Clinical News … putative antipsychotics … depressive equivalents … mortality … relapse ... immune dysfunction ... mobile health …

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Update on Putative and Established Antipsychotics

A real-world, pragmatic, clinical trial of once-monthly paliperidone palmitate injection versus oral antipsychotics showed that the long-acting intramuscular antipsychotic decreased relapse, rehospitalization, and incarceration among almost 450 patients. This study, called PRIDE, was of 15 months' duration and uniquely focused on psychotic patients with a history of criminal incarceration, a notoriously difficult group to treat and a group most often excluded from clinical trials. Although this study was conducted several years ago, the U.S. Food and Drug Administration (FDA) has now approved the inclusion of these results in the product label for paliperidone palmitate.

The biopharmaceutical company Minerva Neurosciences has launched a 12-week, double-blind and placebo-controlled Phase 3 trial of MIN-101 (32 mg and 64 mg) in patients with schizophrenia who have prominent negative symptoms. The study is being conducted in the U.S. and Europe, and it is anticipated that approximately 500 patients will be enrolled. MIN-101 is an interesting putative antipsychotic, with low affinity for dopamine receptors yet has strong affinity at 5HT2A and sigma receptors. Stay tuned for results later.

Valbenazine is a drug of novel pharmacology, as previously featured in ***CS***, which is FDA approved for the treatment of tardive dyskinesia (TD). It is one of a new class of highly-selective agents called vesicular monoamine transporter 2 (VMAT-2) inhibitors. Valbenazine has no significant affinity for dopamine, serotonin, cholinergic, or noradrenergic receptors. In the 48-week, open-label trial (called KINECT 4) of valbenazine in over 160 patients with TD, movement scores declined and the drug was well tolerated. An 80-mg dose of valbenazine is now FDA approved.

Cariprazine, another novel antipsychotic that is FDA approved for the treatment of schizophrenia, is now being studied in a Phase 3 clinical trial for bipolar I depression. Results of this 6-week study showed efficacy for both 1.5-mg and 3-mg doses of cariprazine. The companies Allergan and Richter expect to submit a Supplemental New Drug Application to the FDA during 2018.

Lurasidone, already FDA approved for both schizophrenia and mood disorders, is now also FDA approved for use in bipolar depression in the pediatric (ages 10–17 years) population. The approval is based upon the favorable results of a 6-week, placebo-controlled, double-blind trial of lurasidone in children and adolescents with bipolar depression.

Genetics and Schizophrenia: Compulsory Reading for Our Trainees?

Dr. Patrick Sullivan and a cadre of leading psychiatric geneticists have provided us with a "tour-de-force" review of psychiatric genetics. In large part they review the outstanding work of the Psychiatric Genomics Consortium (PGC). They span the landscape from copy number variant to large, genome-wide assessment studies (GWAS). Although the genetics field is complex, dynamic, and without being immersed in it, hard to track progress, this article is really comprehensive and would make great reading (compulsory reading?) for our psychiatric students. The extent to which they are conversant with genetics will also determine how they bridge genetics findings, personalized medicine, and treatment advances in schizophrenia.

Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Borglum AD, Breen G, et al.; Psychiatric Genomics Consortium. Psychiatric genomics: an update and an agenda. Am J Psychiatry 2018;175(1):15-27.

Nature Versus Nurture in Major Depression: Implications for Schizophrenia?

Understanding the etiological heterogeneity of schizophrenia is undoubtedly challenging. However, these same considerations also pertain to other disorders. Peterson and colleagues (2018) exemplify the issues and trajectories of etiological diversity in major depression. In an elegant analysis of international data from almost 10,000 subjects, 13% of the liability for major depression resided in genome-wide interaction with environmental adversities. Given the current focus on early adversities, childhood trauma, and prodromal psychosis, these findings, as well as the study methodology itself, hold significance for schizophrenia research.

Peterson R, Cai N, Dahl AW, Bigdeli T, Edwards AC, Webb BT, et al. Molecular genetic analysis subdivided by adversity exposure suggests etiologic heterogeneity in major depression. Am J Psychiatry 2018 Mar 2:appi.ajp.2017.17060621. doi: 10.1176/appi.ajp.2017.17060621. [Epub ahead of press]

Depression and Schizophrenia

Depression in schizophrenia is common and is the major contributor to the heightened risk and actual rate of suicide among patients with schizophrenia. Gregory and colleagues (2017) describe a meta-analysis of depressive symptoms and their treatment in schizophrenia. It is stark that while depressive symptoms are common in schizophrenia, the number and quality of studies addressing the treatment of comorbid depression is inadequate. In their meta-analysis—which ultimately included just seven studies—the trials were varied in definition of depression and in the reporting of treatment outcomes. Also, studies tended to be solely pharmacologic in design, with inadequate understanding, therefore, of psychological interventions that in place likely synergize with medication therapies.

Gregory A, Mallikarjun P, Upthegrove R. Treatment of depression in schizophrenia: systematic review and meta-analysis. Br J Psychiatry 2017;211(4):198-204.

"Dopamine Dysregulation Syndrome" Rises Again

In response to the complexity of heterogeneity in psychosis, the appreciation of the central role of dopamine and abnormalities thereupon in schizophrenia, and the efforts to diminish the stigma about schizophrenia, there was a move several years ago to rename schizophrenia as "dopamine dysregulation syndrome." This interesting functional neuroimaging study of 22 psychotic patients with bipolar disorder, 16 with schizophrenia, showed a tight relationship between dopamine synthesis and positive psychotic symptoms, with a similar overall profile between bipolar and schizophrenic patients. It's a very well-conducted study. It is similar in outcome to the BSNIP study described earlier in ***CS***.

Jauhar S, Nour MM, Veronese M, Rogdaki M, Bonoldi I, Azis M, et al. A test of the transdiagnostic dopamine hypothesis of psychosis using positron emission tomographic imaging in bipolar affective disorder and schizophrenia. JAMA Psychiatry 2017;74(12):1206-1213.

Increasing Mortality with Serious Mental Illness?

The higher mortality among people with serious mental illness is well known, with estimates suggesting a 15-year premature death statistic for people with schizophrenia. Hayes and colleagues (2017), based upon a primary care cohort evaluated by electronic medical records between 2000–2014, suggest that this mortality gap is increasing—both for schizophrenia and bipolar disorder. The heightened mortality rate was 2.08 (observed/expected adjusted hazard ratio) for schizophrenia, with 1.79 for bipolar disorder patients. Looking over the study period from 2000–2014, mortality rates increased by 0.14/year for bipolar patients and a sharper increase (0.34/year after 2010) in patients with schizophrenia. This study highlights the need to address multiple adverse and social factors, polypharmacy, suicide, and physical comorbidities.

Hayes JF, Marston L, Walters K, King MB, Osborn DPJ. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. Br J Psychiatry 2017;211(3):175-181.

Danish Clozapine Registry Study Shows Reduced Mortality

Wimberley and colleagues (2017) conducted an important longitudinal, cross-registry Danish study involving 1,300 people receiving clozapine for treatment-refractory schizophrenia in comparison to 1,000 patients also treatment-refractory on other antipsychotics. Over the study period, 15% remained on clozapine alone, 17% were on clozapine with another antipsychotic, 17% were on non-clozapine monotherapy with 26% on polypharmacy, and 26% of patients were off medications. One hundred and fifty-eight patients died and 602 (25%) of patients had some deliberate self-harm. Clozapine treatment was associated with lower mortality—largely driven by reduced suicidality—compared to non-clozapine antipsychotic therapy. Higher mortality was observed in patients who

discontinued clozapine. The findings are important, though teasing out reasons for death is limited from this cross-registration pharmacoepidemiologic study.

Wimberley T, MacCabe JH, Laursen TM, Sørensen HJ, Astrup A, Horsdal HT, et al. Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia. Am J Psychiatry 2017;174(10):990-998.

Risk Factors for Schizophrenia: Variability of Effect

Clearly, there is no single factor that causes schizophrenia. In a comprehensive review (Radua et al., 2018) of a myriad of previously studied risk factors for schizophrenia, only ultra-high risk status and Black-Caribbean status in England were robust and compelling associations with psychosis. Other, less compelling, yet still noteworthy, risk factors were identified: season of birth, childhood trauma, childhood social withdrawal, toxoplasma gondii exposure, presence of minor physical anomalies, anhedonia, olfactory impairment, left-handedness, and poor premorbid IQ. The level of each effect is variable and the study did not address additive/synergistic effects.

Radua J, Ramella-Cravaro V, Ioannidis JPA, Reichenberg A, Phiphopthatsanee N, Amir T, et al. What causes psychosis? An umbrella review of risk and protective factors. World Psychiatry 2018;17(1):49-66.

Relapse and Maintenance Antipsychotics: Symptom Profiles

Takeuchi and colleagues (2017) conducted an analysis of symptom profiles over one year in relapse prevention studies. Among 11 studies, placebo assignment yielded more turbulent and persistent psychotic symptoms culminating in greater rates of relapse. This review included stable patients and with only a one-year follow-up. In an accompanying provocative editorial, Leucht and Davis (2017) suggest that there is more heterogeneity of results among treatment studies, and that there are concerns of drug-related brain volume loss and potentially dopamine supersensitivity effects.

In another important study, Leucht and colleagues (2017) analyzed data on over 28,000 patients participating in placebo-controlled trials of first-generation (FGAs) and second-generation antipsychotics (SGAs). The response was sobering, with substantial improvement in only a minority of patients. Evaluations of quality of life or social functioning were limited to a handful of studies. There was a differential time effect in this meta-analysis, although it was driven more by a larger placebo effect in more recent studies and in pharmaceutically funded studies. The authors recommend more selective recruitment strategies into modern day clinical trials.

Takeuchi H, Kantor N, Sanches M, Fervaha G, Agid O, Remington G. One-year symptom trajectories in patients with stable schizophrenia maintained on antipsychotics versus placebo: meta-analysis. Br J Psychiatry 2017;211(3):137-143.

Leucht S, Davis JM. Do antipsychotic drugs lose their efficacy for relapse prevention over time? Br J Psychiatry 2017;211(3):127-129.

Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. Am J Psychiatry 2017;174(10):927-942.

Authoritative Review of Long-Term Antipsychotic Therapy

An important and provocative 7-year follow-up of first-episode psychosis patients randomized to either early dose reduction or sustained drug therapy demonstrated similar relapse rates (61.5% vs. 68.6%, respectively) yet (paradoxically) superior functional remission in patients who had discontinued medications (Wunderink et al., 2013). This study casts serious doubt on the long-term benefits of antipsychotics as well as the risk of adverse effects of drugs that might have contributed to a poorer outcome in the maintenance-therapy group. Provocative thoughts, indeed. Moreover, the questions can only be best addressed by further drug-free, long-term trials, which are no longer ethical.

Given that, senior clinical researchers (Goff et al., 2017) have provided us with an authoritative review of available clinical trials and related basic science evidence to address these concerns. They affirm the benefit and effectiveness of initial antipsychotic therapy—recognizing there is a small (as yet indistinguishable) group of patients (perhaps under/about 25%) who remit and remain remitted with therapy alone—as well as the absence of any negative effect on outcome and/or worsening of illness course with medications and the importance of closing the gap on duration of unrelated illness. Evidence that antipsychotics are "neurotoxic" (by damaging neurons, by reducing brain volume) is not compelling but is, of course, a concern. The corollary—that antipsychotics are "neuroprotective"—is not proved either. The article is clear and authoritative.

Wunderink L, Nieboer RM, Wiersma D, Systema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. JAMA Psychiatry 2013;70(9):913-920.

Goff D, Falkai P, Fleischhacker W, Girgis RR, Kahn RM, Uchida H, et al. The long-term effects of antipsychotic medication on clinical course in schizophrenia. Am J Psychiatry 2017;174(9):840-849.

Immune Therapy for Schizophrenia

Our former colleague and schizophrenia researcher leader published an influential paper in the early 1980's showing that dialysis was not an effective treatment for schizophrenia, believing the hypothesis that this approach would cleanse the body of noxious chemicals. In an almost similarly provocative manner, an intriguing case report by Miyaoka and colleagues (2017) reports an 8-year continued remission of psychosis in a 24-year-old man with treatment-refractory schizophrenia who underwent bone marrow transplantation (for treatment of leukemia). The authors also cite another similar case report and they ascribe the sustained resolution of psychosis directly to this immune cellular therapy.

Miyaoka T, Wake R, Hashioka S, Hayashida M, Oh-Nishi A, Azis IA, et al. Remission of psychosis in treatment-resistant schizophrenia following bone marrow transplantation: a case report. Front Psychiatry 2017 Sep 21;8:174. doi: 10.3389/fpsyt.2017.00174. eCollection 2017.

Lack of Effect of Interleukin-6 Receptor Antibody in Schizophrenia

We have covered many reports of neuroinflammation in schizophrenia, including some studies of anti-inflammatory agents as adjunctive treatments. Girgis and colleagues (2018) conducted an important double-blind, placebo-controlled, 12-week trial of tocilizumab—an interleukin-6 antibody—in 36 patients with chronic schizophrenia. Contrary to prevailing neurobiological findings, this well-conducted study found no effect for this selective anti-inflammatory agent. The decline in symptoms in the placebo group is noteworthy and may have marked an effect of the tocilizumab. The authors also provide an alternative hypothesis: namely that this agent does not cross the blood brain barrier and so even if it has peripheral effects (indeed, reductions were observed in plasma C-reactive protein) perhaps it may not have exerted an effect on inflammation in the brain. A very nice study.

Girgis RR, Ciarleglio A, Choo T, Haynes G, Bathon JM, Cremers S, et al. A randomized, double-blind, placebo-controlled clinical trial of tocilizumab, an interleukin-6 receptor antibody, for residual symptoms in schizophrenia. Neuropsychopharmacology 2017 Nov 1. doi: 10.1038/npp.2017.258. [Epub ahead of print]

Whither Psychiatry? Implications for Schizophrenia

Under the leadership of the World Psychiatric Association (WPA), Dr. Dinesh Bhugra and 40 other leaders published a "tour-de-force" review and state-of-affairs of psychiatry as a field. Priority areas that were identified included mental health law, psychiatry and healthcare systems, digital psychiatry, training and workforce needs development of biomarkers. All of these aspects are extremely relevant to how our research and clinical practice will evolve for schizophrenia. The extent to which emergent neuroscience can inform and advance public opinion, policy, and global strategies for schizophrenia will be important.

Bhugra D, Tasman A, Pathare S, Priebe S, Smith S, Torous J, et al. The WPA-Lancet Psychiatry Commission on the future of psychiatry. Lancet Psychiatry 2017;4(10):775-818.

"Mobile Biotypes"

There is a "coming of age" of telecommunication and science, with a growing appreciation that harnessing mobile phone technology and behavioral information can yield important and valid phenotyping data. Thomas Insel (2017) highlights this potential and his enthusiasm is echoed in an accompanying "Viewpoint" by Miner and colleagues (2017) who also detail how this approach can be advanced in clinical trials. They also highlight how artificial intelligence could influence neuroscience research as well.

Insel TR. Digital phenotyping: technology for a new science of behavior. JAMA 2017;318(13):1215-1216.

Miner AS, Milstein A, Hancock JT. Talking to machines about personal mental health problems. JAMA 2017;318(13):1217-1218.

*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.*