# Alpha-7 nicotinic agonist improves cognition in schizophrenia

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**ABSTRACT FROM:** Keefe RS, Meltzer HA, Dgetluck N, *et al*. Randomized, double-blind, placebo-controlled study of encenicline, an α7 nicotinic acetylcholine receptor agonist, as a treatment for cognitive impairment in schizophrenia. *Neuropsychopharmacology* 2015;40:3053–60.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

The cognitive impairments that are common in schizophrenia are associated with impairments across multiple domains, including attention/vigilance, verbal learning and memory, executive functioning, verbal fluency, and speed of processing. As a result, they are targets for drug development. There is a clear need for pharmacological agents that target cognitive impairment in schizophrenia for which there are currently no approved medications. The α7 nicotinic acetylcholine receptors (α7 receptors) have been shown to play an important role in cognition in animals and humans. Encenicline is an agonist exhibiting priming behaviour at the α7 receptor by potentiating the response to the natural agonist acetylcholine (ACh). Encenicline may work as a neuromodulator, with its impact on cognition mediated in part by modulating multiple neurotransmitter systems including dopamine (DA), ACh and glutamate (Glu) in the prefrontal cortex and other brain regions.[1] Although α7 nicotinic agonists have shown promise for improving cognition, the results have been mixed.

## METHODS OF THE STUDY

Participants in the study were 319 individuals with schizophrenia or schizoaffective disorder (aged 18–55 years inclusive and residing in a stable living situation) from the USA and elsewhere (of 319 randomised patients, 317 were included in the safety population, and 307 were included in the intent-to-treat population). They were outpatients who had been stabilised on a second-generation antipsychotic other than clozapine. This was a 12-week double-blind trial that involved randomisation to one of the two doses of the experimental drug encenicline 0.27 or 0.9 mg (equivalent to 0.3 and 1.0 mg encenicline hydrochloride, respectively) or placebo once daily (added to the participants current antipsychotic). The primary end point was changed in the CogState Overall Cognition Index[2] which was derived from a performance-based test. Patients in the USA were also administered with the MATRICS Consensus Cognitive Battery (MCCB)[3] as well as an interview-based assessment, the Schizophrenia Cognition Rating Scale (SCoRS).[4]

## WHAT DOES THIS PAPER ADD

- Encenicline at 0.27 mg led to significantly greater improvement on the CogState (least squares (LS) mean difference 0.117; Cohen's d=0.257; p=0.034), but not at the higher dose (LS mean difference 0.042; Cohen's d=0.093; p=0.255).
- For the MCCB—which was administered to 154 US patients—there were trends indicating improvement on both doses (the mean change from baseline to day 84 was 2.9 and 3.3 for encenicline 0.27 and 0.9 mg, respectively, and 1.2 for placebo (0.27 mg: p=0.142, Cohen's d=0.17 and 0.9 mg: p=0.069, Cohen's d=0.28 vs placebo)).
- For the SCoRS, the higher dose led to a significantly greater improvement than placebo (p=0.011, effect size: 0.36), but not for encenicline 0.27 mg versus placebo (p=0.970, Cohen's d=0.01).
- Although the results are complex, the pattern suggests that this α7 nicotinic agonist improves cognition in this population.
- In general, the adverse event rates were consistent across all treatment groups with the highest rate (39%) observed in the placebo group. Headache was the most common treatment-emergent adverse event experienced by encenicline-treated patients (4.7% in the 0.27 mg group and 4.8% in the 0.9 mg group vs 1.9% in the placebo group).
- In total, treatment-emergent adverse events were the cause for early study discontinuation in 12 patients: 2 patients with encenicline 0.27 mg, 5 patients with encenicline 0.9 mg and 5 patients with placebo.
- Four patients experienced an extrapyramidal symptom (EPS)-related adverse event: two patients in the encenicline 0.9 mg group (tremor and extrapyramidal disorder) and two patients in the placebo group (tremor and akathisia). All EPS-related events were of mild severity, and no event was serious or required concomitant anti-EPS medications.
- No significant weight gain was noted in any of the treatment arms.

## LIMITATIONS

- The size of the sample was probably too small for what appear to be modest effect sizes.
- The average age of participants was nearly 40 suggesting that these individuals may have limited plasticity.

## WHAT NEXT IN RESEARCH

These findings need to be replicated with a substantially larger sample size. The MCCB is now available in multiple languages and the findings suggest that it may be more sensitive to encenicline's effects. In addition, negative symptoms on the Positive and Negative Syndrome Scale showed greater improvement than placebo with encenicline. This finding can be evaluated in participants selected for negative symptoms.

## DO THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

This will not change my current practice. However, if the effects seen in this study are replicated and if encenicline is approved by regulatory bodies, this will encourage me to prescribe this agent to a substantial number of patients with schizophrenia and schizoaffective who have a goal of functional improvement.

**Competing interests** None declared.

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