

## COMMENTARY

The enduring nature of cognitive and negative symptoms of schizophrenia represents an unmet therapeutic need. We recently suggested that the study of cognition and antipsychotics is not always driven by logic and that research into effective pro-cognitive or “anti-negative” drug treatments must be guided by a better understanding of the biochemical mechanisms underlying cognitive processes and deficits.<sup>1</sup> Many clinicians and researchers are currently considering augmentation strategies in an effort to improve the effectiveness of antipsychotics. Recently, serious consideration has been given to agents such as D-cycloserine or ampakines that aim to enhance the function of the neurotransmitter glutamate in the brain. A dysfunction of glutamatergic neurotransmission could play a key role in cognitive deficits associated with schizophrenia.

During the last 50 years or so, the dopamine hypothesis of schizophrenia has dominated the field and oriented psychopharmacological research into developing incrementally more effective agents that target the central dopamine system and in particular dopamine D2 receptors. However, the hypothesis that schizophrenia is mainly due to excessive release of this neurotransmitter in limbic structures is now recognised by most neuroscientists as insufficient to account for the complexity of this disease. The discovery, 40 years ago, that a class of drugs (such as PCP and ketamine) now known to block NMDA-type glutamate receptors could induce symptoms in humans that resemble some of the symptoms of schizophrenia gave rise to the hypothesis that this disease also involves some dysfunction implicating the neurotransmitter glutamate. A current focus of research is thus on dopamine-glutamate interactions. In this context, it is interesting to note that recent work suggests that dopamine neurons may themselves have the capacity to use glutamate as a cotransmitter.<sup>2</sup> One of the hopes is that molecules that target other neurotransmitter systems besides dopamine could perhaps be effective in augmentation strategies along with conventional or atypical antipsychotics, leading to improvements of both positive and negative symptoms. The biological rationale supporting the idea that schizophrenia involves a deficit in glutamate neurotransmission is rather limited at the moment. In addition, the prospect of tinkering with the brain’s most abundant neurotransmitter may seem a little risky to some neuroscientists. Nonetheless, drugs that act as co-agonists at the NMDA receptors show some promise.

A meta-analysis of various clinical trials in this field was required to account for matters on the grounds of evidence-based medicine. This has been done recently by a group of Finland.<sup>3</sup> They obtained from the Schizophrenia Group’s Register of Trials all relevant randomised controlled trials. Eighteen short term trials with 343 subjects were included in the meta-analysis. The last trial included in their analysis was published in 2002. The methodology of this meta-analysis was excellent. Most patients had negative symptoms. In the case of a cross over design, the authors analysed only the first segment to avoid a carry over effect (6/18 trials). The scales used were varied (CGI, PANSS, BPRS, SANS). One possible weakness is that for assessing cognition, only the cognitive factor of the PANSS was considered. The results show that positive symptoms failed to respond to pro-glutamatergic medication. However, the meta-analysis concludes that these agents caused modest decreases in negative symptoms. Since 2002, new trials have been completed. An important multisite trial with 171 patients meeting the criteria for

persistent negative symptoms was conducted using a random assignment to placebo, glycine, or d-cycloserine.<sup>4</sup> The trial failed to confirm the efficacy of glycine or d-cycloserine to improve negative symptoms.

The same team analysed a data set in this trial on cognition and event related potential. There was no significant effect on objective measures of cognition.<sup>5</sup> The only anomaly on ERP was an increase of the P-50 amplitude on glycine, relative to placebo usually related to the sensory gating.<sup>6</sup> Interestingly there was no difference between the classes of antipsychotic medication that the patient received during the augmentation. What must be concluded from such contradictory results? One would be tempted to say “previously we were indecisive, now we are not so sure of it”.

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## References

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