Clinical News … antipsychotic drug developments … strategic directions and biomarker development … NIH strategic plan … neuroinflammation beyond schizophrenia … cannabis and neurodegeneration … schizophrenia diagnoses and social media … ACT changes with the times …

Peter F. Buckley, MD
Editor-in-Chief

Putative New Antipsychotics Update

Our field can be encouraged by several developments in the psychopharmacology of schizophrenia. We have previously described the initial clinical trials program of ITI-007. Results of two Phase 3 trials of ITI-007 have been reported as positive, with demonstrated antipsychotic efficacy and a favorable side effect profile (most prominently, mild sedation).

Cariprazine is a high affinity D2/5-HT1A receptor partial agonist that is now FDA approved for the treatment of schizophrenia and marketed as Vraylar. Results of two studies have been reported that also show efficacy for bipolar depression and for negative symptoms of schizophrenia.

Another recently FDA-approved antipsychotic, brexpiprazole (Rexulti), had a supplemental New Drug Application (sNDA) submitted for an expanded indication as a maintenance treatment for adults with schizophrenia. The sNDA is based upon demonstrated efficacy with a longer time to relapse during a 52-week, randomized, withdrawal trial.

Further studies of lurasidone (Latuda) in schizophrenia and bipolar depression were recently presented and showed efficacy in these populations. On the other hand, results of two Phase 3 trials in schizophrenia of encenicline—an alpha-7 nicotinic receptor agonist under consideration as a cognitive enhancer for schizophrenia—were equivocal, with a high-placebo rate, and did not demonstrate superior efficacy in these studies.

Minerva Neurosciences now has an FDA Investigational New Drug (IND) application for MIN-101, a novel compound that is a 5-HT2A and sigma-2 receptor antagonist. A European study of MIN-101 is currently in progress. Finally, the FDA has approved pimavanserin (Nuplazid) for the treatment of hallucinations and delusions in Parkinson's disease. The drug has a unique pharmacology in being a 5-HT2A agonist, yet without activity on dopamine receptors—launching a potentially new class of antipsychotic drugs; selective serotonin inverse agonists (SSIA). Time will tell whether or not this is the advent of a new class of drugs.

Biomarkers for Schizophrenia

Lawrie and colleagues (2016) provide a terrific review of the state-of-play of the context and opportunities for developing biomarkers for schizophrenia. In addition to a comprehensive review of the historical antecedents of psychosis, the article also highlights key areas of scientific inquiry. These include biomedical technologies research, population-based studies and register-related epidemiological research.

Lawrie SM, O'Donovan MC, Saks E, Burns T, Lieberman JA. Towards diagnostic markers for the psychoses. Lancet Psychiatry 2016;3(4):375-385.

National Institutes of Health Strategic Plan: Mental Health Opportunities Too

The National Institutes of Health (NIH) has released its strategic plan for 2016–2020, with objectives in advancing biomedical research in scientific cures and disease prevention, promoting innovation, developing the biomedical research work force, and achieving operational efficiencies as the premiere federal research organization (www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf). Naturally, the NIH plan is broad and focuses on vaccines, biosensors, pharmacogenetics, precision medicine, rare diseases, and regenerative medicine. A search is currently underway for a new Director for the National Institute of Mental Health (NIMH), following the excellent service by Tom Insel as NIMH Director.

International Biomarker Effort for Autism

Loth and colleagues (2016) provide an intriguing account of a concerted, international, collaborative program to develop biomarkers for autism. This longitudinal study—the EU-AIMS Longitudinal European Autism Project (LEAP)—will enroll 450 people with autism spectrum disorders and 350 people with mild disability disorders. The broad age range and longitudinal nature of comprehensive evaluations will also facilitate exploration of putative biomarkers over the developmental trajectory in autism also. This project has parallels with the BSNIP project described earlier in ***CS***.

Loth E, Spooren W, Ham LM, Isaac MB, Auriche-Benichou C, Banaschewski T, et al. Identification and validation of biomarkers for autism spectrum disorders. Nat Rev Drug Discov 2016;15(1):70-73.

Against Modern Research Criteria—Is this a Valid Perspective?

The Research Domain Criteria (RDoC) represents the "holy grail" of the research vision for the National Institute of Mental Health and the U.S. mental health research community. RDoC seeks to understand neural pathways and how molecules relate to circuitry. In a damning appraisal, Paris and Kirmayer (2016) provide a theoretical counterpoint. They suggest that the RDoC approach is overly simplistic and pays insufficient attention to the complexities of "mind-brain" dynamic and social interrelationships. Time will tell.

Paris J, Kirmayer LJ. The National Institute of Mental Health Research Domain Criteria: a bridge too far. J Nerv Ment Dis 2016;204(1):26-32.

More on Cannabis … Brain Rot?

As reported in prior issues of ***Clinical News***, there is emergent information that shows neurotoxic effects of cannabis use. Pagliaccio and colleagues (2015) from Washington University suggest a genetic/environmental sensitivity to reduction in amygdala as evidenced in MRI brain analyses as part of the Human Connectome Project. French and colleagues (2015) take a different population-based approach and report that higher marijuana use is associated with cortical thinning. The accompanying commentary by David Goldman highlights how these scientific data fit in the broader societal context of marijuana use and legalization thereof.

Pagliaccio D, Barch DM, Bogdan R, Wood PK, Lynskey MT, Heath AC, et al. Shared predisposition in the association between cannabis use and subcortical brain structure. JAMA Psychiatry 2015;72(10):994-1001.

French L, Gray C, Leonard G, Perron M, Pike GB, Richer L, et al. Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence. JAMA Psychiatry 2015;72(10):1002-1011.

Goldman D. America's cannabis experiment. JAMA Psychiatry 2015;72(10):969-970.

Voices in the Community—A WHO study

The World Health Organization survey data from eighteen countries covering 2001–2009 provide a prevalence rate of 5.8% for psychotic experiences in apparently normal individuals. The rate of hallucinations at 5.2% is higher than that of delusions. Of interest are the socioeconomic correlates, in that middle- to upper-income countries have higher rates of psychotic experiences.

McGrath JJ, Saha S, Al-Hamzawi A, Alonso J, Bromet EJ, Bruffaerts R, et al. Psychotic experiences in the general population: a cross-national analysis based on 31,261 respondents from 18 countries. JAMA Psychiatry 2015;72(7):697-705.

Zooming in on the Genetics of Neuroinflammation and Schizophrenia: Intriguing New Findings

Sekar and colleagues (2016) have really "drilled down" on the genetics of neuroinflammation and schizophrenia, drawing from complementary sources of the patient samples of the Psychiatric Genomics Consortium, patient post mortem brain tissue from the Stanley Medical Research Institute, and mice genome. They focused on the complement component 4 (C4) genes of the major histocompatibility complex (MHC) locus on chromosome 6. They reported elevated C4 activity, of relevance since the human C4 protein is implicated in neuronal development and functional integrity of brain cells. The findings from each component of this study converge to highlight the fundamental role of neuroinflammation in schizophrenia.

Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, et al. Schizophrenia risk from complex variation of complement component 4. Nature 2016;530(7589):177-183.

Inflammation and Schizophrenia-Mood Disorder Distinctions

Although this Danish study focuses more on bipolar disorder and neuroinflammation, Wium-Andersen and colleagues (2016) also showed in this epidemiological study that C-reactive protein was elevated in patients with schizophrenia as well as bipolar disorders and major depression,

with odds ratios of 1.64, 1.41, and 1.24, respectively. This study was based upon analysis of Copenhagen population-based databases involving some 79,000 subjects.

Wium-Andersen MK, Orsted DD, Nordestgaard BG. Elevated C-reactive protein and late-onset bipolar disorder in 78,809 individuals from the general population. Br J Psych 2016;208(2):138-145.

Immune Attacking of Alzheimer's Disease

Fu and colleagues, in a mice model that resembles the neuropathology of Alzheimer's disease (AD), report an exciting exploratory study of immunotherapy for AD. Interleukin (IL)-33, an immune mediator that in signaling activates T-helper cells, mast cells, and macrophage response, was studied in mice. IL-33 treatment turned around synaptic changes and cognitive deficits in an AD mice model that exhibited features of the neuropathology of AD. This is a provocative paper that also has implications for the evolving neuroimmunology of schizophrenia.

Fu AK, Hung KW, Yuen MY, Zhou Z, Mak DS, Chan IC, et al. IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline. Proc Natl Acad Sci U S A 2016;113(19):E2705-2713.

Substance Abuse and Schizophrenia

In another post hoc analysis from the CATIE schizophrenia study, Mohamed and colleagues (2015) examined the trajectory of drug and alcohol and cigarette use by patients over the 18 months of this landmark pragmatic trial. At baseline, 23% of patients used illicit drugs, 35% used alcohol, and 61% smoked cigarettes. However, only 4 to 6% of patients abused drugs or alcohol during the schizophrenia CATIE trial and so the ability to detect antipsychotics drugs' different potential to influence substance use–misuse was diminished. That said, it was intriguing that relatively less smoking was observed among patients who received ziprasidone.

Mohamed S, Rosenheck RA, Lin H, Swartz M, McEvoy J, Stroup S. Randomized trial of the effect of four second-generation antipsychotics and one first-generation antipsychotic on cigarette smoking, alcohol, and drug use in chronic schizophrenia. J Nerv Ment Dis 2015;203(7):486-492.

Writing the Diagnosis of Schizophrenia? ... "Old Wine in a New Bottle"?

In the prior era of 1940–1960, research analyses of writings and speech of people with schizophrenia was somewhat of a "cottage industry." Buck and Penn (2015) provide a more contemporary analysis of writings and words per sentence and the use of pronouns, which are overrepresented in schizophrenia in comparison with nonpsychiatric controls subjects.

Beginning in the 1940s–50s, there has been a plethora of studies examining speech and even writing patterns in people with schizophrenia. Most often, associations were made between abnormalities of speech and distant subtypes of schizophrenia—the most notable being the disorganized speech and syntax that characterize the disorganized subtype of schizophrenia. Bedi and colleagues (2015), appearing in the new online journal *npj Schizophrenia*, have conducted a very clever computer-based analysis of speech patterns in 34 prodromal youths, 5 of whom went on to become psychotic. A speech analysis called "latent semantic analysis" predicted psychosis in all 5 cases. It is an interesting read. Too early to know whether this approach yields consistent results.

Buck B, Penn DL. Lexical characteristics of emotional narratives in schizophrenia: relationships with symptoms, functioning, and social cognition. J Nerv Ment Dis 2015;203(9):702-708.

Bedi G, Carrillo F, Cecchi GA, Slezak DF, Sigman M, Mota NB, et al. Automated analysis of free speech predicts psychosis onset in high-risk youths. npj Schizophrenia 2015; doi:10.1038/npjschz.2015.30. Published online 26 August 2015.

Differences between Patient and Clinical Evaluations of Schizophrenia

Fervaha and colleagues (2015) published an interesting and potentially provocative study that compared both patient and clinical evaluations of symptoms on the Clinical Global Impression-Severity of Illness scale (CGI-S). The study was based upon an analysis of the data from the CATIE schizophrenia study. While there was some overlap between patients and clinicians, it was noteworthy that clinicians related CGI-S severity more to positive and disorganized symptoms, in contrast to patients who associated CGI-S severity with depressive, anxiety, and cognitive symptoms. This study offers important evidence in support of multiple sources of information when evaluating treatment response and well-being.

Fervaha G, Takeuchi H, Agid O, Lee J, Foussias G, Remington G. Determinants of patient-rated and clinician-rated illness severity in schizophrenia. J Clin Psychiatry 2015;76(7):924-930.

Social Media and Stigma Busting

In previous issues of ***CS***, we have highlighted the pervasive impact of mental illness stigma on patients, their relatives, and society at large. A recent, thoughtful commentary by Betton and colleagues (2015) highlights the opportunities

to harness social media to drive and augment more established media approaches to stigma busting. The immediacy of impact, coupled with the high rate of repetition—"retweeting"—represents a real opportunity for our field to be vigilant and effective stigma busters.

Betton V, Borschmann R, Docherty M, Coleman S, Brown M, Henderson C. The role of social media in reducing stigma and discrimination. Br J Psych 2015;206(6):443-444.

ACT Changes with the Times

Assertive community treatment (ACT) has existed since the early 1980s and has been adopted to provide a high degree of community-based intensive care to people with chronic mental illnesses, mostly with schizophrenia. Bond and Drake (2015) succinctly review the extant literature and they tell us "what's the right stuff" here. Surprisingly, multidisciplinary staffing is no longer viewed as a fundamental ingredient for therapeutic success. Bond and Drake also point out that, while organizational components of ACT remain at the core, ACT in practice has also "grafted on other" mental health innovations including recovery principles, shared decision-making, and broader use of community resources.

Bond GR, Drake RE. The critical ingredients of assertive community treatment. World Psychiatry 2015;14(2):240-242.

*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.*