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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 Schizophrenia is a multifaceted illness with positive, negative and cognitive symptom domains. Standard treatments often focus on positive symptoms and may not adequately relieve other symptoms. Previous studies have suggested a role for mirtazapine in schizophrenia, particularly in negative symptoms. This study investigates the efficacy of adding mirtazapine to treatment as usual to alleviate the negative symptoms of schizophrenia.
Methods In a 6 week, double-blind clinical trial, participants with a diagnosis of schizophrenia and currently being treated with atypical antipsychotic medication were randomised to adjunctive treatment with mirtazapine (30 mg/day) or placebo. The primary outcome measure was improvement in the Positive and Negative Syndrome Scale (PANSS). Measures of cognition, collected at baseline and week 6 only, were analysed using an Analysis of Covariance (ANCOVA) model. All other outcome measures were analysed using a linear mixed model.
Results Forty participants were recruited to the study with equal numbers randomised to each treatment arm. There was no significant difference between mirtazapine and placebo treated participants for improvement in PANSS scores or any of the secondary outcome measures at any stage during the 6-week trial.
Conclusions This trial does not confirm previous research supporting the use of mirtazapine adjunctive to atypical antipsychotic treatment for schizophrenia. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — mirtazapine; schizophrenia; negative symptoms; antipsychotics; clinical trial

INTRODUCTION

Negative symptoms are a major contributor to functional impairment in schizophrenia (Marder, 2006) and conventional treatments are of limited benefit in their treatment (Marder *et al*., 2002). Pharmacotherapies adjunctive to antipsychotic treatment may be useful strategies to control negative symptoms. These include anticonvulsants such as lamotrigine (Zoccali *et al*., 2007), antioxidants such as *N*-acetyl cysteine (Berk *et al*., 2008) and antidepressants. Several studies have reported improvement in negative symptoms when antidepressants are administered as an adjunct to antipsychotics. Siris *et al.* (1990) found that imipramine maintenance adjunctive to fluphenazine was superior to fluphenazine and placebo for preventing relapse into psychotic depression or negative symptom states. Monoamine oxidase inhibitors have also been suggested in the treatment of negative symptoms (Rao and Moller, 1994). The efficacy of adjunctive fluvoxamine for the treatment of negative symptoms of schizophrenia has been demonstrated in two clinical trials of 30 (Silver and Nassar,

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1992) and 53 participants (Silver *et al*., 2000), respectively. Fluvoxamine was found to improve alogia, a core negative symptom (Silver *et al*., 2003). Spina *et al.* (1994) found a slight improvement in depressive symptoms using the Hamilton Rating Scale for Depression (HAMD) in a placebo controlled, adjunctive trial of fluoxetine ($N = 30$). Lee *et al*. (1998) found that sertraline was not different to placebo in haloperidol treated patients with schizophrenia ($N = 36$) for change in Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) Scale scores. However in a similar trial ($N = 28$) by Mulholland *et al.* (2003) sertraline was superior to placebo for improvement in Beck Depression Inventory (BDI), HAMD and CGI scores. Salokangas *et al.* (1996) found no difference between adjunctive citalopram or placebo with neuroleptic treatment ($N = 90$) for change in PANSS scores, although the citalopram treated patients reported improved subjective well-being. In a meta-analysis of selective serotonin reuptake inhibitor (SSRI) adjunctive therapy for the negative symptoms of schizophrenia, Sepehry *et al.* (2007) concluded that there was no evidence to support the efficacy of SSRIs for the treatment of schizophrenia. Goff *et al.* (2001) comment that reports of benefits of therapy with antidepressant adjunctive with antipsychotics are not consistently replicated.

The 5-HT_{2A} receptor has an established role in schizophrenia, and antidepressants that act on this system have shown efficacy in components of the symptomatology. Wynchank and Berk (2003) found a reduction in extrapyramidal side effects with the 5-HT_2 antagonist nefazodone. Total scores on the Scale for the Assessment of Negative Symptoms (SANS) decreased significantly for mianserin treated, but not for trazodone treated, participants in a trial of adjunctive therapy in a trial of elderly, neuroleptic treated, patients with schizophrenia (Hayashi *et al*., 1997). Shiloh *et al.* (2002) found mianserin was superior to placebo for improvement in Brief Psychiatric Rating Scale (BPRS) scores in patients with treatment resistant schizophrenia ($N = 18$). Poyurovsky *et al.* (2003) found mianserin was superior to placebo for improvement in cognitive dysfunction in patients with chronic schizophrenia ($N = 30$). Hence these data show some support for antidepressant induced 5-HT_{2A} receptor antagonism in the treatment of some symptom domains in schizophrenia.

This support was extended by Berk *et al.* (2001) who found that adjunctive mirtazapine was superior to adjunctive placebo with haloperidol for the reduction of PANSS negative symptoms scores in a 6-week trial of patients with schizophrenia ($N = 30$). This was replicated by Zoccali *et al.* (2004) who found that mirtazapine was superior to placebo for reduction of total scores on the SANS in a 8-week trial of patients with schizophrenia ($N = 24$) treated with clozapine. Mirtazapine has a novel pharmacological profile with antagonist effects at the α_2-adrenergic, 5-HT_2 and 5-HT_3 receptors and indirect agonist effects at the 5-HT_{1A} receptor. Its clinical utility may also be different to that of other antidepressants. There is data for a role of the 5-HT_{1A} receptor and 5-HT_3 receptor in schizophrenia as well. In addition, the noradrenergic system has been examined by Litman *et al.* (1996) who investigated α_2-antagonism by adding idazoxan or placebo to fluphenazine treatment in patients with treatment resistant schizophrenia ($N = 17$). Idazoxan was superior to placebo for reduction of scores on the BPRS. Mirtazapine has α_2-antagonist effects as well.

It appears evident that there is no 'class-effect' for antidepressants for treatment of the negative symptoms of schizophrenia. Most currently used antidepressants have no affinity for the α_2-adrenergic receptor, acting primarily on the serotonergic system. Antidepressants that do act on the adrenergic system, do so either through re-uptake inhibition or affinity to the α_1-adrenergic receptor. A study by Schutz of the noradrenergic reuptake inhibitor reboxetine found no benefit on any item of the PANSS, or on mood symptoms, suggesting that within the noradrenergic system, the α_2-adrenergic receptor may be the most likely therapeutic target. The study described here further investigates the utility of the α_2-adrenergic and 5-HT_2 antagonist Mirtazapine for the treatment of negative symptoms of schizophrenia. We hypothesised that antidepressants that antagonise the α_2-adrenergic receptor such as Mirtazapine, may be effective for the adjunctive treatment of negative symptoms of schizophrenia.

METHOD

To further investigate the role of mirtazapine in the treatment of negative symptoms of schizophrenia a double-blind, placebo-controlled, randomised trial of mirtazapine as adjunctive treatment with atypical antipsychotics commenced in 2003. The trial was registered with the Australian Clinical Trials Registry (ACTR012605000577617). Participants were recruited at two sites in Adelaide and Melbourne, Australia, and the relevant ethics committees gave approval for the trial. All participants gave written informed consent prior to commencing the study.

The trial was a 6-week trial of mirtazapine (30 mg/day) or placebo in addition to atypical

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antipsychotic treatment as usual. Participants needed to have a diagnosis of schizophrenia confirmed using the mini international neuropsychiatry interview (MINI), and be currently treated with an atypical antipsychotic. Participants between 18 and 65 years of age were eligible, and exclusion criteria included if they had any significant medical illness, were on any other psychotropic agent except benzodiazepines, met criteria for substance abuse or were pregnant or not on contraceptives if female and in the reproductive age. A flow diagram of treatment allocation pathways is included in Figure 1.

PANSS was the primary outcome measure. Additional scales included the CGI, the Simpson Angus Scale (SAS), Calgary Depression Scale for Schizophrenia (CDSS) and HAMD. Age, weight, gender and blood pressure data were collected. Records were collected for each participant at baseline, week 1, week 2, week 4 and week 6. Cognition was assessed using tests for digit span, word learning, trail making and verbal fluency with data collected at baseline and week 6 only.

On some occasions, scores were missing on a small number of items (usually only one, and never more than two) on a scale. In these cases, scores for the missing items were imputed using multiple regression models fitted to the data for all of the items in the relevant scale, at that visit.

A linear mixed model was fitted (using the statistical package 'R') with treatment (Mirtazapine or Placebo), status (in-patient, out-patient or unknown), site, week (baseline, week 1, week 2, week 4 or week 6), age, sex and current primary antipsychotic agent as fixed effects, and participant as a random effect. The within-patient variance for participants was allowed to differ between sites. For the Cognition scales, data were only available at baseline and at week 6, and were analysed using Analysis of Covariance (ANCOVA) models, with baseline values used as a covariate.

RESULTS

A total of 40 participants, 20 at each study site, were enrolled in the trial. There were 34 males and 6 females, aged 36.8 ± 9.8 (mean $\pm$ SD). Primary antipsychotic medications were clozapine ($N = 15$), quetiapine ($n = 7$), risperidone ($n = 6$), olanzapine

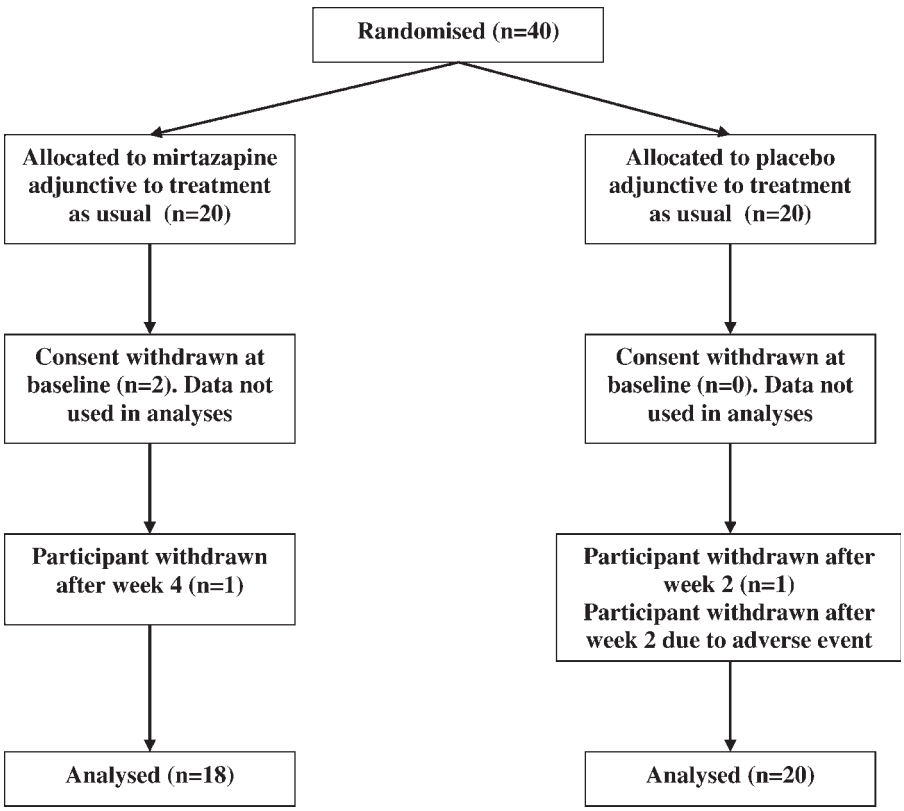

Figure 1. Flowchart describing the allocation pathways

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($n = 3$) and aripiprazole ($n = 2$). Two participants withdrew their consent, at baseline, and were omitted from the analyses. One participant had a current major depressive episode with melancholic features, was a high suicide risk, current hypomania with a past history of mania, panic disorder, agoraphobia, generalised anxiety disorder and alcohol dependence. One participant had dysthymia, post-traumatic stress disorder, antisocial personality disorder and was a high suicide risk. One participant had dysthymia and a past history of mania and was withdrawn from the study by the investigators after week 2. Two others had antisocial personality disorder and one other had post-traumatic stress disorder. No comorbidities were detected in any of the other participants, however one participant had an adverse event and was withdrawn after week 2, and one was withdrawn by the investigators after week 4. The two patients who withdrew consent at baseline had both been randomised to receive mirtazapine; of the other three patients who were withdrawn, two had been randomised to the placebo and one to mirtazapine.

The difference between mirtazapine and placebo was not statistically significant for any of the scores in primary outcome measures for the 6-week trial (Table 1). Change from baseline in PANSS positive score was not significant for participants treated with adjunctive mirtazapine, however a significant within group decrease ($p < 0.05$) was observed for patients receiving adjunctive placebo. The difference between the two treatment arms was not significant. There was a non-significant trend for participants in both treatment arms to improve on the PANSS negative score and PANSS general psychopathology. Improvement from baseline was observed in CGI-severity scores for both treatment arms and was statistically significant for the placebo arm ($p = 0.001$) with the difference between the two treatment arms significant ($p = 0.043$). No significant difference was found between treatment arms or in change from baseline for each treatment for HAMD, SAS or CDSS. Improvement from baseline to week 6 was observed in both treatment arms for all measures of cognition. No significant difference was seen between treatment arms or between baseline and week 6 for digit span and word learning, however improvement was significantly greater for placebo treated participants than mirtazapine treated participants for trail making and verbal fluency.

CONCLUSION

This was essentially a negative trial with no significant difference between adjunctive mirtazapine and placebo on the primary outcome measure, the PANSS. Significant improvement from baseline for any of the outcome measures was only observed in the placebo treated arm of this 6-week study. The study did not replicate the findings of Berk *et al.* (2001) or Zoccali *et al.* (2004), who both found that mirtazapine was effective in reducing negative symptoms in schizophrenia when added to standard treatment. It is possible that augmentation of typical antipsychotics (Berk *et al.*, 2001) would differ from augmentation of atypical agents as documented in this trial due to differences in receptor binding affinities between the two classes of agents; atypical agents have intrinsic properties at the 5-HT_2 receptors, that are in part shared

Table 1. Comparisons in outcome measures at baseline and 6 weeks for study participants with schizophrenia treated with adjunctive mirtazapine (30 mg/day) or placebo, in addition to atypical antipsychotic treatment as usual

		Active treatment	Placebo	*p*-value
	Gender (M/F)	14/4	18/2	—
	Mean age (SD.), years	37.80 ± 10.86	35.90 ± 9.20	0.659[d]
	Mean antipsychotic daily dose[a]	7.10 ± 3.29[b]	6.33 ± 3.54[c]	0.553[e]
Baseline	Mean PANSS positive score (SD)	17.72 ± 6.20	17.60 ± 7.83	0.958[d]
Active treatment $n = 18$	Mean PANSS negative score (SD)	25.61 ± 5.18	26.95 ± 7.37	0.518[d]
Placebo $n = 20$	Mean PANSS general score (SD)	42.28 ± 10.21	39.45 ± 9.56	0.386[d]
	Mean HAMD score (SD)	12.65 ± 5.52	11.90 ± 7.00	0.719[e]
	Mean calgary score (SD)	5.69 ± 4.09	5.18 ± 4.84	0.745[e]
	Mean PANSS positive score (SD)	18.47 ± 6.44	14.44 ± 5.65	0.059[d]
Week 6	Mean PANSS negative score (SD)	22.06 ± 5.07	22.17 ± 6.16	0.955[d]
Active treatment $n = 16$	Mean PANSS general score (SD)	38.41 ± 10.23	32.72 ± 8.17	0.080[d]
Placebo $n = 17$	Mean HAMD score (SD)	12.23 ± 5.88	9.94 ± 5.77	0.259[e]
	Mean calgary score (SD)	3.94 ± 3.73	3.35 ± 3.35	0.639[e]

[a]In mg of risperidone equivalents.
[b]Missing data: $n = 6$ (33.34%).
[c]Missing data: $n = 5$ (25%).
[d]Student's *t*-test.
[e]Mann–Whitney test.

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by mirtazapine. For example, recent data suggest mirtazapine may have inverse agonist effects at neuronal 5-HT_{2C} receptors (Chanrion *et al*., 2008) similar to some but not all atypical antipsychotic drugs(Rauser *et al*., 2001). The negative results may also be due to sample size, although positive results have been reported in studies of a similar size. Heterogeneity and chronicity may be additional possibilities explaining the failure to replicate prior studies. The study therefore failed to replicate the suggested role of the α_2-receptor in the negative symptoms of schizophrenia (Litman *et al*., 1996). The role of antidepressants in general and of mirtazapine in particular remains unclear, with this negative trial failing to support the two published positive randomised controlled trials.

CONFLICTS OF INTEREST

Professor Michael Berk has received Grant/Research Support from the Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier and Astra Zeneca. He has been a paid consultant for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck and Pfizer and a paid speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Organon, Pfizer, Sanofi Synthelabo, Solvay and Wyeth.

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