Clinical News

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Antipsychotic Drug Development Update: Pipeline and Progress

America's Biopharmaceutical Research Companies' 2012 Annual Report (PhRMA, 2012) provides encouragement for the drug development pipeline for the treatment of schizophrenia. The report details 36 drugs under consideration for schizophrenia, compared with 52 compounds under investigation for depression, 26 for anxiety disorders and 26 for addictions. The listing comprises drugs at various stages of development, from additional FDA indications for already FDA-approved drugs through to Phase I studies of putative antipsychotic compounds in early development. By contrast, only 3 drugs are under development for eating disorders and 10 drugs under development specifically for cognitive disorders. For schizophrenia drug development, the drugs represent an interesting and encouraging array of putative mechanisms of action: alpha-7 nicotinic receptor antagonism, serotonin 6 receptor antagonism, glutamate receptor antagonism, PDE 10A inhibitor, and neurotransmitter receptor modulators. The majority of drugs listed are in Phase II/III of development. It will be of interest to see how all this pans out. As an interesting counterpoint, Chris Fibiger (2012)—a noted psychopharmacologist—recently made a plea for a more innovative approach to drug development, with his assessment drawing the conclusion that we have engendered a "me-too psychopharmacology."

America's Biopharmaceutical Research Companies. Medicines in development for mental illnesses 2012 Report. Retrieved from http://www.phrma.org/sites/default/files/422/phrmamedsindevmentalillness2012.pdf.

Fibiger HC. Psychiatry, the pharmaceutical industry, and the road to better therapeutics. Schizophr Bull 2012;38(4):649-650.

Update on Long-Acting Injectable Antipsychotics

The past few years have witnessed second-generation antipsychotic medications become available in long-acting injectable formulations. This trend continues. The development of a depot form of aripiprazole—previously described in ***CS***—has been slowed down by the FDA pending additional information on the preparation of the injectable formulation. The launch of this depot preparation remains as the plan. Interestingly, there is now a three-month formulation of paliperidone palmitate under consideration. This preparation will now be tested in Phase III clinical trials, with a plan to study this formulation in some 1,800 patients with schizophrenia.

Update on Staccato Loxapine, Another Novel Formulation

In previous issues of ***CS***, we have kept you informed of the development and FDA review of this vaporized (inhalant) formulation of loxapine. The FDA appears to be in the final stages of review of this putative antipsychotic … more later.

New Pomaglumetad Methionil Clinical Trials Data Yield Future Decision

The field has become energized by the potential of glutamatergic agents under development to exhibit putative antipsychotic efficacy. Several are now under consideration. As described in previous issues of ***CS***, pomaglumetad methionil (mGlu2/3 or LY 2140023) is a novel glutamatergic agent that does not directly bind to dopamine D2 receptors. Accordingly, extant data suggest that it is less associated with extrapyramidal and other side effects. Eli Lilly and Company has indicated that, in a recent trial, this agent did not perform better than placebo (while risperidone did outperform placebo) in an interim analysis from a key study. Safety in this study was not an issue. While data from a study of mGlu2/3 as an adjunctive agent is awaited, Eli Lilly has judiciously decided not to pursue a schizophrenia indication for this agent. This outcome represents an important decision for our field.

Schizophrenia Trials Network (STN) Study of Cognitive Remediation Shows Promise to Advance Further Study

Keefe and colleagues (2012) provide a real-world "proof-of-concept" study—the so called "Cognitive Remediation in the Schizophrenia Trials Network" (CRSTN)—on the efficacy and tolerability of cognitive remediation in schizophrenia among 9 academic sites. The study comprised patients enrolled from sites that are part of the Schizophrenia Trials Network (STN). Forty-one patients participated, with 31 patients completing the entire 40 cognitive remediation sessions. The results indicate that cognitive remediation is applicable to clinical settings and produces some improvements.

The study was also an impetus for a new cognitive remediation study in schizophrenia: Evaluation of a Cognitively Adaptive e-treatment in Schizophrenia–diagnosed Adults: A Remediation-based Approach ("e-CAeSAR"). This 6-month treatment study is being conducted at 11 STN sites and is being funded by the National Institute of Mental Health in association with the company Brain Plasticity, Inc. It will be interesting to see whether this more extensive study of cognitive remediation also demonstrates meaningful clinical efficacy and tolerability of this approach for treating schizophrenia … more later.

Keefe RS, Vinogradov S, Medalia A, Buckley PF, Caroff SN, D'Souza DC, et al. Feasibility and pilot efficacy results from the multisite cognitive remediation in the schizophrenia trials network (CRSTN) randomized controlled trial. J Clin Psychiatry 2012;73(7):1016-1022.

Mobile Phone Technology Can Be Used to Monitor Psychotic Symptoms

Ben-Zeev and colleagues (2012) report on a simple yet intriguing study to compare weekly recall of psychotic symptoms by retrospective "logging" of experiences as compared with intermittent, real-time self-evaluation using mobile telephone technology. Perhaps not surprisingly, they found that symptoms varied within patients across the week. Retrospective recall did account for symptoms as patients experienced them although the affect and intensity were less well recorded by this approach. The real-time mobile phone self-assessments were effective in recording symptoms and providing a chronology of symptoms. Although the study is short of details, it appears that patients tolerated well the mobile phones and this approach did not appear to be too intrusive or to worsen patient's paranoia. Conversely, it would be instructive to know whether this approach could improve insight over time. We are likely to see the emergence of social media and mobile phone technologies as clinically meaningful aids in the treatment of patients with schizophrenia.

Ben-Zeev D, McHugo GJ, Xie H, Dobbins K, Young MA. Comparing retrospective reports to real-time/real-place mobile assessments in individuals with schizophrenia and a nonclinical comparison group. Schizophr Bull 2012;38(3):396-404.

Uncommon Autoimmune Conditions are Overrepresented in Patients with Schizophrenia

A study using a database linkage among just over 10,000 schizophrenia patients and over 108,000 control subjects in Taiwan (Chen et al., 2012) found an overrepresentation of many uncommon anti-immune conditions. These included Graves' disease, pernicious anemia, psoriasis, hypersensitivity vasculitis, and celiac disease. However, the strength of these associations was at best modest, with the most pronounced overrepresentation being for the rare condition of hypersensitivity vasculitis. This study is of interest and it extends an emergent literature on immune abnormalities in schizophrenia. There are also similar epidemiological studies that demonstrate overrepresentation of autoimmune disorders in schizophrenia. There is, as well, intense interest in examining for genetic abnormalities in schizophrenia within regions that are known to code for immune function. Results thus far of these latter studies have been inconclusive.

Chen SJ, Chao YL, Chen CY, Chang CM, Wu EC, Wu CS, et al. Prevalence of autoimmune diseases in in-patients with schizophrenia: nationwide population-based study. Br J Psychiatry 2012;200(5):374-380.

Anti-Inflammatory Drugs may have a Role in the Treatment of Schizophrenia?

As detailed in this and in prior editions of ***Clinical News***, there is growing evidence of immune dysfunction in schizophrenia. This provides the rationale for considering nonsteroidal anti-inflammatory drugs (NSAIDs) as a putative augmentation strategy to treat symptoms of schizophrenia. The literature in this area of treatment is quite sparse and a recent meta-analysis by Sommer and colleagues (2012) identified five rigorous, double-blind studies that carefully evaluated NSAIDs. Although the number of studies is clearly small, the results are actually of interest and are potentially encouraging. NSAIDs were found to modestly improve overall symptoms with also some (lesser) effect on positive symptoms. There was some signal of effect for negative symptoms, although this did not appear to be clinically meaningful. This area merits additional attention. Furthermore, the authors point out that NSAIDs might even have an additional (unintended) benefit of potentially ameliorating some cardiovascular and metabolic comorbidities … more later.

Sommer IE, de Witte L, Begemann M, Kahn RS. Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis. J Clin Psychiatry 2012;73(4):414-419.

New Study Confirms Old Finding: Discontinuing Medications Carries Much Heightened Risk of Symptom Recurrence

Several senior members of the ***CS*** Editorial Board (including Drs. Kane, Schooler, and Carpenter) provided seminal evidence decades ago that discontinuing antipsychotic medications (even in first-episode schizophrenia patients who had responded well to treatment) was a risky business. Emsley and colleagues (2012) now reach a similar conclusion in an informative follow-up study of first-episode patients, wherein they report that "intermittent antipsychotic treatment, even after two years of successful treatment, may not be in the best interest of patients who have experienced a single psychotic episode." Their study also shows that symptoms can return abruptly and that detecting "early warning signs" may not be possible or even early enough to obviate an impending relapse. This is an important message that remains true now in an era of pharmacotherapy with second-generation antipsychotics as it did over two decades ago when our ***CS*** Editorial Board leaders made their formative observations on the impact of first-generation antipsychotic medications, treatment discontinuation, and relapse in schizophrenia.

Emsley R, Oosthuizen PP, Koen L, Niehaus DJ, Martinez G. Symptom recurrence following intermittent treatment in first-episode schizophrenia successfully treated for 2 years: a 3-year open-label clinical study. J Clin Psychiatry 2012;73(4):e541-547.

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.*