Clinical News

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A New Possible Class of Drugs for the Treatment of Schizophrenia

A clinical trial in the September issue of *Nature Medicine* describes a drug, LY2140023, which may be effective in people with schizophrenia psychosis. This drug is thought to work by targeting glutamate-mediated neurotransmission. Previously, glutamate neurotransmission has been touted as an important factor in schizophrenia, but clinical evidence of efficacy has been lacking. All current antipsychotic drugs target dopamine receptors. It is this mode of action that is thought to be responsible for extrapyramidal side effects, including tardive dyskinesia and dysphoria, which cause many patients to frequently discontinue their medication. LY2140023 is a selective agonist of a specific subtype of glutamate receptor, known as mGlu2/3. It is reported that Lilly Research Laboratories will begin a larger clinical trial for the drug immediately. If that trial confirms the results seen so far, the new drug could mark a breakthrough in the treatment of schizophrenia.

The research team tested LY2140023 in a double-blind, placebo-controlled trial of 196 patients with schizophrenia and compared how well it worked versus olanzapine, which, as we know, targets dopamine receptors. The trial was conducted in Russia from August 2005 to June 2006. People who were treated with LY2140023 showed improvements in both the positive symptoms (hallucinations, delusions and thought disorder) and the negative symptoms (social withdrawal, apathy and emotional blunting) of schizophrenia compared to placebo after four weeks of treatment. Treatment with LY2140023 was safe and well tolerated. People treated with LY2140023 did not differ from placebo-treated patients with respect to prolactin elevation, extrapyramidal symptoms or weight gain. Adverse events linked to LY2140023, including insomnia, nausea, headache and somnolence, were mild to moderate in severity and were not treatment-limiting. The drug must still be evaluated on many more patients to test for the possibility of side effects that have not yet emerged, and thus is still years from completing regulatory review.

Lilly's new drug emerged from almost two decades of research by Dr. Darryle D. Schoepp. The work is based on consistent observations that interference with the action of the n-methyl-d-aspartate (NMDA) ionophoric receptor in neurons caused by drugs like phencyclidine (PCP) and ketamine can lead to symptoms similar to those of people with schizophrenia. PCP and ketamine action at NMDA receptors is linked to the presence of glutamate. This led Dr. Schoepp and others to study ways to stimulate glutamate receptors as a treatment for schizophrenia. However, understanding how to affect the many different kinds of glutamate receptors in medically beneficial ways has proved complicated and has not lead to any beneficial therapies. So, instead of focusing on the receptors blocked by PCP and ketamine, Dr. Schoepp and colleagues concentrated on modulating the action of glutamate receptors in the brain's prefrontal cortex, an area responsible for personality and learning. Dr. Schoepp left Lilly in March to become the head of neuroscience research for Merck. However, it has been reported that Dr. Schoepp and Dr. Steven Paul, the president of Lilly Research Laboratories, have both said that his departure would not hurt the development of LY2140023.

Because this was a "proof-of-concept" study designed to test the efficacy of LY2140023 in the treatment of schizophrenia, no rigorous comparison was made against olanzapine in terms of efficacy. However, in the reported study, the effects of the drugs were similar. Optimal dosing of LY2140023 has not yet been determined.

Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, et al. Nat Med 2007;13(9):1102-1107.

Allon Therapeutics and TURNS Begin Collaborations for Phase II Schizophrenia Cognition Trial

Schizophrenia is associated with a range of impairments in cognition. These impairments are a core clinical feature of schizophrenia. They are largely untouched by current pharmacotherapy. Antipsychotic medications may lead to some improvement in cognition in schizophrenia, although the overall effects are relatively weak. This gap in the effectiveness of antipsychotic drugs for neurocognition has inspired a search for co-treatments that can be added to an antipsychotic to improve cognition.

There is a new set of academic and industry collaborations called the Treatment Units for Research on Neurocognition and Schizophrenia (TURNS). The TURNS program is a National Institute of Mental Health (NIMH) supported network providing an infrastructure for clinical studies of pharmacological agents for enhancing neurocognition in people with schizophrenia. Goals of the TURNS project include:

- Establishing a clinical research network where clinical studies on the safety, efficacy, pharmacokinetics and pharmacodymanics of new agents for the treatment of cognitive deficits of schizophrenia can be investigated.

- Characterize and define key aspects of cognition in schizophrenia as potential treatment targets.
- Identify and select promising compounds for studies.
- Define optimal experimental designs to evaluate the efficacy of primary and augmentation strategies to enhance cognition in schizophrenia.
- Identify and develop opportunities for industry/academia/government collaboration in testing compounds of potential utility in alleviating cognitive deficits in schizophrenia.
- Promote broad adoption and utilization by academia and the pharmaceutical industry of standardized methods and measures to accelerate testing and regulatory approval of new compounds targeting cognitive deficits in schizophrenia.
- Broadly and equitably disseminate state-of-the-art measurement tools and methodological strategies to evaluate the efficacy of treatments for cognitive deficits in schizophrenia.

Allon Therapeutics announced that in collaboration with TURNS, and with support from the National Association for Research in Schizophrenia and Affective Disorders, it will add an imaging-biomarker component to the current Phase II efficacy trial evaluating AL-108 as a treatment for schizophrenia-related cognitive impairment. This drug is administered as a nasal spray. Studies in animals suggest that this drug may protect neurons and may improve cognition in schizophrenia. The current studies include a twelve-week, double-blind, randomized clinical trial of two doses of AL-108 (5 and 30 mg/day intranasally) versus placebo in the treatment of persistent cognitive dysfunction in schizophrenia. The study medication will be added to patients' current atypical antipsychotic medication or to their current injectable first-generation antipsychotic medication. The primary outcome measure will consist of the composite score on a neuropsychological battery. Secondary outcome measures will include scores on symptoms, functional outcome, and safety measures. Sixty clinically stable patients with schizophrenia, drawn from eight sites, will participate in the study. Three different imaging techniques will be used to investigate whether AL-108 treatment results in a change in the brain structures affected by schizophrenia, Allon said. The TURNS-Allon study has received institutional review board approval to begin patient enrollment for the Phase II efficacy trial in schizophrenia-related cognitive impairment, the company added. The company said it expects the TURNS network to begin the study shortly. This is a promising new treatment and, hopefully, this new collaborative effort will lead to some hope in this vexing clinical problem.

http://trials.counsellingresource.com/clinical-trials/trials/NCT00505765.html

Further Work on Schizophrenia Cognition Drugs Using Nicotine Receptors as a Target

Another cognition-related clinical trial is set to begin. Targacept reported that its collaborator, AstraZeneca, has initiated a Phase IIb clinical trial of AZD3480 in cognitive deficits in schizophrenia (CDS). AZD3480 is a selective agonist at the neuronal nicotinic receptor of the alpha4beta2 subtype. The CDS trial is a double-blind, placebo-controlled study being conducted at sites in the U.S. and Canada. The trial design provides for approximately four hundred patients currently taking medication from the class known as atypical antipsychotics to be randomly assigned to one of three dose groups of AZD3480 or to placebo, and to be dosed over a twelve-week period, Targacept and AstraZeneca said. The primary outcome measure of the trial is a test battery that includes assessments of cognitive functions across nine different domains. Secondary measures include measures of life functioning, such as performance in day-to-day tasks and social skills, the companies added. The companies said they expect the trial to be complete by the end of 2008. AZD3480 has been evaluated to date in twelve clinical trials in approximately 540 subjects. In a previous Phase IIb clinical trial conducted by Targacept in age-associated memory impairment, AZD3480 achieved statistically significant results on all of the primary endpoints, reflecting improved cognitive performance by memory-impaired older adults. It has been shown that administration of AZD3480 over ten days produced statistically significant enhancement of several cognitive measures in healthy adults, attention and episodic memory, compared to placebo. The EEG pattern shown for AZD3480 was consistent with that previously described with other drugs known to improve attention and vigilance, including nicotine. In addition, subjects given AZD3480 showed improvements of preattentional cognition mechanisms. It has long been known that many people with schizophrenia smoke tobacco, and recently it has been observed that smoking may reduce the likelihood of a person developing Alzheimer's disease. Possibly, medications such as AZD3480 will bring some of the cognitive benefits of nicotine receptor agonism to the clinic without the serious health risks of smoking tobacco.

In related news on the basic science front, axons themselves may influence the threshold at which the cells send signals, research on mouse-brain tissue shows. The finding challenges the conventional view of neurons. In that scenario, processes within a nerve cell determine whether or not to fire an electrical impulse. The axon is a passive carrier of that signal. A recent report in *Nature Neuroscience* suggests a more active role for axons and could be important for understanding how the brain processes sensory information. It could also have implications for the understanding

of neurological diseases such as schizophrenia, as well as the functioning of drugs that interact with nicotinic receptors.

The scientists exposed the axons of isolated mouse neurons to nicotine, which mimics the neurotransmitter acetylcholine. Previous research had shown that axons in several regions of both mouse and human brains have receptors for acetylcholine, but the function of those receptors was not clear. Without nicotine, a weak input signal triggered the neurons to fire only thirty-five percent of the time. With axons exposed to nicotine, neurons in the tissue samples fired twice as often in response to the same signal. This may be why nicotine enhances cognitive functioning. This new work with nicotinic receptors on axons demonstrates the role they play in modulating sensory input. Enhancing axonal communication within the brain could help people with disorders such as schizophrenia. This research also could help explain why most people with schizophrenia smoke tobacco. The mechanism by which acetylcholine receptors on axons lower neurons' firing thresholds remains uncertain. However, receptors located close to the base of an axon, where nerve impulses originate, had a larger influence on the threshold than did receptors farther away.

Dunbar G, Boeijinga PH, Demazieres A, Cisterni C, Kuchibhatia R, Wesnes K, Luthringer R. Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers. Psychopharmacology (Berl) 2007;191(4):919-929.

Kawai H, Lazar R, Metherate R. Nicotinic control of axon excitability regulates thalamocortical transmission. Nat Neurosci 2007;10(9):1168-1175.

High Schizophrenia Rates among Pacific Islanders

The Republic of Palau in Micronesia has one of the highest rates of schizophrenia in the world. While researchers routinely state that the prevalence of schizophrenia is about one percent worldwide, the incidence in Palau is higher, 1.7 percent. Among Palauan men, schizophrenia's prevalence soars as high as 2.8 percent.

Such variations, which also crop up elsewhere in the world, illustrate the dangers of assuming that an average prevalence rate of one percent applies to any particular location. New research suggests that schizophrenia effects people more in Palau than it does in many other parts of the world. This finding challenges a widespread assumption—based on an ongoing mental-health study launched by the World Health Organization (WHO) in 1967—that family and social life in developing countries provide buffers against psychosis that are not available in big cities and developed regions. These findings, published in *Current Anthropology*, contribute to growing evidence that schizophrenia especially targets two groups: men and recent immigrants to various countries. Small-scale societies could aggravate schizophrenia more than modern, industrialized ones. In a major city, a person who hears hectoring voices and feels controlled by space aliens can retreat from the stress of social life into anonymity and solitude. However, in a small-scale setting, you can't choose not to participate in social interactions, even if you have schizophrenia. Negative expressed emotion from close friends and family is known to play a part in poor outcome from this illness.

Schizophrenia seems to be the same illness in Palau as it is in the United States and other developed countries. In standard psychiatric interviews, Palauan patients reported the same array of symptoms as individuals hospitalized for schizophrenia in New York City, at approximately the same time in a separate study. A common biological marker of schizophrenia also characterizes many of the Palauan patients, according to the study. About fifty-five percent of the islanders display disturbed eye tracking of objects moving through their visual fields. Several previous studies had found that a comparable proportion of people with schizophrenia living in developed countries, as well as many of their immediate relatives without the disorder, share this genetically influenced trait.

Some researchers suspect that excessive consumption of alcohol and other drugs among individuals with schizophrenia on Palau exacerbates the condition. However, in the new study, those who engaged in such behavior actually displayed milder symptoms. Among the Palauan patients, the forty frequent betel nut chewers suffered from milder hallucinations and delusions than did the thirty others who never or rarely chewed the substance. The researchers propose brain-altering chemicals in betel nuts may quell hallucinations and delusions.

Sullivan RJ, Andres S, Otto C, Miles W, Kydd R. The effects of an indigenous muscarinic drug, Betel nut (Areca catechu), on the symptoms of schizophrenia: a longitudinal study in Palau, Micronesia. Am J Psychiatry 2007;164(4):670-673.

The Benefits of Depot Antipsychotic Medication May Extend to "Second-Generation" Drugs

Depot antipsychotics are effective as long-term maintenance therapy in chronic schizophrenia and are widely used in Europe. In the United States, however, physicians have been reluctant to use them. We often assume that depot drugs present an increased risk of major side effects, that patients do not accept or tolerate them as well as oral agents, and that prescribing depot antipsychotics may increase the possibility of medicolegal problems. Data from the first head-to-head trial of Johnson & Johnson's injectable long-acting risperidone versus olanzapine has highlighted the benefits of depot medication compared to oral, using only

second-generation drugs. A new report in the *British Journal of Psychiatry* shows that patients receiving risperidone long-acting injection experienced a higher incidence of significant clinical improvements at twelve months, as well as greater improvements in measures of disorganized thinking, than patients taking oral olanzapine did. The data showed that both treatments were efficacious and generally well tolerated, but efficacy results suggested that in the long term patients might benefit more from treatment with the depot.

The study was conducted at forty-eight sites and had 318 patients who were randomized to long-acting risperidone injection and 300 patients to olanzapine of which 160 and 187 patients, respectively, completed the twelve-month trial. The primary measure of efficacy was the change in total score on the Positive and Negative Syndrome Scale (PANSS) for both short-term (thirteen weeks) and long-term (twelve months) outcomes. Risperidone long-acting injection use was associated with 20% minimum reduction in PANSS total scores in more patients (91% versus 79%) compared with olanzapine at twelve months. The data also showed that at the trial's end-point, twelve months, there was greater improvement on one PANSS factor score (disorganized thoughts), but greater improvements were seen in anxiety/depression in the olanzapine group. The trial results also suggested that long-acting risperidone may have a less pronounced effect on weight gain (1.7 kg versus 4 kg) and body mass index (0.6 kg/m^2 compared to 1.4 kg/m^2) than olanzapine. The study was not blinded to treatment, so the real test was more the method of treatment (depot versus oral) than the drugs themselves. It appears the benefits of long-acting injectable antipsychotic medication that have been seen with older antipsychotics may extend to the newer medications as well.

Keks NA, Ingham M, Khan A, Karcher K. Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder: Randomised, controlled, open-label study. Br J Psychiatry 2007;191:131-139.

Priority FDA Review for Combined Pharmacotherapy Therapy for Major Depression

Antipsychotic medications are commonly used in combination therapy for major depression. Two combination formulations, amitriptyline with perphenazine and fluoxetine with olanzapine, are now marketed. However, there is still too little work in the area to guide clinicians. Recently, there has been published evidence that aripiprazole combined with several antidepressants may be safe and effective for major depression. The drug was added in a blinded manner to people treated with any of the following antidepressants: escitalopram, fluoxetine, paroxetine controlled-release, sertraline, or venlafaxine extended-release. Generally the adjunctive aripiprazole was efficacious and well tolerated. The FDA has now granted priority review to a supplemental new drug application from Otsuka Pharmaceuticals and Bristol-Myers Squibb regarding aripiprazole used together with antidepressant therapy. With priority review status, the U.S. Food and Drug Administration will make its decision on whether to approve the drug for new use within six months, rather than the usual ten-to-twelve-month review period. This should mean a decision by the end of the year. The agency usually grants priority review only to products that are considered to be potentially significant therapeutic advancements over existing therapies. In addition to schizophrenia, aripiprazole is already approved to treat bipolar disorder and is being reviewed on a priority basis for pediatric schizophrenia in people aged 13 to 17. It is very good to see these critical areas for review being recognized by the FDA.

Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, Khan A. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007;68(6):843-853.

BioLineRx Begins a Phase II Trial of BL-1020

BioLineRx announced the initiation of a Phase II clinical trial with people who have schizophrenia to seek the maximal tolerated dose determination of BL-1020. BL-1020 is a very unusual compound. It is a compound that essentially is gamma-aminobutyric acid (GABA) covalently linked to perphenazine, a conventional antipsychotic with proven efficacy. BL-1020 is converted in the body to perphenazine and GABA, and thus, is an orally active dopaminergic antagonist with GABAergic activity. BL-1020 thus may target dopamine hyperactivity and GABA hypoactivity. Exogenously administered GABA alone is ineffective as a therapeutic agent due to its inability to cross the blood brain barrier. Pharmacokinetic studies demonstrate that BL-1020 provides effective transport of GABA into the brain, overcoming this challenge. Receptor binding studies indicate that BL-1020 has a high affinity to dopamine and specific GABA-A agonist activity. The pharmacologic properties and therapeutic effectiveness of BL-1020 in animal models of schizophrenia are similar to perphenazine with less extrapyramidal symptoms. BL-1020 significantly increases the secretion of prolactin in rats, so further investigation of its side effects in humans is clearly warranted. Unlike other GABAergic drugs, BL-1020 does not have sedating effects when administered at doses up to 20 mg/kg. The results of these studies indicate that BL-1020 possesses both the characteristics of a first-generation antipsychotic and a GABAergic agonist. This may be another prototype for a new class of

antipsychotic agents. In recently completed Phase I clinical studies with healthy volunteers, BL-1020 was shown to elicit an improved toxicity profile to that of equimolar amounts of perphenazine. The trial was conducted in healthy volunteers, and dosage was determined by results from previous clinical studies of perphenazine. The new trial is an open-label, multicenter, six-week, sequential-cohort study. The primary objective of the study is to determine the maximal tolerated dose of BL-1020 in sixty people with schizophrenia or schizoaffective disorder.

Acadia Pharmaceuticals Initiates Clinical Trials with Two Novel Compounds

Acadia Pharmaceuticals has two interesting drugs under development. The first compound is pimavanserin, previously referred to as ACP-103, a potent and selective 5-HT2A inverse agonist, as a cotherapy for schizophrenia. This cotherapy may result in enhanced efficacy and lower side effects. In 2004 and 2005, the company announced results from studies designed to evaluate the ability of pimavanserin to treat akathisia. The double-blind, placebo-controlled clinical study involved thirty-four patients and eighteen healthy volunteers. Results of the study showed a reduction of haloperidol-induced akathisia. Pimavanserin was safe and well tolerated and no serious adverse events were reported.

In March 2007, the company announced results from a Phase II study evaluating pimavanserin cotherapy used with either risperidone or haloperidol. The cotherapy arms with pimavanserin demonstrated statistically significant antipsychotic efficacy as measured by reduction in the Positive and Negative Syndrome Scale (PANSS), which was the primary endpoint of the trial. In addition, pimavanserin cotherapy with low-dose risperidone demonstrated a statistically significant improvement in antipsychotic efficacy as compared to low-dose risperidone plus placebo, and comparable efficacy to high-dose risperidone plus placebo. Cotherapy with pimavanserin also led to an improved side-effect profile, including less gain in weight and lower prolactin levels. Acadia is also developing pimavanserin for treatment of Parkinson's disease psychosis and sleep maintenance insomnia.

The second drug, ACP-104, or N-desmethylclozapine, is the major metabolite of clozapine. It is being developed as a novel, stand-alone therapy for schizophrenia. ACP-104 combines M1 muscarinic agonism, 5-HT2A inverse agonism, and D2 and D3 dopamine partial agonism, which are similar actions to clozapine. In 2004 an analysis of drug blood levels relative to clinical response was obtained in two clinical trials that included ninety-two schizophrenia patients treated with clozapine. This analysis showed that high ratios of N-desmethylclozapine relative to clozapine resulted in better response by patients in a wide range of clinical measures reflecting cognitive performance. In 2005 work was published showing that N-desmethylclozapine is a partial-agonist that causes weak activation of dopamine D2 and D3 receptors, whereas clozapine and most other antipsychotic drugs block these receptors. The partial agonist properties of N-desmethylclozapine may lead to fewer motor side effects than seen with most other antipsychotic drugs. In 2006, results from three initial clinical studies of N-desmethylclozapine in people with schizophrenia were presented. The three studies enrolled an aggregate of seventy-four patients with schizophrenia and were conducted in collaboration with Professor Carol Tamminga, MD, from the University of Texas Southwestern Medical School in Dallas, Texas. The results of these clinical studies demonstrated that N-desmethylclozapine is safe and well tolerated after repeated dosing of up to 600 mg per day, and that initial signals of antipsychotic effects were observed within the tolerated dose range. In addition, plasma levels of N-desmethylclozapine correlate with brain receptor occupancies indicating good penetration of N-desmethylclozapine into the brain. In June 2007, Acadia initiated a Phase IIb clinical trial with N-desmethylclozapine in people with schizophrenia. The trial is designed to evaluate the safety and efficacy of N-desmethylclozapine as a treatment for patients with schizophrenia. The multicenter, double-blind, placebo-controlled study will evaluate the safety and efficacy of N-desmethylclozapine in approximately 250 patients with schizophrenia who are experiencing an acute psychotic episode. Patients in the six-week trial will be randomized to three different study arms, which will include two different doses of N-desmethylclozapine (twice-daily 100- or 200-mg dose) and one placebo arm, the company said. The primary endpoint of the trial is antipsychotic efficacy as measured using the Positive and Negative Syndrome Scale, an industry standard rating scale commonly used in schizophrenia trials. The clinical program for N-desmethylclozapine is supported in part through a development agreement with The Stanley Medical Research Institute, the leading nonprofit organization focused on cutting edge research into treatments for schizophrenia. It appears that there is less penetration into the bone marrow by N-desmethylclozapine compared to clozapine, but a clear signal regarding hematological, as well as metabolic safety, will be important for the successful development of this drug.