Peter F. Buckley, MD
Editor-in-Chief

Are Prodromal Criteria of Psychosis Valid?

As you know, *DSM-5* is considering the inclusion of prodromal psychotic syndrome as a distinct category. This has fueled much debate regarding the accuracy of these prodromal symptoms in predicting schizophrenia. Predicting schizophrenia earlier could lead to early intervention with the hope that this would avert a "full-blown" psychosis and/or ameliorate the course of illness. On the other hand, this could heighten stigma, raise concerns about schizophrenia that are not (yet) warranted, and potentially expose people to unwarranted trials of antipsychotic medications. A recent meta-analysis by Chuma and Mahadun (2011) reports that the sensitivity and specificity of ultra-high risk criteria was 0.81 and 0.67, respectively. Unfortunately, this analysis is based only on a handful of studies of ultra-high risk groups. On the other hand, the sensitivity and specificity for basic criteria for prodromal status was expressed at 0.97 and 0.59. The accuracy of these basic criteria is below expectations for clinical viability, so that "picking up" schizophrenia before it's schizophrenia remains very challenging.

Chuma J, Mahadun P. Predicting the development of schizophrenia in high-risk populations: systematic review of the predictive validity of prodromal criteria. Br J Psychiatry 2011;199(5):361-366.

First-Episode Schizophrenia and Traumatic Episodes

Posttraumatic stress disorder (PTSD) is common among patients with other psychiatric disorders and recent studies also suggested that patients with schizophrenia experience an excess of traumatic life events. To that end, Dr. Schafer and colleagues (2011) assessed traumatic events by interviews and through the Impact of Event Scale (IES) in 38 patients with first-episode psychosis and controls. The study group sample is drawn from the British AESOP study (Aetiology and Ethnicity of Schizophrenia and Other Psychoses), which has produced important findings on the trajectory of early psychosis. The authors found that there were similar rates of reported traumas among patients and controls, and that the IES was a robust scale. Previous studies have shown an excess in patients with schizophrenia of childhood abuse, sexual abuse, physical abuse and related events. It is also true, of course, that patients with schizophrenia are more likely the victims of violence rather than the perpetrators. This is an important area of clinical research that could impact clinical care and that resonates well with recovery-based principles of care.

Schafer I, Morgan C, Demjaha A, Morgan K, Dazzan P, Fearon P, et al. Assessment of posttraumatic symptoms in patients with first-episode psychosis. J Nerv Ment Dis 2011;199(11):896-898.

Study Distinguishes Early Brain Changes between Schizophrenia and Bipolar Disorder

The Child and Adolescent First-Episode Psychosis Study (CAFEPS) is headed up by ***CS*** Editorial Board member Celso Arango, MD, PhD. A recent report from this Spanish multicenter, naturalistic, two-year, follow-up of first-episode psychosis patients who thereafter received a diagnosis of schizophrenia (n=25), bipolar disorder (n=16), or other psychoses found progressive brain changes. In contrast to other cross-sectional comparative studies, these changes were confined to the schizophrenia group alone and were significant when compared with the pattern of brain changes over time among normal adolescents (n=70). This is an important MRI study. Surprisingly, the bipolar group did not distinguish from either normal controls or the patients with schizophrenia. Additionally, the authors reported that frontal gray matter loss (in the left hemisphere) was associated with the poorer outcome of prolonged hospitalization. Medications did not account for these changes. The results complement earlier studies, as well as clinical experience, in highlighting that childhood/adolescent-onset schizophrenia is a more severe form of illness.

Arango C, Rapado-Castro M, Reig S, Castro-Fornieles J, Gonzalez-Pinto A, Otero S, et al. Progressive brain changes in children and adolescents with first-episode psychosis. Arch Gen Psychiatry 2012;69(1):16-26.

Petra Rattue. (2012, January 4). "Brain Changes Among Adolescents Diagnosed With Schizophrenia." Medical News Today. Retrieved from http://www.medicalnewstoday.com/articles/239915.php.

Neural Stem Cells and Schizophrenia

Another ***CS*** Editorial Board member, Dr. John McGrath and his colleagues recently published a very interesting report of olfactory (neural) cell line excessive proliferation in a small sample (n=9) of patients with schizophrenia (Fan et al., 2012). Although it is possible that other factors like smoking status or the presence of antipsychotic medications potentially could have influenced these results, it is noteworthy that the cell line derived from nasal epithelium of schizophrenia patients multiplied itself 1.7 times faster than the line of normal controls. The cell doubling time for patients was 70% that of cells in control subjects. Cells from schizophrenia patients were also arrested at different rates in the cell-cycle, although overall the extent of apoptosis was

similar in both groups. This is a very elegant study, and we are likely to see more of this type of research over the coming years.

Fan Y, Abrahamsen G, McGrath JJ, Mackay-Sim A. Altered cell cycle dynamics in schizophrenia. Biol Psychiatry 2012;71(2):129-135.

Elsevier. (2012, January 27). "A Path To The Brain Through The Nose Aids Schizophrenia Research." Medical News Today. Retrieved from http://www.medicalnewstoday.com/articles/240796.php.

New Information about Inhaled Loxapine for Schizophrenia

In previous issues of ***CS***, we highlighted both the pharmacology, delivery route, and some initial findings about Staccato loxapine—an inhaled formulation of the "classical," first-generation antipsychotic loxapine. However, loxapine may be not so "classical" as Dr. Kapur and colleagues previously surmised that loxapine's binding to dopamine and serotonin receptors resembles that of risperidone. The U.S. Food and Drug Administration (FDA) has extended its time in studying the data regarding Staccato loxapine. A new study published by Michael Allen and colleagues (2011) shows a robust effect of both 5 mg and 10 mg of inhaled loxapine upon agitation measures in 129 acutely psychotic patients. The most common side effects were sedation and dysgeusia. The study resembles the methodology of previous studies examining intramuscular treatments with second-generation antipsychotic medications within a two-hour time frame using multiple measures of agitation.

Allen MH, Feifel D, Lesem MD, Zimbroff DL, Ross R, Munzar P, et al. Efficacy and safety of loxapine for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2011;72(10):1313-1321.

New Model to Explain Antipsychotic-Induced Metabolic Disturbances?

A substantial paper by Cohen and colleagues (2012) proposes a new model based upon an analysis of a gene expression database. The authors propose complex effects that target directly insulin metabolism. In a series of studies, Cohen and colleagues found that both first- and second-generation antipsychotics modulate the insulin promoter gene, apparently through activation of SMAD3. This regulatory protein SMAD3 affects the main pathway of insulin synthesis through the transforming growth factor beta (TGFβ) pathway. This is complex, yet the data presented are compelling. Interestingly, the only two antipsychotics studied that did not activate SMAD3 were molindone and ziprasidone—two drugs that are generally appreciated as having a low liability for weight gain and metabolic disturbances. The results were also confirmed in a second gene expression database derived from a post mortem brain study in schizophrenia.

Cohen T, Sundaresh S, Levine F. Antipsychotics activate the TGFβ pathway effector SMAD3. Mol Psychiatry 2012 Jan 31. doi: 10.1038/mp.2011.186. [Epub ahead of print]

Sanford-Burnham Medical Research Institute. (2012, February 3). "Metabolic Side Effects Such As Obesity And Diabetes Caused By Antipsychotic Medications." Medical News Today. Retrieved from http://www.medicalnewstoday.com/releases/241084.php.

Continued Information Concerning "Off-Label" Use of Antipsychotic Medications

In previous issues of ***CS*** we have described other studies of the prevalence and use of antipsychotic medications beyond FDA indications for psychosis and mood disorders. The *British Medical Journal* has just posted online a study from Harvard (Huybrechts et al., 2012) examining the mortality among 75,000 patients in nursing homes who have dementia and had received antipsychotic medications. Compared with risperidone, haloperidol was associated with the greatest risk of premature death (hazard ratio of 2.07), while quetiapine was least associated with death (hazard ratio of 0.81). These data are important and further inform the FDA "black box" warning on mortality risk with antipsychotics when used for managing behavioral disturbance in patients with dementia. An accompanying editorial by McCleery and Fox (2012) suggests that we must look for local, non-medication service solutions for managing behavioral problems in dementia. This continues as a contentious area, especially given the absence of any primary and clearly superior treatment options for these distressing features.

Turning to the use of antipsychotic medications in another FDA non-approved circumstance—that of anxiety disorders—Comer and colleagues (2011) noted that antipsychotic use for anxiety disorders when assessed for outpatient visits for anxiety has risen from 6.9% in the 1990's (1996–1999) to a rate of 14.5% in the mid-2000's (2004–2007). The off-label use of antipsychotic medications in anxiety disorders is a concern, especially given the availability of current treatments and given the side effect profile of antipsychotics.

Huybrechts KF, Gerhard T, Crystal S, Olfson M, Avorn J, Levin R, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ 2012 Feb 23;344:e977. doi: 10.1136/bmj.e977.

McCleery J, Fox R. Antipsychotic prescribing in nursing homes. BMJ 2012 Feb 23;344:e1093. doi: 10.1136/bmj.e1093.

Comer JS, Mojtabai R, Olfson M. National trends in the antipsychotic treatment of psychiatric outpatients with anxiety disorders. Am J Psychiatry 2011;168(10):1057-1065.

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.*