Clinical News … new antipsychotics … autism and schizophrenia … genetic and other biomarkers … auditory cortex morphology in schizophrenia … phenotyping through drug and nonpharmacologic response … treatment-refractory schizophrenia … smartphones …

Peter F. Buckley, MD
Editor-in-Chief

Update on Putative and New Antipsychotics

The clinical extension of antipsychotic medications to bipolar conditions and also to pediatric circumstances continues. Sunovion Pharmaceuticals has submitted a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) to have lurasidone considered for use in children and adolescents with bipolar depression. The sNDA is based on a Phase 3, six-week, double-blind study of lurasidone in 347 children/adolescents with bipolar depression. The results revealed statistically significant effects on depressive symptoms and, overall, lurasidone was well tolerated.

The FDA approved the use of extended-release injectable suspension of aripiprazole (Abilify Maintena) in bipolar I disorder in adults. This was based upon a 52-week, placebo-controlled randomized withdrawal Phase 3 trial of injectable aripiprazole. The trial showed a delay in reemergence of mania and mixed symptoms but no delay in forestalling depressive symptoms.

Alkermes plc has reported initial results of the Phase 3 trial of ALKS 3831 in over 400 patients with schizophrenia. This pivotal study (called Enlighten-1) compared olanzapine, placebo, and ALKS 3831, an innovative combination of olanzapine and samidorphan which is being developed to "mimic" the demonstrated efficacy of olanzapine but without its marked weight gain. The study confirmed the efficacy of ALKS 3831, with more detailed analysis of clinical effects and adverse effects forthcoming.

MIN-101 (Minerva Neurosciences, Inc.) is a novel, putative antipsychotic devoid of direct effect on dopamine receptors as previously described in ***Clinical News***. Results of a 12-week, double-blind, placebo-controlled trial showed improvements in negative symptoms in schizophrenia, an intriguing finding given the unique pharmacological profile of this novel agent.

The FDA has approved deutetrabenazine, a novel agent that is a vesicular monoamine transporter 2 (VMAT-2) inhibitor, for the treatment of tardive dyskinesia. The drug is already FDA approved for chorea associated with Huntington's disease. The approval for tardive dyskinesia is based upon two clinical trials in patients with established tardive dyskinesia.

Kudos for Kelly!

CS Managing Editor Deanna Kelly has been awarded the Brain & Behavior Research Foundation's Maltz Prize for Innovative & Promising Schizophrenia Research. This prestigious prize will be presented to Dee at the Foundation's upcoming 2017 International Awards Dinner. Congratulations, Dee, and thank you for all you do!

Autism and Schizophrenia

It has been posited that schizophrenia and autism may share some neurobiological overlap as neurodevelopmental disorders. Larson and colleagues (2017) provide important observations on the relatively little known area of overlap between schizophrenia and autism. Comparisons were made between 116 patients with autism spectrum disorder (ASD) who had some comorbid psychotic disorder (89 males, 27 females) and patients from the British first-episode (AESOP) study. Psychosis-NOS and schizophrenia were the most common diagnosis (32% of patients psychosis-NOS, 21% schizophrenia) in the ASD group. Half of the patients were receiving an antipsychotic medication, with 35% being on two medications and 11% on three antipsychotic medications. Atypical psychosis was more common in the ASD group than in the AESOP sample. Those patients with ASD and psychosis had less stereotypic behaviors than those with ASD alone. This is a large sample of patients and the descriptive detail in this study is informative.

Larson FV, Wagner AP, Jones PB, Tantam D, Lai MC, Baron-Cohen S, et al. Psychosis in autism: comparison of the features of both conditions in a dually affected cohort. Br J Psych 2016;210(4):269-275.

Cannabis and Schizophrenia: Causality of Effect

Vaucher and colleagues (2017) provide an illustrative analysis—derived from available epidemiological and genetic studies—of the relationship between cannabis use and the risk of schizophrenia. Their study used a Mendelian statistical analysis, which determined that cannabis use causes a 43% increase in the risk of schizophrenia and related psychotic disorders. Surprisingly—and contrary to an earlier study from the Dundee cohort—the genetic markers did not confer additional interactional risk of schizophrenia in association with cannabis use. The study does not address the effect of "dose" of cannabis (i.e., heavy vs. mild users) and/or the composition of cannabis—an earlier report in ***Clinical News*** highlighted a greater risk of psychosis in smokers of impure cannabis products.

Vaucher J, Keating BJ, Lasserre AM, Gan W, Lyall DM, Ward J, et al. Cannabis use and risk of schizophrenia: a Mendelian randomization study. Mol Psychiatry 2017 Jan 24. doi: 10.1038/mp.2016.252. [Epub ahead of print]

Biomarkers for Schizophrenia: Progress or More Complex Data?

Two provocative articles, one data driven (Ivleva et al., 2017) and the other a commentary (Barch, 2017), offer a thoughtful appraisal of where we sit regarding biomarkers for schizophrenia. We have previously highlighted the ongoing, formative study Bipolar-Schizophrenia Network for Intermediate Phenotypes (BSNIP), which in this report by Ivleva and colleagues presents data on brain morphology with respect to three already described (neurobiologically derived) "biotypes." Biotype I was characterized by widespread gray matter loss, with some predilection for further loss in frontotemporal and cingulate cortex. In contrast, biotype II had less diffuse gray matter loss and was characterized by more selective frontotemporal and insular cortex loss. Biotype III differed from the other two types by being (even more) selective in tissue loss in the anterior limbic area. Relatives of biotypes I and II showed similar, yet more attenuated, profiles of loss while biotype III's relatives were indistinguishable from normal subjects in gray matter morphology. In a commentary on this work and the field in general, Barch endorsed this approach as meaningful, yet complicated, given the inevitable (over) reliance on cluster analytics. Dr. Barch also advocates for the use of hybrid statistical approaches so that, as a field, we don't simply adopt a "lumper or splitter" dichotomous approach to such complex data sets. This may aid replication of findings—a major requirement for validation of such provocative and important nosological constructs.

Ivleva EI, Clementz BA, Dutcher AM, Arnold SJM, Jeon-Slaughter H, Asian S, et al. Brain structure biomarkers in the psychosis biotypes: findings from the Bipolar-Schizophrenia Network for Intermediate Phenotypes. Biol Psychiatry 2017;82(1):26-39.

Barch D. Biotypes: promise and pitfalls. Biol Psychiatry 2017;8(1):2-3.

Genome-Wide Association Studies (GWAS) and Cognition in Schizophrenia

Given the preeminence of cognitive deficits in schizophrenia, this study by Smeland and colleagues (2017) aggregated genome-wide association studies (GWAS)—encompassing some 250,000 participants—from disparate large cohorts that had genetic data, data from schizophrenia samples, cognitive data (including from heart and aging studies), and normative samples. Interestingly, they found overlap at 21 different genetic loci: 14 overlaps between overall cognition and schizophrenia, 6 between reaction time and schizophrenia, and 2 with verbal reasoning; most of which related to cognitive deficits. The most robust associations resided in chromosome 22. While this study moves us beyond the "needle in the haystack" of associating cognitive impairment in schizophrenia and genetic vulnerability, findings from this very large data set should be replicated. Replication in genetics studies is a real imperative.

Smeland OB, Frei O, Kauppi K, Hill WD, Li W, Wang Y, et al. Identification of genetic loci jointly influencing schizophrenia risk and the cognitive traits of verbal-numerical reasoning, reaction time, and general cognitive function. JAMA Psychiatry 2017 Jul 26. doi:10.1001/jamapsychiatry.2017.1986. [Epub ahead of print]

Cancer Genetics Approaches: Implications for Schizophrenia Research?

Cancer biology discovery and treatment often holds implications for many other areas of medicine. A current robust example of this is the immunology of cancer, which has led to a plethora of treatments using different immunologically based techniques. Similarly, this important genetic biomarker-based study (Abbosh et al., 2017) of early lung cancer has broader implications than for the condition itself. Using data from several large cancer multinational consortia, Abbosh and colleagues describe complex genetic testing for CT (circulating tumor) DNA as a marker of early recurrence of lung cancer. The sensitivity of this test is impressive and suggests that, with further development, this test

could be used to guide selective therapies for lung cancer. By analogy, our ability to detect any genetic footprint that could guide relapse and/or treatment for relapse in schizophrenia would be a huge step forward.

Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, Salari R, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature 2017;545(7655):446-451.

Lancet Commission for Dementia: Implications for Schizophrenia

Livingston and colleagues (2017) provide a remarkable appraisal of dementia—its prevalence, risk factors, and management. Of particular interest, and relevance to schizophrenia research, is the description (and computation) of the contribution of modifiable risk factors to the development of dementia (65% potentially not modifiable, 35% potentially modifiable), including late-life factors such as diabetes (1% risk), social isolation (2%), physical inactivity (3%), depression (4%), smoking (5%); mid-life risks including obesity (1%), hypertension (2%) and then hearing loss (9%); and, early-life risk factors including less education (8%) and APOE-4 genetic predisposition (7%). With this model, one can really conceptualize—and then activate accordingly—a robust, multipronged approach to prevention with realistic expectations for each of the primary, secondary, and tertiary prevention approaches. The commission proposes nine interventions/changes that could reduce the prevalence of dementia. Such a model would be helpful for schizophrenia too. The *Lancet Commissions* are a useful and provocative series … well worth a read!

Livingston G, Sommerlad A, Orgeta V, Costfreda S, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017 Jul 19. doi:10.1016/S0140-6736(17)31363-6. [Epub ahead of print]

Auditory Cortex Morphology in Schizophrenia

A convergence of imaging and earlier post-mortem studies implicates the temporal lobe region in the pathogenesis of schizophrenia. In a meticulous neuropathology study of the auditory cortex among 20 post-mortem brains, MacDonald and colleagues (2017) report a differential loss of smaller rather than larger spines. This differential and localized effect also had a genetic association, in that there was overexpression of a particular peptide (ALFDFLK) that is related to a schizophrenia-risk gene (CACNB4). This is an elegant and important study, which also shows the level of sophistication that this area of schizophrenia research has evolved to.

MacDonald ML, Alhassen J, Newman JT, Richard M, Gu H, Kelly RM, et al. Selective loss of smaller spines in schizophrenia. Am J Psychiatry 2017;174(6):586-594.

Phenotyping through Drug Response

In the search to better understand the biology of mental illnesses, medication response has been variously used to decipher any distinct biological phenotypes. Building on previous studies on the variation of responsivity to lithium therapy, Stern and colleagues (2017) provide a provocative neuroscience-derived account of differential response to lithium therapy among pluripotent stem cells from neurons of patients with bipolar disorder. They identified a hyper excitability among neurons, with distinct electrophysiological measure teasing out (with 92% accuracy) responsivity to lithium. This is an elegant and important study, whose outcome and methodology also make relevance to our understanding of the neurobiology of schizophrenia.

In a related study, Tobe and colleagues (2017) profile the neurons also derived from human-induced pluripotent stem cells. Using proteomics, the authors discovered that the distinct impact of lithium on these cells was an alteration of phosphorylation among collapsin response mediator protein-2. These findings suggest that lithium, through this mechanism, influences brain cytoskeletal organization.

Stern S, Santos R, Marchetto MC, Mendes AP, Rouleau GA, Biesmans S, et al. Neurons derived from patients with bipolar disorder divide into intrinsically different sub-populations of neurons, predicting the patients' responsiveness to lithium. Mol Psychiatry 2017 Feb 28. doi:10.1038/mp.2016.260. [Epub ahead of print]

Tobe BTD, Crain AM, Winquist AM, Calabrese B, Makihara H, Zhao WN, et al. Probing the lithium-response pathway in hiPSCs implicates the phosphoregulatory set-point for a cytoskeletal modulator in bipolar pathogenesis. Proc Natl Acad Sci U S A 2017;114(22):E4462-E4471.

Consensus on Treatment-Refractory Schizophrenia

It is almost 30 years since Kane and colleagues (Kane et al., 1988) published their seminal paper on clozapine for treatment-refractory (TR) schizophrenia. Much has changed since, including many new antipsychotics of (highly) variable efficiency that necessarily have advanced the enquiry into TR schizophrenia. Howes and colleagues (2017) have led a veritable "who's who" of schizophrenia psychopharmacology to address the rigor and consistency of modern-day clinical trials' definitions of TR schizophrenia. The consensus criteria emphasize a trial of antipsychotics—two drugs at adequate dose and duration—as well as adherence evaluation and a prospective trial of an antipsychotic. While rigorous, these criteria will work best in investigator initiated fed-

eral and multicenter pharmaceutically funded trials, though they are likely too constraining for pragmatic and small trials.

Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, et al. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group consensus guidelines on diagnosis and terminology. Am J Psychiatry 2017;174(3):216-229.

Will Cognitive Remediation Come of Age?

Kendrick and Yao (2017) provide a thoughtful synthesis of the "state-of-play" concerning cognitive remediation for mental illnesses. They point out the broader opportunity in mobile technologies—not just computer-based training. As the literature bears out, they also highlight the need for sufficient sample sizes in studies that seek to demonstrate the utility of computer-based cognitive therapy as well as the dissonance between therapeutic optimism, media and commercial "hype," and scientific affirmation.

Kendrick KM, Yao D. Can computer-based cognitive therapy become a front-line option for prevention and treatment of mental disorders? Am J Psychiatry 2017;174(4):303-304.

Getting Smart about Schizophrenia

Sandoval and colleagues (2017) describe an intriguing case report of a patient whose use of a smartphone aided in his self-management of schizophrenia. This case report "brings alive" the great potential of mobile health for schizophrenia, including symptom awareness, relapse prevention, and medication adherence. The article also describes some of the challenges of mobile health, not least of which is the relative absence of clinical trials at this stage. This will change shortly.

Sandoval LR, Torous J, Keshavan MS. Smartphones for smarter care? Self-management in schizophrenia. Am J Psychiatry 2017;174(8):725-728.

Nonpharmacologic Treatments for Negative Symptoms in Schizophrenia

Colleagues from McGill University (Lutgens et al., 2017) demonstrate the importance of psychosocial treatments in schizophrenia, specifically for negative symptoms. While this meta-analysis shows only modest statistical effects across 95 studies, the effect is broadly similar across modalities: cognitive behavioral therapy, social skills training, occupational therapy, cognitive adaptation training, exercise therapies, art and music therapies and family-based therapies. All that said, the number of studies in each modality differ. Additionally, it's important to note that group therapy faired just as well as individual therapy.

Lutgens D, Gariepy G, Malla A. Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis. Br J Psych 2017;210(5):324-332.

*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.*