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Mirtazapine add-on therapy in the treatment of schizophrenia with atypical antipsychotics: A double-blind, randomised, placebo-controlled clinical trial

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Objective: Control of negative symptoms is an important part of the management of schizophrenia. Some studies have reported improvement in negative symptoms when antidepressants are administrated as an adjunct to antipsychotics. However, reports of benefits of therapy with antidepressant adjunctive with antipsychotics are not consistently replicated. We hypothesise that antidepressants which antagonise the O2-adrenergic receptor, may be effective for the treatment of negative symptoms of schizophrenia. These include mirtazapine and mianserin, and with less potency trimipramine, amitriptyline and trazadone.

Methods: A 6-week, double-blind, placebo-controlled, randomised trial of mirtazapine (30 mg/day) or placebo as adjunctive treatment with atypical antipsychotics was conducted at sites in Adelaide and Melbourne, Australia. The trial was registered with the Australian Clinical Trials Registry (ACTR01260500577617) and approval was given by the relevant ethics committees. All participants (N = 40) gave written informed consent prior to commencing the study. Diagnosis of schizophrenia was confirmed using the Mini International Neuropsychiatry Interview (MINI). Participants were between 18 and 65 years of age and excluded if they have any significant medical illness, are on any other psychotropic agent except benzodiazepines, meet criteria for substance abuse or are pregnant. Outcome measures included the Positive and Negative Symptom Scale (PANSS), the Clinical Global Impression (CGI), the Simpson Angus Scale (SAS) and the Hamilton Depression Rating Scale (HAMDS). Data was collected for each participant at baseline, week 1, week 2, week 4 and week 6. Adverse events are tabulated.

Results: There were no significant differences between mirtazapine and placebo treated groups at baseline or from baseline to 6-week endpoint for any of the outcomes measures. For the PANNS-ve there was a general tendency for
patients on Mirtazapine and those on Placebo to “improve” at both sites with little difference between the two treatments. Overall, the difference in slopes between Mirtazapine and Placebo was not significant ($p = 0.463$).

**Conclusion:** In contrast to other studies that have shown a difference, in this study mirtazapine was not superior to placebo as adjunctive therapy for negative symptoms of schizophrenia. It is possible that the efficacy of adjunctive treatment with mirtazapine, and other antidepressants, varies depending on antipsychotic treatment.