Clinical News … update on putative antipsychotics … selective effects and adjunctive treatments … resilience … plasma levels … biotypes for schizophrenia … recovery, suicide and schizophrenia … texting study … home health …

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Update on Putative Antipsychotics

Indivior PLC has conducted a 12-month, open-label trial of a subcutaneous formulation of risperidone (RBP-7000) that is given monthly by injection. Results were in line with earlier studies, with demonstrated efficacy and safety. The study also includes quality-of-life and patient preference measures. The subcutaneous formulation is prepared by a novel two-syringe system that remains sterile while mixed at time of injection.

Another company—Delpor, Inc.—has filed a patent for a long-term delivery approach (PROZOR technology) for subcutaneous implants of antipsychotic medications. The company is currently working on a six-month formulation of risperidone, with corporate expectations that this novel subcutaneous implant will also prove feasible for a three-month formulation of olanzapine. This approach offers the opportunity for sustained delivery of antipsychotic therapy under a condition of guaranteed adherence, yet still with the potential for (easy) withdrawal of the product if difficult adverse effects arise. More to follow on this.

The U.S. Food and Drug Administration (FDA) has approved Alkermes' two-month ARISTADA (aripiprazole lauroxil) extended-release injectable suspension for the treatment of schizophrenia. ARISTADA is now FDA approved in four doses and three dosing duration options (441 mg, 662 mg or 882 mg once monthly, 882 mg once every six weeks and 1,064 mg once every two months) and can be initiated at any dose or interval. Once administered, the prodrug converts to aripiprazole.

The FDA is also reviewing a sNDA for cariprazine (Vraylar), based upon a large randomized, double-blind trial showing that cariprazine reduced relapse rates in patients with schizophrenia.

Another novel antipsychotic—brexpiprazole—has also been studied for agitation related to Alzheimer's disease, with favorable efficacy results from two Phase 3 clinical trials.

Minerva Neurosciences, Inc. is planning a Phase 3 clinical trial of MIN-101 for negative symptoms in patients with schizophrenia. This ambitious study is projected to include some 500 patients in the U.S. and Europe. More on this later.

Sunovion Pharmaceuticals Inc. presented results of a Phase 3 clinical study evaluating lurasidone HCI in children and adolescents (10 to 17 years of age) with major depressive episodes associated with bipolar I disorder (bipolar depression). Improvements in depressive symptoms were observed based on the primary efficacy endpoint of change from baseline to Week 6 on the Children's Depression Rating Scale, Revised.

"Antihostility" Effects of Newer Antipsychotics

Citrome and colleagues (2016) evaluate the "antihostility" effect of cariprazine, a newly approved antipsychotic. While interesting and encouraging, this study (like many before) is an analysis of data pooled from several clinical trials. This observation is important since "antihostility" here is more apt to be described as "anti-agitation" or "anti-anxiety."

Citrome L, Durgam S, Lu K, Ferguson P, Laszlovszky I. The effect of cariprazine on hostility associated with schizophrenia: post hoc analyses from 3 randomized controlled trials. J Clin Psychiatry 2016;77(1):109-115.

Diuretics for Schizophrenia?

The application of drugs used for other conditions to schizophrenia is often serendipitous—most notably, of course, the historical discovery of the anesthetic chlorpromazine's calming effect in psychotic patients. Colleagues in Iran (Rahmanzadeh et al., 2016) describe a small (24 patients), yet provocative, clinical trial of the diuretic bumetanide, which was found to reduce hallucinations over

seven months of treatment under the double-blind, placebo-controlled condition. The results are of interest because bumetanide is a selective inhibitor of a sodium-potassium-chloride cotransporter that, through that effect, enhances the inhibitory effect of GABAergic neurones. This study is a small, intriguing "proof-of-concept" of the GABAergic hypothesis as it relates to dopamine overactivity in schizophrenia.

Rahmanzadeh R, Eftekhari S, Shahbazi A, Khodaei Ardakani MR, Rahmanzade R, Mehrabi S, et al. Schizophr Res 2016. doi: 10.1016/j.schres.2016.12.002. [Epub ahead of print]

Selective Treatment for Tardive Dyskinesia

Hauser and colleagues (2017) present data from a placebo-controlled trial of valbenazine in just over 200 patients (mostly with schizophrenia-schizoaffective disorder diagnoses) who had established tardive dyskinesia (TD). Valbenazine is an inhibitor of vesicular monoamine transporter 2 (VMAT2) that is now FDA approved for the treatment of TD. In a six-week study of 63 centers that had a 42-week extension phase, TD scores reduced with both 80 mg/day and 40 mg/day doses of valbenazine, with essentially similar rates of sedation (at just over 5% of patients) among each dosage group. There were no other major adverse effects.

Hauser RA, Factor SA, Marder SR, Knesevich MA, Ramirez PM, Jimenez R, et al. KINECT 3: A phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. Am J Psychiatry 2017;174(5):476-484.

Antipsychotic Plasma Levels: Old Wine in a New Bottle?

Horvitz-Lennon and colleagues (2017) provide a thoughtful synthesis—coupled with four illustrative, brief case scenarios—on the current utility of antipsychotic plasma levels. Their appraisal suggests a continued role, however selective, that is most evident in medication nonadherence and in neuroleptic-responsive circumstances where intolerable side effects curtail treatment. The role of clozapine plasma levels in informing and managing adverse effects of this drug is also highlighted in this review.

Horvitz-Lennon M, Mattke S, Predmore Z, Howes OD. The role of antipsychotic plasma levels in the treatment of schizophrenia. Am J Psychiatry 2017;174(5):421-426.

Brainless Psychiatry?

Stephen Heckers (2017), the editor of *JAMA Psychiatry*, makes an impassioned plea for better integration of neuroscience into the training of psychiatry residents. His piece is part of a new series launched by the journal, Clinical Challenge and Review, which complements a national initiative—the National Neuroscience Curriculum Initiative—to improve neuroscience literacy among psychiatry trainees. Important stuff.

Heckers S. Project for a scientific psychiatry: neuroscience literacy. JAMA Psychiatry 2017;74(4):315.

Biotypes for Schizophrenia: Gathering Momentum?

In an earlier issue of ***Clinical News***, we described a fascinating study by Clements and colleagues (2015) that identified three neurobiologically distinct groups—so-called "biotypes" of psychosis that, while of similar phenomenology, were separable on the basis of clustering of neurobiological measures. In another sample of 549 patients with schizophrenia, Dickinson and colleagues (2017) performed a cluster analysis of symptom profiles that identified three groups: low-symptom (n=301), distress (n=121), and deficit (n=127) groups. Comparing these subset of patients that clustered into each of these three groups, Dickinson and colleagues found meaningful between-group differences on functional magnetic resonance imaging and cognitive measures. There is some general, but not specific, semblance between Clements and colleagues' new findings versus their earlier findings describing three biotypes. Of greater significance is the delineation of research strategies that go beyond symptom profiles in an attempt to define neurobiological signature(s) for psychosis.

Dickinson D, Pratt DN, Giangrande EJ, Grunnagle M, Orel J, Weinberger DR, et al. Attacking heterogeneity in schizophrenia by deriving clinical subgroups from widely available symptom data. Schizophr Bull 2017 Mar 20. doi: 10.1093/schbul/sbx039. [Epub ahead of print]

Domains of Psychopathology in Schizophrenia

Cuesta and Peralta, Spanish phenomenologists who have contributed to the understanding of the phenomenology and nosology of schizophrenia, provide a thoughtful account of symptom domains, plausible psychobiology, and schizophrenia. They propose a research strategy toward symptom understanding and clinical heterogeneity in schizophrenia. An interesting read.

Cuesta MJ, Peralta V. Going beyond classic descriptions to future phenomenology of schizophrenia. JAMA Psychiatry 2016;73(10):1010-1012.

Recovery, Suicide and Schizophrenia

Suicide in schizophrenia is a major concern, with rates at about 4% and rates of deliberate self-harm being about

50%. Jahn and colleagues (2016) provide an analysis of data from 169 patients with schizophrenia and they found that patients who were advanced in their recovery journey had lower suicidality. The extent of recovery focus is unrelated to positive or negative symptoms.

Jahn DR, DeVylder JE, Drapalski AL, Medoff D, Dixon LB. Personal recovery as a protective factor against suicide ideation in individuals with schizophrenia. J Nerv Ment Dis 2016;204(11):827-831.

Positive Psychiatry: Understanding Resilience in Schizophrenia

Jeste, Palmer and Saks (2017) provide an impassioned and cogent "call for action" to better understand the nature of better outcomes, of resilience, and of optimism among patients with schizophrenia. Approximately 30 years ago, Harding and colleagues—in the Vermont longitudinal study—rocked our field with the positive outcomes many years later among heretofore long-stay, institutionalized patients with chronic schizophrenia. Jeste, Palmer and Saks refer to a broad handbook called *Positive Psychiatry* that turns our orientation from studying deficits to understanding strengths, resilience, and positive outcomes. This approach resonates with recovery, offers hope, and might produce meaningful changes in treatments. Time will tell.

Jeste DV, Palmer BW, Saks ER. Why we need positive psychiatry for schizophrenia and other psychotic disorders. Schizophr Bull 2017;43(2):227-229.

Texting Study Lowers Cholesterol Level

Chow and colleagues (2016) report on the Tobacco, Exercise and Diet Messages [TEXT ME] Australian six-month clinical trial among 710 (nonpsychiatric) patients with known heart disease. Using text messaging to provide reminders as well as recommendations on exercise and health behaviors, the study showed impressive reductions in LDL cholesterol (by 5 points), systolic blood pressure (8 points), and body mass index (1.3 points). A further confirmatory is underway. Clearly, this approach holds wide applicability for schizophrenia research.

Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, et al. Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. JAMA 2015;314(12):1255-1263.

Home Health and Metabolic Indices for Serious Mental Illness

Druss and colleagues (2017) report on an innovative pragmatic trial comparing a home health integrated medical and psychiatric care approach to usual care among 447 outpatients with schizophrenia (89 of whom had diagnoses of schizophrenia or schizoaffective disorder). Although the innovative behavioral home health model was shown to improve metabolic health in these patients, there were also similar improvements in the usual core group. Chwastiak and Fortney (2016) provide a nice synthesis of findings to date and how this important study should be interpreted. A stepped approach, ultimately favoring individualization of care, is advocated.

Druss BG, von Esenwein SA, Glick GE, Deubler E, Lally C, Ward MC, et al. Randomized trial of an integrated behavioral health home: the health outcomes management and evaluation (HOME) study. Am J Psychiatry 2017;174(3):246-255.

Chwastiak L, Fortney J. Learning to integrate cardiometabolic care in serious mental illness. Am J Psychiatry 2017;174(3):199-201.

*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.*