Glutamate-N-methyl-D-aspartate receptor modulation and minocycline for the treatment of patients with schizophrenia: an update


CRD summary
This review concluded that modulation of NMDA-R transmission was a promising therapeutic approach and may represent future monotherapy or add-on strategies in the treatment of schizophrenia. A potential discrepancy between the conclusion about monotherapy and the evidence presented, together with potential biases in the review process and uncertain quality of studies, made the reliability of the conclusion unclear.

Authors' objectives
To evaluate Glutamate-N-methyl-D-aspartate receptor (NMDA-R) transmission modulation and minocycline for the treatment of patients with schizophrenia.

Searching
Published trials in any language were identified through a search of PubMed, Web of Science, SciELO and Lilacs to September 2008. Reference lists of included studies were searched. Search terms were reported.

Study selection
Clinical trials of NMDA-R transmission modulation in patients with schizophrenia were eligible for inclusion. Most of the included studies involved adjuvant therapy for antipsychotic treatment in people with a diagnosis of schizophrenia and administered glycine, D-cycloserine, D-alanine, D-serine, sarcosine or minocycline.

For glycine trials, study duration ranged from six to 28 weeks. Some studies used low doses (10 to 30g/day); most trials administered higher doses (60g/day or 0.8g/kg/day). For D-cycloserine trials, study duration ranged from four to 24 weeks and administered doses from 5mg/day to 250mg/day. Most D-alanine, D-serine and sarcosine trials lasted six weeks and used a range of doses.

Positive symptoms, negative symptoms and cognitive symptoms were assessed for each included study and graded improved, worsened or no effect. Included studies used a variety of scales to evaluate efficacy, including Positive and Negative Symptoms Scale (PANSS), Brief Psychiatric Research Scale (BPRS), Scale for Assessment of Negative Symptoms (SANS), Global Assessment Scale (GAS) and Clinical Global Impression (CGI). PANSS and/or SANS were used in most studies. Eleven trials assessed specific cognitive tests.

The authors did not state how the studies were selected for the review.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data on change in symptoms were extracted from each study.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined using a narrative synthesis, supported by tables.

Results of the review
Thirty-six studies were included in the review: 27 RCTs; eight non-randomised trials; and one case report. Sample sizes ranged from five to 109 participants; most trials included fewer than 50 participants.
**Glycine**: Nine RCTs and three non-randomised trials investigated the addition of glycine to antipsychotic treatment. The results of glycine trials were conflicting. In addition to conventional antipsychotics, glycine showed: no effect on positive symptoms; a beneficial effect on negative symptoms; and conflicting results for cognitive symptoms. In combination with second-generation psychotics, glycine showed conflicting results for changes in positive, negative and cognitive symptoms. In combination with clozapine, glycine showed no effect on positive or negative symptoms, but showed a beneficial effect in cognitive symptoms.

**D-cycloserine**: Nine RCTs and five non-randomised trials investigated the addition of D-cycloserine to antipsychotic treatment; results were conflicting. In addition to conventional antipsychotics, D-cycloserine showed no effect on positive symptoms and conflicting results for negative and cognitive symptoms. In combination with second-generation psychotics, D-cycloserine showed no effect on positive or cognitive symptoms and conflicting results for changes in negative symptoms. In combination with clozapine, D-cycloserine showed no effect on positive or cognitive symptoms but showed a worsening effect on negative symptoms.

**D-alanine, D-serine and sarcosine**: Eight RCTs investigated the addition of D-alanine, D-serine and sarcosine to antipsychotic treatment. D-serine and D-alanine showed a potential effect on positive, negative and cognitive symptoms (three RCTs). Sarcosine data from indicated a considerable improvement as adjunctive therapy (one RCT).

**Minocycline**: One RCT, one non-randomised trial and one case report investigated the addition of minocycline to antipsychotics. Improvements were shown for positive, negative and cognitive symptoms.

**Authors’ conclusions**
The modulation of NMDA-R transmission was a promising therapeutic approach and may represent future monotherapy or add-on treatment strategies in the treatment of schizophrenia.

**CRD commentary**
This review addressed a clear question in terms of study design, interventions and participants, but the inclusion criteria did not give clinical criteria for a diagnosis of schizophrenia. It was unclear whether all relevant databases were searched, given the topic area can be indexed across a wide range of data sources, including mental health. It appeared that there were no attempts to identify unpublished data. Publication bias was not considered in the report. There were no reported steps taken to minimise reviewer bias and error in the processes of study selection or data extraction, which increased the likelihood that the review was subject to bias. There was no reported validity assessment. The authors recognised some of the methodological difficulties with the review, specifically the small sample sizes of included studies and short durations of therapy. There appeared to be a discrepancy between the authors’ conclusion about monotherapy and the evidence presented. This, together with the potential biases in the review process and the absence of quality assessment, made the reliability of the conclusion unclear.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that further studies with larger numbers of subjects and longer follow-ups were needed. The authors suggested that further investigation of minocycline add-on treatments for patients with schizophrenia were needed.

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**Bibliographic details**
Subject indexing assigned by NLM

MeSH
Animals; Antipsychotic Agents /therapeutic use; Brain /drug effects; Clinical Trials as Topic; Glycine Agents /therapeutic use; Humans; Minocycline /therapeutic use; Neuroprotective Agents /therapeutic use; Receptors, N-Methyl-D-Aspartate /agonists /physiology; Schizophrenia /drug therapy /physiopathology; Signal Transduction /drug effects

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.