Clinical News … putative antipsychotics … Kraepelin and psychosis continuum … obsessive-compulsive disorder and schizophrenia … psychosis trajectory … Toxoplasmosis gondii exposure and cognitive impairment … clozapine and polypharmacology …

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Update on New Antipsychotics

There has been forward movement on the development of several putative antipsychotic drugs. Gedeon Richter plc and Actavis plc recently reported results from a 97-week, Phase 3 relapse-prevention trial of cariprazine, a dopamine D3/D2 partial agonist, in 200 patients with schizophrenia. In comparison to placebo (47.5%), only 24.8% of cariprazine-treated patients experienced a relapse. No major side effects were observed, beyond extrapyramidal side effects and nosopharyngitis.

Alkermes plc recently reported on a 12-week study of ALKS 3831—a samidorphan mu-opioid antagonist-olanzapine combination that was previously highlighted in ***Clinical News***—in 300 patients with schizophrenia. While overall efficacy between ALKS 3831 and olanzapine was comparable, the investigational drug had less weight gain than olanzapine alone. As also previously discussed in ***Clinical News***, the U.S. Food and Drug Administration (FDA) is currently reviewing data for Alkermes' putative long-acting injectable antipsychotic, Aripiprazole Lauroxil. Alkermes is also proceeding with a Phase 1 clinical trial to test extended-dosing schedules—specifically, once every 2 months or once every 6 weeks—for this agent.

Intra-Cellular Therapies, Inc. is conducting a Phase 3 clinical trial of ITI-007, an investigational drug of complex pharmacology that includes dopamine receptor phosphoprotein and glutamate receptor moderation, serotonin 5-HT2A receptor antagonism and serotonin reuptake inhibition.

The FDA previously approved the once-monthly long-acting injection of aripiprazole (Abilify Maintena). A supplemental New Drug Application (sNDA) has been submitted to the FDA to consider the deltoid region of the arm as an additional potential injection site.

The FDA has also recently approved asenapine for bipolar disorder in pediatric patients.

The FDA is also reviewing data regarding an extended-dosing interval for paliperidone palmitate. This long-acting antipsychotic drug is already approved as a monthly injection. Data from a relapse prevention study involving over 500 patients with schizophrenia showed efficacy for a 3-month formulation of paliperidone palmitate.

Brexpiprazole (OPC-34712), a serotonin-dopamine activity modulator of complex pharmacology, was recently studied as an adjunct to standard antidepressant therapy in two clinical trials among patients with major depressive disorder. Adjunctive brexpiprazole produced significant improvements over placebo in depression and was associated with pharyngitis, weight gain, somnolence, and extrapyramidal side effects—with a low discontinuation rate overall in this study.

Schizophrenia is the Severe End of a Spectrum of Psychotic Experiences with Sporadic Inconsequential Hallucinations in the Normal Population at the other End?

Jim van Os, a leading Dutch psychiatrist, provides a provocative and persuasive review of psychosis liability in a recent *JAMA Psychiatry* editorial (van Os, 2014). He argues for the similarity of risk factors and effect of psychosis in the general population and in various "at-risk mental states" groups of people. Interesting read.

Jim van Os. The many continua of psychosis. JAMA Psychiatry 2014;71(9):985-986.

Shared Neuropathology: More on the Continuum between Schizophrenia and Bipolar Disorder

Konopaske and colleagues (2014) conducted an important post mortem study of frontal lobe cellular structure in patients with schizophrenia (n=14) and bipolar disorder (n=9). There were similar cell changes in pyramidal cells, namely less spines and dendrites (by about an 18% reduction compared to normal post mortem brains), between both patient groups. This is a powerful and scientifically robust finding.

Konopaske GT, Lange N, Coyle JT, Benes FM. Prefrontal cortical dendritic spine pathology in schizophrenia and bipolar disorder. JAMA Psychiatry 2014;71(12):1323-1331.

Kraepelin Distinction: Will it Carry into the 21st Century?

Roalf and colleagues (2015) report an important study on the heritability of limbic structure and volumes among a large genetics study in schizophrenia. The article itself is interesting, although one appeal of reading this is heightened by two provocative commentaries from two independent collaborative research groups. Light and Makeig (2015) provide a synopsis on the various ways functional electroencephalography (EEG) can be used as a credible biomarker for psychosis. The other commentary—by Clementz and colleagues (2015) from the collaborative group Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP)—illustrates the potential of aggregating a battery of biomarkers to understand the neurobiology of psychosis. They also illustrate the power of EEG as one component of that battery (Ethridge et al., 2015).

Roalf DR, Vandekar SN, Almasy L, Ruparel K, Satterthwaite TD, Elliott MA, et al. Heritability of subcortical and limbic brain volume and shape in multiplex-multigenerational families with schizophrenia. Biol Psychiatry 2015;77(2):137-146.

Light GA, Makeig S. Electroencephalographic biomarkers of psychosis: present and future. Biol Psychiatry 2015;77(2):87-89.

Clementz BA, Sweeney J, Keshavan MS, Pearlson G, Tamminga CA. Using biomarker batteries. Biol Psychiatry 2015;77(2):90-92.

Ethridge LE, Hamm JP, Pearson GD, Tamminga CA, Sweeney JA, Keshavan MS, et al. Event-related potential and time-frequency endophenotypes for schizophrenia and psychotic bipolar disorder. Biol Psychiatry 2015;77(2):127-136.

Renewed Interest in Obsessive-Compulsive Disorder and Schizophrenia

Phenomenologists have long recognized the potential overlap between delusional and obsessional thinking, as well as the apparently higher prevalence of obsessive symptoms in people with schizophrenia. Some have gone so far as to suggest that these symptomatic aggregates constitute a potentially distinct phenotype of schizophrenia; hence, the term "schizo-obsessive disorder" (Pasternak; 2014). Meier and colleagues (2014) bring an epidemiological focus to this topic in their longitudinal Danish register analysis of over 30,000 patients with schizophrenia/schizophrenia spectrum disorders. Obsessive-compulsive disorder (OCD) was seen—and diagnosed—almost seven times more frequently before the schizophrenia diagnosis in patients with schizophrenia. Conversely, relatives of patients diagnosed with OCD had a higher rate of schizophrenia (4.31, relative risk). The authors report a 6.9 incidence rate ratio (IRR) of schizophrenia among people with a prior hospital admission diagnosis of schizophrenia. The risk is pretty high and this itself is surprising. Moreover—and perhaps a detraction from this message—there are also heightened rates of schizophrenia among inpatients with former diagnoses of ADHD (IRR of 3.58), autism (IRR of 3.06), and even bulimia nervosa (IRR of 3.01). These are provocative findings, although the lower expression of OCD in schizophrenia spectrum conditions is somewhat counterintuitive.

Meier SM, Petersen L, Pedersen MG, Arendt MC, Nielsen PR, Mattheisen M, et al. Obsessive-compulsive disorder as a risk factor for schizophrenia: a nationwide study. JAMA Psychiatry 2014;71(11):1215-1221.

Trajectory of Brain Development in Schizophrenia

The National Institute of Mental Health (NIMH) has had a longstanding and highly informative study of childhood onset schizophrenia (COS), led by Dr. Judith Rapoport. The study has drawn from young patients all over the U.S. who come to NIMH for intensive evaluation as well as treatment. There has also been the opportunity to evaluate patients over time. Alexander-Bloch and colleagues (2014) from Dr. Rapoport's team at NIMH report on serial MRI evaluations among 103 patients with COS and 102 healthy individuals. Using developmental modeling of MRI data over time, they observed that there was particular "fall off" in growth in fronto-temporal regions in COS patients. In an elegant commentary by Dr. Bilder that accompanies this article, the similarities between these findings from this sample and another young high-risk sample are explained. All very interesting reading.

Alexander-Bloch AF, Reiss PT, Rapoport J, McAdams H, Giedd JN, Bullmore ET, et al. Abnormal cortical growth in schizophrenia targets normative modules of synchronized development. Biol Psychiatry 2014;76(6):438-446.

Bilder RM. Finding pieces to the puzzle of brain structure in schizophrenia. Biol Psychiatry 2014;76(6):432-433.

Prodrome Study

This is an important study by Cannon and colleagues (2015) that adds to an important—and kind of intuitive—finding that there are subtle brain changes that occur among high-risk individuals as they "convert" to psychosis. This was first observed by Pantellis and colleagues (2003) in high-risk-for-psychosis "patients" who were followed over time in the ground-breaking PRIME early intervention clinical program in Australia. Here, Cannon and colleagues (2015) report on another major longitudinal study of high-risk individuals—the study of North America (U.S. and Canadian study centers) where MRI changes were compared across 35 people who "converted" to psychosis and 135 "patients" without psychosis. They found subtle cortical thinning in the psychotic group. Importantly, exposure of antipsychotic medications was unrelated to this effect. Actually, the cortical changes were robustly associated with proinflammatory markers—cytokines—in the blood of patients who converted to psychosis. This is a particularly interesting finding that

adds to the neurotoxic hypothesis of psychosis itself and the potential role of neuroinflammation in schizophrenia.

Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TG, et al.; North American Prodrome Longitudinal Study Consortium. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. Biol Psychiatry 2015;77(2):147-157.

Pantellis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet 2003;361(9354):281-288.

The Mother of all Meta-Analysis

This French group (Dechartres et al., 2014) conducted an intensive review of 163 meta-analytic studies that (themselves) covered some 1,240 randomized clinical trials across an array of treatments and conditions in medicine that were published between 2008 and 2013. They aimed to determine whether it is wise to take "all comers" (including small studies that might potentially show a strong effect) or simply confine a meta-analysis to large clinical trials. Their results are interesting and predictable … you get out what you put in! The inclusion of smaller trials that can have large effects introduces more "noise" than remaining focused on large studies. Meta-analysts beware!

Dechartres A, Altman DG, Trinquart L, Boutron I, Ravaud P. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. JAMA 2014;312(6):623-630.

Anomalous Findings of *Toxoplasmosis Gondii* Exposure and Cognitive Impairment?

Toxoplasmosis gondii, a parasite, has been quite extensively studied as a risk factor for schizophrenia. Findings suggest a higher risk of schizophrenia of the order of 4.5 times between individuals who have and have not been exposed to this infectious agent. In a cross-sectional study, Dickerson and colleagues (2014) do not find any association between exposure to Toxoplasmosis gondii and cognitive performance in patients with schizophrenia. This is surprising. They do, however, find strong inverse relationships between exposure and cognitive performance in the comparison groups, both in patients with bipolar disorder and in healthy control subjects.

Dickerson F, Stallings C, Origoni A, Katsafanas E, Schweinfurth L, Savage C, et al. Antibodies to Toxoplasma gondii and cognitive function in schizophrenia, bipolar disorder, and nonpsychiatric controls. J Nerv Ment Dis 2014;202(8):589-593.

Clozapine Use Results in Lower Polypharmacy

It is well known that clozapine use over time is associated with a lower use of other antipsychotic drugs. A counter balance is that augmenting of clozapine with other drugs has been shown in small studies to enhance response in patients who are partially refractory to clozapine and, in some instances, might even mitigate (through a lower dose of clozapine) the adverse effect profile—especially metabolic effects—associated with long-term clozapine therapy. In this pharmacovigilance study of a U.S. nationwide Medicaid database that tracked outcomes over time from initiation on either clozapine monotherapy or antipsychotic polypharmacy (Velligan at el., 2014), it was reported that patients on clozapine monotherapy had less use of the emergency room and had less healthcare costs overall: at a figure "all in" of some $21,000. These are interesting findings, although there are also methodological and sampling issues in this study that require consideration for all patients on clozapine.

Velligan DI, Carroll C, Lage MJ, Fairman K. Outcomes of Medicaid beneficiaries with schizophrenia receiving clozapine only or antipsychotic combinations. Psychiatr Serv 2015;66(2):127-133.

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.*