# Clinical News … antipsychotic updates … prodrome detection … first-episode schizophrenia management … brain inflammation … MRI brain "fingerprint" … long-acting injectable antipsychotics … fish oil and schizophrenia … metformin for metabolic dysfunction … legacy through philanthropy …

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## Update on Antipsychotics

We had a recent informative review on brexpiprazole (McEvoy and Citrome, 2016). A supplemental New Drug Application (sNDA) has now been submitted to the U.S. Food and Drug Administration (FDA) for consideration of brexpiprazole as a maintenance treatment for schizophrenia. The application is based upon a one-year withdrawal study in which stabilized patients were randomized to either continue on brexpiprazole (n=94) or withdraw brexpiprazole to be on placebo (n=104). The study ended early because brexpiprazole was demonstrated to be efficacious.

Minerva Neurosciences, a biopharmaceutical company based in Waltham, MA, has completed a Phase 2b clinical trial of a putative antipsychotic MIN-101, which has an interesting proposed mechanism of action as a combined serotonin 5-HT2A and sigma2 antagonist. Minerva has submitted an Investigational New Drug application to the FDA.

Intra-Cellular Therapies (ITP) has completed a Phase 3 clinical trial of ITI-007, a putative antipsychotic previously described in ***Clinical News***, with both 40 mg and 60 mg doses being efficacious. The metabolic profile was similar to placebo. ITP has also initiated patient enrollment for a Phase 3 ITI-007 clinical trial in bipolar depression.

Alkermes plc has launched another component of their Phase 3 clinical schizophrenia research program for ALKS 3831, an investigational drug that is a combination of samidorphan and olanzapine. The study, called ENLIGHTEN-2, will evaluate the weight gain profile of ALKS 3831 compared to olanzapine over six months.

The FDA has removed a partial clinical hold on FORUM Pharmaceuticals' Phase 3 clinical schizophrenia study of encenicline, an alpha-7 receptor partial agonist. Phase 3 trials of encenicline to treat Alzheimer's disease remain on clinical hold while FORUM gathers and analyzes trial data.

## Interesting Scientific and Policy Articles Regarding Prodromal Psychosis and Prevention

*JAMA Psychiatry* hosts several articles that are as representative as any of the welcome shift in focus in psychiatry toward early intervention. As a follow-up on reports in prior issues of ***Clinical News***, Fusar-Poli and colleagues (2016) attempt to discriminate particular at-risk trajectories within the broad population of prodromal subjects. In a meta-analysis of 4,227 at-risk subjects from thirty-three follow-up studies, they found that the subgroup characterized more by Brief Limited Intermittent Psychotic Symptoms (BLIPS) was at a higher risk of conversion to psychosis than those subjects more characterized through outer symptoms and/or genetic risk. From a different, yet complimentary vantage point, Mollon and colleagues (2016) drew from a community sample of some 1,600 people and reported that individuals with subclinical/subthreshold psychotic symptoms also exhibited mild cognitive impairments, especially in working memory.

In two accompanying commentaries, Gur (2016) and Cornblatt/Carrión (2016) highlight how such subtle findings can be harnessed toward primary prevention strategies. Their insights are amplified by Srihari and colleagues (2016), who take a systems approach to service delivery, and they delineate realistic and aspirational goals for population health-early intervention. All-in-all, a provocative series of articles that advances our appreciation of where our field has traveled from and is going to.

Fusar-Poli P, Cappucciati M, Borgwardt S, Woods SW, Addington J, Nelson B, et al. Heterogeneity of psychosis risk within individuals at clinical high risk: a meta-analytical stratification. JAMA Psychiatry 2016;73(2):113-120.

Mollon J, David AS, Morgan C, Frissa S, Glahn D, Pilecka I, et al. Psychotic experiences and neuropsychological functioning in a population-based sample. JAMA Psychiatry 2016;73(2):129-138.

Gur RC. Prospective community studies linking cognitive deficits to subclinical symptoms and a step toward precision medicine. JAMA Psychiatry 2016;73(2):109-110.

Cornblatt BA, Carrión RE. Deconstructing the psychosis risk syndrome: moving the field of prevention forward. JAMA Psychiatry 2016;73(2):105-106.

Srihari VH, Jani A, Gray M. Early intervention for psychotic disorders: building population health systems. JAMA Psychiatry 2016;73(2):101-102.

## More Refined Analyses of Risk of Later Psychosis among High-Risk Samples

There have been several recent studies and commentaries (Cornblatt et al., 2015; Fusar-Poli et al., 2015; Castle

and Singh, 2015; Yung, 2015) that sharpen the focus on risk detection and potentially early intervention among patients with prodromal features and/or high-risk populations. Cornblatt and colleagues report an impressive 82% positive predictive value (60% sensitivity, 97% specificity) over six years in a large community-based sample. Fusar-Poli and colleagues conducted an area-under-curve analysis of eleven high-risk studies and showed how high-risk instruments and interviews can aid in accurate detection of risk of later psychosis. In an interesting debate, Castle and Singh discuss the pros and cons of developing (ultra) special at-risk services versus integration within improved overall mental health services. Alison Yung, ***CS*** Editorial Board Member, provides a thoughtful commentary on the state of this important focus of schizophrenia research.

Cornblatt BA, Carrión RE, Auther A, McLaughlin D, Olsen RH, John M, et al. Psychosis prevention: a modified clinical high risk perspective from the Recognition and Prevention (RAP) program. Am J Psychiatry 2015;172(10):986-994.

Fusar-Poli P, Cappucciati M, Rutigliano G, Schultze-Lutter F, Bonoldi I, Borgwardt S, et al. At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. World Psychiatry 2015;14(3):322-332.

Castle DJ, Singh SP. Early intervention in psychosis: still the "best buy"? Br J Psych 2015;207(4):288-292.

Yung AR. Toward improved risk prediction in individuals at high risk of psychotic disorders. Am J Psychiatry 2015;172(10):932-933.

## Brain Inflammation Antedates Florid Psychosis—Provocative New Findings

Two small European studies of positron emission tomography (PET) suggested enhanced microglial activity, reflecting active neuroinflammation in patients with schizophrenia. Now, a leading British group of investigators (Bloomfield et al., 2015) has shown that this evidence of neuroinflammation also exists in "patients" who are at ultra risk (n=14) for later development of psychosis. This study also included both schizophrenia patient and healthy control groups. The advancement in PET imaging now allows a tracer (specific for the 18kD translocator protein; TSPO) that can track inflammation in microglia (that had heretofore been largely considered as unaffected in schizophrenia). In both high-risk patients and in schizophrenia patients, elevated inflammation was confirmed with heightened microglial activity. In high-risk subjects, this was also highly related (r=0.730) to symptom severity. Very provocative findings.

Bloomfield PS, Selvaraj S, Veronese M, Rizzo G, Bertoldo A, Owen DR, et al. Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [(11)C]PBR28 PET brain imaging study. Am J Psychiatry 2016;173(1):44-52.

## Irish High-Risk Cohort Shows White Matter MRI Differences

An interesting study by O'Hanlon and colleagues (2015) shows white matter tract changes in 28 children-adolescents who had psychotic experiences. The findings are subtle, focus on striatum and related regions, and may antedate psychotic experiences although, since this is a population-based, cross-sectional study, this can't be proven.

O'Hanlon E, Leemans A, Kelleher I, Clarke MC, Roddy S, Coughlan H, et al. White matter differences among adolescents reporting psychotic experiences: a population-based diffusion magnetic resonance imaging study. JAMA Psychiatry 2015;72(7):668-677.

## "Star Wars" Functional MRI Study Suggests Individual Brain "Fingerprint"

While we can recall with excitement the original findings by Dr. Tim Crow in England and Dr. Daniel Weinberger in the U.S. concerning brain changes in schizophrenia, the pace of brain imaging advancement has been staggering. To that end, this study examining connectomes—neural networks—suggests that there is a remarkable individual variability in normal subjects. This formative study takes this connectomics approach up a notch further and suggests that we have come to a point where it might be possible to discern a fingerprint related to each individual. Time will tell.

Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, et al. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. Nat Neurosci 2015;18(11):1664-1671.

## Early-Stage Schizophrenia Treatment Advances

Two studies from South Africa by Dr. Chiliza and colleagues reflect advances in both pharmacological and psychosocial treatments of early-stage schizophrenia. The first describes the longitudinal study of depot antipsychotic in first-episode psychosis: a 12-month prospective pragmatic trial of a depot antipsychotic combined with an assertive monitoring program among 207 patients with first-episode psychosis. Eighty-two percent of patients responded to treatment, while 5% were classified as treatment refractory based upon a priori, appropriate criteria.

The second study details the metabolic profile of first-episode psychosis followed for one year. Chiliza and colleagues then describe the metabolic profile over twelve months in their first-episode psychosis sample, drawn mainly from South Africa yet also including some patients

from Nigeria. In contrast to other reports of American and European patient populations, there is relatively little known of the prevalence and trajectory of metabolic disturbances in patients from this large continent. Dr. Chiliza and colleagues report that over the course of twelve months of treatment with long-acting injectable flupenthixol (a first-generation antipsychotic [FGA] in depot formulation), there were significant increases in triglyceride levels, high diversity lipoproteins, overall body mass index and waist circumference. Given the use of an FGA in this cohort, only one-third of patients had extrapyramidal side effects and these were, overall, mild.

Chiliza B, Ojagbemi A, Esan O, Asmal L, Oosthuizen P, Kidd M, et al. Combining depot antipsychotic with an assertive monitoring programme for treating first-episode schizophrenia in a resource-constrained setting. Early Interv Psychiatry 2016;10(1):54-62.

Chiliza B, Asmal L, Oosthuizen P, van Niekerk E, Erasmus R, Kidd M, et al. Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic. Eur Psychiatry 2015;30(2):277-283.

## Early Use of Long-Acting Injectable Antipsychotic Medication?

Typically, long-acting injectable (LAI) antipsychotics are underutilized—as well as used later on in the illness trajectory—by clinicians in the U.S. compared to their European counterparts. Of relevance to this observation is a twelve-month study by Subotnik and colleagues (2015) comparing LAI risperidone to oral risperidone among eighty-six first-episode schizophrenia patients. Relapse was noted among 5% of LAI-treated patients compared with 33% among oral risperidone-treated patients. It appeared that this benefit was driven by superior medication adherence in one LAI group. This is an important and very well conducted study.

Subotnik KL, Casaus LR, Ventura J, Luo JS, Hellemann GS, Gretchen-Doorly D, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. A randomized clinical trial. JAMA Psychiatry 2015;72(8):822-829.

## Fish Oil for First-Episode Schizophrenia

Omega-3-polyunsaturated fatty acids (PUFAs) have long been considered as a potential adjunctive treatment for schizophrenia, especially earlier as a treatment for antipsychotic-induced tardive dyskinesia. The results of efficacy studies in chronic schizophrenia have been mixed. With the shift in our field toward early intervention, there has been renewed interest in strategies—especially relatively safe ones—that could be used early in treatment. To this end, Powelczyk and colleagues (2016) report on an interesting 26-week, placebo-controlled study of PUFAs in seventy-one first-episode schizophrenia patients. The symptom improvements were impressive in extent, broad across symptom profiles, and most pronounced for depressive symptomology.

Pawelczyk T, Grancow-Grabka M, Kotlicka-Antczak M, Trafalska E, Pawelczyk A. A randomized controlled study of the efficacy of six-month supplementation with concentrated fish oil rich in omega-3 polyunsaturated fatty acids in first episode schizophrenia. J Psychiatr Res 2016;73:34-44.

## Antipsychotic-Induced Diabetes in Adolescents

Galling and colleagues (2016) have conducted an important review and meta-analysis of published studies—thirteen studies in all—of childhood-adolescent populations and antipsychotic exposure and risk of type 2 diabetes mellitus. Notably, eleven of the studies were retrospective in nature. That said, the authors found a higher risk of diabetes in adolescents exposed to antipsychotics. Duration of exposure and use of olanzapine stood out. Sobering results.

Galling B, Roldán A, Nielsen RE, Nielsen J, Gerhard T, Carbon M, et al. Type 2 diabetes mellitus in youth exposed to antipsychotics: a systematic review and meta-analysis. JAMA Psychiatry 2016 Jan 20. doi:10.001/jamapsychiatry.2015.2923. [Epub ahead of print]

## Earlier Use of Metformin for Metabolic Dysfunction in Schizophrenia?

Wu and colleagues (2016) have produced another compelling report of the effect of metformin in reducing dyslipidemia in first-episode schizophrenia patients, combining results from two Chinese studies. While the drug interactions with metformin as well as selective effects of metformin on specific antipsychotics is not addressed in this study, where patients received one of four antipsychotics (including clozapine) the impact is nevertheless compelling.

Wu RR, Zhang FY, Gao KM, Ou JJ, Shao P, Jin H, et al. Metformin treatment of antipsychotic-induced dyslipidemia: an analysis of two randomized, placebo-controlled trials. Mol Psychiatry 2016 Jan 26. doi: 10.1038/mp.2015.221. [Epub ahead of print]

## Another Perspective on Antipsychotic-Induced Weight Gain

Nielsen and colleagues (2016), in a positron emission tomography study of amisulpride in first-episode psychosis patients, show an intriguing association between dopamine-related reward activation in the striatum and antipsychotic-induced weight gain during six weeks of treatment with the selective dopamine-blocking antipsychotic amisulpride. An editorial by Kapur and Marques (2016)

highlights the importance of this Danish study, although also points out that many other obesity-related aspects—genetics, neuropeptides, insulin, ghrelin, orexin, and non-dopamine neurotransmitters (e.g., serotonin)—may also be in play.

Nielsen MØ, Rostrup E, Wulff S, Glenthøj B, Ebdrup BH. Striatal reward activity and antipsychotic-associated weight change in patients with schizophrenia undergoing initial treatment. JAMA Psychiatry 2016;73(2):121-128.

Kapur S, Marques TR. Dopamine, striatum, antipsychotics, and questions about weight gain. JAMA Psychiatry 2016;73(2):107-108.

## RAISE Care Cost Effective

We have reported on the NIMH RAISE study in a previous ***Clinical News***. Rosenheck and colleagues (2016) provide an elegant (yet complicated) economic analysis of the cost effectiveness of the RAISE Navigate intervention (among 223 patients) compared with regular community care (among 183 patients). Interestingly, the intervention was most cost effective in those with shorter duration of untreated psychosis. The paper also highlights that while it's more costly to implement such a concerted approach, it is also "literally" cost effective. Invest more up front is a good takeaway from this important study.

Rosenheck R, Leslie D, Sint K, Lin H, Robinson DG, Schooler NR, et al. Cost-effectiveness of comprehensive, integrated care for first episode psychosis in the NIMH RAISE early treatment program. Schizophr Bull 2016 Jan 31. doi: 10.1093/schbul/sbv224. [Epub ahead of print]

## The Passing of Two Schizophrenia Philanthropists

Mrs. Connie Lieber, who for years headed up the Brain and Behavior Research Foundation (BBRF, formerly "NARSAD") passed away earlier this year. Mrs. Lieber was a remarkable lady whose impact on schizophrenia research was immense. Similarly, Mr. Ted Stanley, who co-founded with his wife the Stanley Medical Research Institute (SMRI), passed away. Mr. Stanley's impact on schizophrenia research has also been profound. Collectively, BBRF and SMRI are the two largest, non-federal institutions that support research on schizophrenia. Both Mrs. Lieber and Mr. Stanley have left an extraordinary legacy.

*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.*