific effort to better understand and find more effective treatments for brain disorders, including schizophrenia. BRAIN—The Brain Research through Advancing Innovative Neurotechnologies Initiative—will be funded through multiple U.S. federal agencies. Details on priorities, funding opportunities, and the granting mechanism(s) are eagerly awaited.

Patients with Schizophrenia have Poorer Surgical Outcomes

This is a study of reimbursement claims data from Taiwan's national healthcare insurance, which has almost everybody enrolled among Taiwan's 22.6 million population. The results are very much in line with a now larger and convergent literature showing that people with schizophrenia die prematurely. There are also other studies showing poorer outcomes for medical conditions. Surgical outcomes were compared between almost 9,000 patients with schizophrenia and almost 36,000 surgical patients without mental disorders. Patients with schizophrenia in this study had higher postoperative complications for pneumonia, septicemia, bleeding, stroke, and renal complications. These effects result also in a 3-times higher 30-day postoperative mortality rate. The study is informative. However, clinical details are not provided and so it is difficult to tease out the reasons for the effects observed in this epidemiological study. Nevertheless, this study highlights the need for closer attention to patients with schizophrenia during the postoperative period of care.

Liao CC, Shen WW, Chang CC, Chang H, Chen TL. Surgical adverse outcomes in patients with schizophrenia: a population-based study. Ann Surg 2013;257(3):433-438.

New *CS* Editorial Board Member Publishes Important Observational Study

Our newest ***CS*** Editorial Board Member, Dr. Brian Miller, has shown that patients with schizophrenia who relapse are also far more likely than stable outpatients to have a concomitant urinary tract infection (UTI). At first glance, the relationship between psychotic relapse and UTI

seems obscure, although it may be a sign of more widespread immunological dysfunction. We have highlighted in prior issues of ***CS*** a growing literature implicating immune dysfunction in schizophrenia. Welcome aboard Brian and congratulations on this study!

Miller BJ, Graham KL, Bodenheimer CM, Culpepper NH, Waller JL, Buckley PF. A prevalence study of urinary tract infections in acute relapse of schizophrenia. J Clin Psychiatry 2013;74(3):271-277.

Smoking and Cognition in Schizophrenia

There is an extraordinary high prevalence of smoking among patients with schizophrenia. This is in part due to genetic findings related to nicotine receptor gene abnormality on chromosome 15 and is thought to be of etiological significance. Thus, the implications of this etiopathological observation for cognition and symptomatic management is particularly relevant. A recent study from Canada from Morisano and colleagues (2013) addresses this issue. Although this study has small sample sizes in each individual group of bipolar, major depression, and schizophrenia patients, the results are interesting in that there are selective differences in cognition in patients with schizophrenia who are smokers. This group has better performance on selected neurocognitive tests, although it is important to note that the study was cross sectional in design. Also, it pooled data across three separate studies. Nevertheless, these data report neurocognitive enhancement among schizophrenia patients who smoke, though this effect is not observed in patients with mood disorders who smoked.

Morisano D, Wing VC, Sacco KA, Arenovich T, George TP. Effects of tobacco smoking on neuropsychological function in schizophrenia in comparison to other psychiatric disorders and nonpsychiatric controls. Am J Addict 2013;22(1):46-53.

German Study of Cognitive Behavioral Therapy: Inclusion in Routine Practice

A German study by Lincoln and colleagues (2012) takes advantage of the availability of both clinical psychologists and cognitive behavioral therapy (CBT) for psychosis for patients with psychoses who are able to access this public system. The main drawback of this study is that there was not a "true" control group—the control was a "waiting list" design and so you can't really control for time effects. This is most relevant here because the effect sizes in this study are remarkably large—larger than two other recent effectiveness studies. It is important because it is more of a "pragmatic" trial than the several other randomized controlled clinical trials that showed efficacy of cognitive behavioral therapy for patients with schizophrenia. The other noteworthy aspect of this study is that in Germany, this approach was "mainstreamed" into clinical practice within its public mental health system.

Lincoln TM, Ziegler M, Mehl S, Kesting ML, Lullmann E, Westermann S, et al. Moving from efficacy to effectiveness in cognitive behavioral therapy for psychosis: a randomized clinical practice trial. J Consult Clin Psychol 2012;80(4):674-686.

N-Acetylcysteine and Oxidative Stress in Schizophrenia

There is a long—and at times conflicting—scientific literature implicating oxidative stress in the pathophysiology of schizophrenia. Cabungcal and colleagues (2013) have taken a novel approach to this issue, wherein they have examined the redox environment in parvalbumin interneurons in knockout mice which have impaired synthesis of glutathione. Glutathione is an antioxidant and N-acetylcysteine (NAC) is its cogener. Parvalbumin interneurons are considered to be particularly sensitive to oxidative stress. Interestingly, the authors found that glutathione deficiency impairs the growth of parvalbumin interneurons. Moreover, when NAC is provided, these changes are reversed. These basic science findings are compelling and of particular interest in light of an earlier clinical trial in patients with schizophrenia, which showed that NAC was an effective (Berk et al., 2008) adjuvant in schizophrenia. Additionally, there is interest in examining antioxidant agents as a potential preventative strategy for individuals at high risk of psychosis.

Cabungcal JH, Steullet P, Kraftsik R, Cuenod M, Do KQ. Early-life insults impair parvalbumin interneurons via oxidative stress: reversal by N-acetylcysteine. Biol Psychiatry 2013;73(6):574-582.

Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetylcysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. Biol Psychiatry 2008;64(5):361-368.

State-of-the-Art Review of Prodromal Research

As highlighted in previous ***CS*** articles, there has been a prodigious growth in the study of "patients" who present with clinical attributes of "high risk" for transition to psychosis. A recent review by Fusar-Poli and colleagues (2013)—written by a veritable "Who's Who" of prodromal research and including our ***CS*** Editorial Board Member Dr. Matcheri Keshavan—delivers on its title and covers remarkably well some twenty years of ever sophisticated research in the now established field of psychosis high risk. The article and the topic are both particularly timely given the earlier robust (and at times almost acrimonious) debate that preceded the inclusion of the psychosis risk syndrome as a new diagnostic category in *DSM-5*.

The authors here chronicle the course and risks of transition to frank psychosis, which has been estimated in high-risk patients upon presentation to be a transition rate

of some 18% after 6 months, 22% by 1 year, 29% by 2 years, 32% by 3 years, and approximately 36% after 3 years. These figures suggest a well-defined, yet not absolute, risk and they propel to the forefront the notions of prediction and early intervention. Possible predictors from the North American Prodromal Study include five parameters: genetic risk markers, unusual thought contents, extreme paranoia, more impaired social functioning, and substance abuse. The authors review imaging findings. These largely resemble neuroanatomical and function deficits that are seen in patients with first-episode psychosis, although the changes are considerably more attenuated. Treatment studies are reviewed with the conclusion that "the jury is still out" on the extent and type of interventions that can really make a difference. This is a fabulous overview of this field.

Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rossler A, Schultze-Lutter F, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 2013;70(1):107-120.

Understanding the Role of Ethnicity in Interactions with Personal Risk and Environmental Stresses Implicated in Schizophrenia

This is a thoughtful commentary that appeared in *The British Journal of Psychiatry* that explores the relationships between ethnic minority status, stress, and the development of psychotic symptoms like paranoia or hallucinations. The relationships are complex and not just a direct effect of either poverty or social class per se. Dr. van Os (a leader in this interface between genes and environment) proposes that the interaction of minority cultural support and personal experiences influences appreciation of experiences as either internally or externally driven perceptual distortion. Additionally, he proposes that these influences might explain the added vulnerability to psychosis among minority ethnic groups. This work is provocative, although it is also fraught with many methodological confounds—not the least of which is the risk of (covert) substance abuse which could explain the findings in these kinds of studies.

van Os J. Psychotic experiences: disadvantaged and different from the norm. Br J Psychiatry 2012;201(4):258-259.

Google Seeking is Seasonal: Implications for Schizophrenia Research and Treatment?

It is well known that there is about a 5% excess of people with schizophrenia (over and above normal seasonal birth variations) born in the first 3 months of the year. This is considered an etiological clue and our colleagues like ***CS*** Editorial Board Member Dr. John McGrath have followed up on aspects of this (e.g., vitamin D deficiency). To this end, this "fun"" report shows also a seasonality among the lay public regarding looking up on Google about mental illnesses, including schizophrenia. This was most evident for eating disorders. There was a 14% difference across seasons in the U.S. and an 11% difference reported for Australia.

Ayers JW, Althouse BM, Allem JP, Rosenquist JN, Ford DE. Seasonality in seeking mental health information on Google. Am J Prev Med 2013;44(5):520-525.

Stigma and Schizophrenia: Experiences through Families

As we have highlighted in prior issues of ***CS***, stigma is a major concern for mental health in general and for schizophrenia in particular. However, stigma is not uniformly distributed across psychiatric patients. A study by Broussard and colleagues (2012) provides a detailed evaluation of patients and their families from Atlanta, Georgia, predominantly focusing on African-American patients. High stigma is associated with a family history of psychiatric treatment while, conversely, low stigma is associated with personal psychiatric history and high personal income. The implications of this study are that we should consider both general and specific anti-stigma strategies in support of patients with schizophrenia.

Broussard B, Goulding SM, Talley CL, Compton MT. Social distance and stigma toward individuals with schizophrenia: findings in an urban, African-American community sample. J Nerv Ment Dis 2012;200(11):935-940.

Stigma and Schizophrenia: A Global Issue and with Similar Profile for Schizophrenia and Depression

Pescosolido and colleagues (2013) studied awareness and stigma of mental illness across 16 countries, based upon feedback and questions on two vignettes, which encompassed over 6,500 respondents. The results confirmed broadly the public appreciation of mental illnesses as brain disorders, with largely similar responses with regard to schizophrenia and depression although it was less specific in assignment as a disorder. The authors concluded that, to an extent, the public now has a good fundamental knowledge basis about mental illness and stigma. It is recommended, therefore, that efforts to reduce bias and stigma should be more targeted to promote inclusiveness and not simply be focused on education.

Pescosolido BA, Medina TR, Martin JK, Long JS. The "backbone" of stigma: identifying the global core of public prejudice associated with mental illness. Am J Public Health 2013;103(5):853-860.

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.*