Clinical News

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Several New Partnerships for Drug Development in Schizophrenia

Although there is much concern regarding the potential "drying up" of the CNS drug development profile globally, there is also encouraging news on this important front. Recently, Lundbeck A/S (a CNS drug giant and the maker of sertindole) and Otsuka Pharmaceutical Company Ltd. (another major CNS drug company and the developers of aripiprazole) have announced a complex, yet exciting, new partnership. This partnership will focus on the joint CNS drug pipeline, and it will include the two companies working together to bring a long-acting injectable form of aripiprazole to clinical practice—pending regulatory approval, of course. A New Drug Application (NDA) for depot aripiprazole is under consideration by the U.S. Food and Drug Administration (FDA). The partnership between Lundbeck and Otsuka will also jointly develop other promising novel agents—including potential treatments for schizophrenia—that they already have "in the works."

Also, Forest Laboratories (who earlier co-launched citalopram with Lundbeck) has teamed up with a leading Hungarian company called Gedeon Richter to develop a highly selective (a dopamine D3/D2 partial agonist) putative antipsychotic called cariprazine. This drug is also currently being studied in patients with mood disorders.

Vanderbilt University is teaming up with a biotech company called Karuna Pharmaceuticals to develop glycine transporter one (GlyT1) inhibitor compounds that may have potential as novel antipsychotic treatments. This work is still in its relative infancy, though it holds great promise. The National Institute of Mental Health (NIMH) has supported initial work by the Vanderbilt neuroscience leaders, as well.

The NIMH has also funded work by another biotech company called Galenea Corp. to develop its novel serotonergically focused putative antipsychotic agents. And, of course, the National Institutes of Health has launched a new program to support drug discovery. So, perhaps we are not in such dire straits after all.

New Study Probes Mechanism of Action of Antipsychotics: Focus on Dopamine Neurotransmission

One of our leading schizophrenia psychopharmacologists, Shitji Kapur, once wrote a paper about antipsychotic drug binding to dopamine receptors that stressed how this pivotal effect was "necessary but not sufficient" for antipsychotic efficacy. New drug development continues to push the limits of the old "dopamine hypothesis" of schizophrenia, as well as advancing our understanding of how antipsychotic medications really work. A recent study by Dr. Valente and colleagues (including Dr. Grace, ***CS*** Editorial Board member), provides another "twist" on how antipsychotics interact with the dopamine system and explains the potential for acute effects of antipsychotics. These investigators conducted an elegant series of studies that examined the impact of haloperidol and sertindole—both in acute and long-term delivery—on dopaminergic neuron firing/depolarization in a mouse model of schizophrenia. The investigators found that both haloperidol and sertindole in acute use caused reduced dopamine cell activity—actually to a similar extent overall. The authors note that these effects are seen in a hyperdopaminergic state. Long-term use had broadly similar and more pronounced effects. The results help illuminate our understanding of how drugs work acutely and also over time.

Valenti O, Cifelli P, Gill KM, Grace AA. Antipsychotic drugs rapidly induce dopamine neuron depolarization block in a developmental rat model of schizophrenia. J Neurosci 2011;31(34):12330-12338.

Olanzapine Goes Generic Too

In an earlier issue of ***CS*** we reported on the FDA's approval of a generic form of risperidone. Recently, the FDA also approved generic versions—both tablet and the wafer formulations—of olanzapine.

Update on Lurasidone

We previously provided results from the PEARL (Program to Evaluate the Antipsychotic Response to Lurasidone) 3 study, which was a six-week, double-blind trial comparing 80 mg/day and 160 mg/day of lurasidone and 600 mg/day of quetiapine, respectively. Results of a one-year extension of this study have become available. The most notable findings are in the metabolic outcomes. Although changes in glucose were similar between both groups, the metabolic profile of cholesterol and lipids, as well as overall weight gain, was more favorable for lurasidone-treated patients. It is important to note that 160 mg/day dosing of lurasidone is not FDA approved in clinical practice.

Continued Concern about Off-Label Use of Antipsychotic Medications

In the last issue of ***CS*** we highlighted an important Veterans Affairs study that reported minimal benefit for antipsychotic medications in the treatment of posttraumatic stress disorder. A forthcoming study of antipsychotic use in foster homes reports that 2% of their children in care were receiving antipsychotic medications (Dosreis et al., 2011). The study, which focused on an analysis of a large Medicaid database (and, consequently, does not contain enough clinical information to clearly explain the patterns of use), has drawn a lot of attention, especially because of the potential to induce weight gain and metabolic disturbances in teenagers. The authors estimated that the risk of developing diabetes mellitus was four times higher among children who received these medications compared with those who did not. The data goes back to 2003 and, of course, prescription patterns, as well as careful monitoring for metabolic side effects, are likely to have changed since then. Nevertheless, the findings are salutary.

Another study (Maher et al., 2011) of the use of antipsychotics in adults also highlights off-label use and evaluates the efficacy and tolerability of antipsychotic medications in published reports from 1995 to the present day. Several conditions are covered and the results—bearing in mind the mixed size and methodologies of studies that were reviewed—are variable, although overall not very encouraging. The most beneficial area of use of antipsychotics was in the management of agitation in patients with dementia—although the FDA warnings for off-label use here are salutary. The best effects in dementia were seen for aripiprazole, olanzapine, and risperidone. Clinicians should be aware of this important study.

Dosreis S, Yoon Y, Rubin DM, Riddle MA, Noll E, Rothbard A. Antipsychotic treatment among youth in foster care. Pediatrics 2011;128(6):e1459-1466. Epub 2011 Nov 21.

Maher AR, Maglione M, Bagley S, Suttorp M, Hu J, Ewing B, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label use in adults: a systematic review and meta-analysis. JAMA 2011;306(1):1359-1369.

Cognitive Behavioral Therapy Study Offers Expanded Treatment Option

Many clinicians are concerned that medications always take "center stage" when talking about the treatment of schizophrenia. Some years ago, there was great interest in cognitive behavioral therapy (CBT) for schizophrenia and initial studies were particularly encouraging. However, as is often the case, subsequent studies produced more inconclusive results. Also, studies were largely from European centers where the applicability to U.S. clinical practice was less clear. Grant and colleagues (most notably with senior author Aaron T. Beck—the founder of CBT) have conducted an exemplary study of CBT over 18 months in 60 patients with schizophrenia. Compared with "standard treatment" (antipsychotic treatment as well as whatever community-based supports [e.g., case management, counseling] that were available), patients receiving CBT showed greater symptomatic gains (in both positive and negative domains) and functional improvements. The effect was robust in this chronically and markedly ill patient population. While it is plausible that either unblended treatment by CBT therapists, as well as potentially greater clinical contact for patients in the CBT group, contributed to these results, it is nevertheless noteworthy that robust outcomes were observed in this more community-based U.S. treatment sample.

Grant PM, Huh GA, Perivoliotis D, Stolar NM, Beck AT. Randomized trial to evaluate the efficacy of cognitive therapy to low-functioning patients with schizophrenia. Arch Gen Psychiatry 2011 Oct 3. doi:10.1001/archgenpsychiatry.2011.129.

Stigma and Schizophrenia

In a previous issue of ***CS*** we highlighted the European study of stigma among people with schizophrenia (the INDIGO study; Thornicroft et al., 2009). Now, the results of a large U.S. study of stigma have been published. Pandya and colleagues (2011) examined attitudes to illness and openness regarding their diagnosis among 258 adults with schizophrenia who took an online survey of 17-minute duration. Perhaps, not surprisingly, people were least open about their diagnosis to law enforcement personnel. Patients who reported better health also tended to be more forthcoming about their illness. There was a relatively low disclosure of illness at place of worship, although respondents felt they were treated better by the religious community. The results suggest that further outreach to spirituality could be an important and, as yet still, underutilized asset in the recovery of people with schizophrenia.

Pandya A, Bresee C, Duckworth K, Gay K, Fitzpatrick M. Perceived impact of disclosure of schizophrenia diagnosis. Community Ment Health J 2010;47(6):613-621.

Correction …

In the Chakos et al. paper (Concomitant Psychotropic Medication Use During Treatment of Schizophrenia Patients: Longitudinal Results from the CATIE Study), which appeared in the October '11 issue of ***CS***, Del Miller was inadvertently omitted as a co-author. Dr. Miller's affiliation is Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, Iowa.

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.*