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Guest Editorial

Schizophrenia – new treatments soon

Jeremy Hall

Antipsychotic medications targeting dopamine receptors were identified 70 years ago. Recent clinical trials have shown that agonists of muscarinic acetylcholinergic receptors can improve both psychotic and negative symptoms in schizophrenia. Here, this new approach to the treatment of schizophrenia is reviewed in anticipation of the drugs being licensed clinically.

Keywords
Schizophrenia; xanomeline; trospium; psychosis; muscarinic.

There is an urgent need for new and improved treatments for schizophrenia. Current antipsychotic medications all act primarily by targeting dopamine D2 receptors. Although antipsychotics are effective in treating psychotic symptoms in many people, they do not alleviate the negative or cognitive symptoms of schizophrenia. Antipsychotics are also associated with serious side-effects spanning extrapyramidal effects, weight gain, metabolic syndrome and sedation. Rates of treatment resistance remain high, with only clozapine showing any benefit in people who are resistant to treatment.

The first antipsychotic drug, chlorpromazine, was identified through astute clinical observation of the effects of a compound originally developed for a separate indication. Subsequent scientific evaluation confirmed the antipsychotic benefits of chlorpromazine and related compounds and their action via D2 dopamine receptors. This process of informed clinical observation followed by scientific confirmation is now excitingly poised to usher in a new generation of treatments for schizophrenia and psychosis based on targeting muscarinic acetylcholine receptors rather than the dopamine receptors.

The cholinergic system has long been of interest as a target in Alzheimer's disease. Loss of forebrain cholinergic neurons is a feature of Alzheimer's disease and has been considered to contribute to the cognitive impairments seen in the condition. In an attempt to enhance cognition in Alzheimer's disease, drugs targeting the cholinergic system, including agonists of muscarinic acetylcholine receptors (mAChRs), were developed. One such drug is xanomeline, an agonist of mAChRs with particular efficacy at M1 and M4 receptors. In a large trial of xanomeline treatment in people with Alzheimer's disease, a small beneficial effect was observed on cognition.[1] However, much more striking and unexpected beneficial effects of xanomeline were noted on psychotic and behavioural symptoms in people with Alzheimer's disease.[1] A subsequent small trial of xanomeline in 20 people with schizophrenia also suggested antipsychotic efficacy.[2] However, the use of xanomeline alone in schizophrenia and Alzheimer's disease was limited by marked side-effects caused by peripheral effects of mAChR agonism, including nausea, vomiting and syncope.[1,2]

Interest in the potential use of muscarinic drugs in schizophrenia and other neuropsychiatric disorders has however persisted. Recently progress has been achieved by combining xanomeline with the peripheral mAChR antagonist trospium to decrease side-effects and improve tolerability. Trospium is a licensed treatment for urinary incontinence which does not cross the blood–brain barrier. Trospium was therefore predicted to decrease the peripheral side-effects of xanomeline, including gastrointestinal and cardiovascular symptoms, without impacting the beneficial effects of xanomeline on the brain. Clinical trials of the combined xanomeline-trospium therapy (known as KarXT/Cobenfy) have been conducted and have shown positive results in individuals with schizophrenia, with reduced side-effects compared with xanomeline alone, although some peripheral side-effects remain.[3–5] Most notably, three large Phase 2/3 clinical trials in schizophrenia KarXT have shown robust antipsychotic effects as well as significant improvement in negative symptoms in schizophrenia.[3–5] There is additionally evidence that KarXT may have beneficial effects on cognition in individuals with schizophrenia and cognitive impairment.[2,6] The potential of KarXT to impact negative and cognitive symptoms would be particularly welcome, as these symptoms remain hard to treat with existing therapeutic options.

Across trials of KarXT in schizophrenia, the side-effect profile has been relatively favourable, and far superior to that seen in trials of xanomeline alone. Whereas symptoms of constipation, nausea and vomiting, dyspepsia and dry mouth were more common in people treated with KarXT than those treated with a placebo, these effects were relatively mild, often self-limiting and not associated with higher rates of medication discontinuation.[3–5] Transient increases in heart rate and blood pressure were also reported in some studies but did not produce clinically significant symptoms.[3–5] Notably, however, KarXT produced no impacts on extrapyramidal symptoms, akathisia, weight gain or sedation – side-effects commonly seen with existing antipsychotics. These results suggest that the combination of xanomeline with trospium is effective in reducing peripheral muscarinic side-effects seen with xanomeline alone, and that KarXT does not have the same side-effect profile as that seen with existing antipsychotics.

The exact mechanisms through which agonism of M1 and M4 receptors by xanomeline produces antipsychotic effects are not fully understood. However, preclinical studies have shown that agonism of M4 receptors in the midbrain and basal ganglia can exert a specific suppressive effect on dopaminergic signalling in the midbrain and limbic striatum.[7] This suggests that at least part of the antipsychotic effects of xanomeline may derive from modulation of the dopaminergic system, but in a manner that is more selective to ventral tegmental area dopamine neurons than current antipsychotic treatments, limiting side-effects.[7] M1/M4 receptor agonists are also known to have additional central effects, which may account for the ability of xanomeline to improve not only psychotic symptoms but also cognitive and negative symptoms. Important additional effects of xanomeline are likely to include, but not be limited to, effects of M1 receptor agonism on cortical interneuron firing.[7]

KarXT is likely to soon be licensed in the USA by the FDA for the treatment of schizophrenia as a landmark moment in the development of treatments for the condition. However, additional promising therapeutics based on targeting the mAChRs are also in development. In particular, it is hoped that by developing receptor-specific allosteric modulators of muscarinic receptors, drugs may be identified that have the clinical benefits of KarXT but with even better side-effect profiles.

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Most advanced among these is emraclidine, a highly selective M4 receptor positive allosteric modulator.[8] Early clinical trials of emraclidine in schizophrenia have shown evidence of beneficial effects on both positive and negative symptoms without evidence of the gastrointestinal side-effects seen with the broader M1/M4 agonist xanomeline.[8] Notably these findings suggest that the antipsychotic effects of xanomeline are primarily mediated through the M4 receptor. The outcome of larger trials of emraclidine are awaited. Positive allosteric modulators of the M1 receptor are also in development and early stage clinical testing.

A number of questions remain to be answered in relation to this new class of muscarinic treatments for schizophrenia and psychosis. First, will they be effective for all people, or will only some individuals respond to KarXT and related muscarinic therapies? Second, will the effects of these treatments be maintained (or even enhanced) over time? Third, will they be useful in combination with existing antipsychotic medications? Fourth, will KarXT and other muscarinic drugs be effective in people who show treatment resistance on current antipsychotic medications? Fifth, will this new class of treatment be beneficial in related conditions such as bipolar disorder or psychotic depression? However, it is already clear that a long-awaited and much-needed new class of therapies for schizophrenia and related disorders is likely to soon be available for clinicians and most importantly, patients suffering with schizophrenia and related conditions.

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