Treatment of cognitive dysfunction in chronic schizophrenia by augmentation of atypical antipsychotics with buspirone, a partial 5-HT$_{1A}$ receptor agonist

Danijela Piškulic$^1$, James S. Olver$^1$, Paul Maruff$^2$ and Trevor R. Norman$^1$*

$^1$Department of Psychiatry, Austin Health, University of Melbourne, Australia
$^2$CogState, Melbourne, Victoria, Australia

Objectives To assess effects of a semi-acute administration of buspirone in comparison to a placebo on cognitive function and negative symptoms in patients with schizophrenia and schizoaffective disorder.

Methods In a 6-week, double-blind, placebo-controlled, independent groups study 18 subjects (14 males, four females) received in random order either placebo or buspirone (15–30 mg/day). A neuropsychological assessment using the Hopkins verbal learning test (HVLT) simple reaction time (SRT), choice reaction time (CRT), n-back spatial working memory task and the stroop colour and word test was performed at baseline and final visit. Symptom rating scales were administered at testing weeks 0, 2, 4 and 6.

Results Repeated measures ANOVA was used to examine changes in performance on tests over time. There were no statistically significant differences between placebo and buspirone treatments on either cognitive function measures or symptom ratings.

Conclusion Semi-acute adjunct treatment with buspirone may be too short to be clinically efficacious in patients with schizophrenia. Intrinsic activation of 5-HT$_{1A}$ receptors by atypical antipsychotics may hinder the ability of buspirone to further improve cognitive functions. Buspirone did not affect clinical outcomes for this chronically ill group of patients being treated with atypical antipsychotic drugs.

INTRODUCTION

Cognitive deficits are considered important features of schizophrenia. Despite the strong consensus regarding the presence of cognitive dysfunction in a large majority of patients, there has been a lack of agreement in terms of level, pattern, frequency and course of this impairment. According to meta-analytic studies of cognitive dysfunction in schizophrenia (Heinrichs and Zakzanis, 1998; Aleman et al., 1999; Johnson-Selfridge and Zalewski, 2001; Lee and Park, 2005; Piškulic et al., 2007), there is a broad compromise of cognitive function in the disorder, ranging from 0.5–1.75 standard deviations below the normal mean. A relative independence from other symptoms and a lack of response to pharmacological treatment leaves cognitive symptoms in a distinct category (different to positive and negative symptomatic manifestations) that deserves separate therapeutic approaches (Gold, 2004). As suggested by Green et al. (2000), effectiveness of psychosocial treatment is reliant on degree of cognitive dysfunction rather than on other illness symptoms. Therefore, pharmacological approaches targeting cognitive improvement in schizophrenia may have the added benefit of accentuating the impact of psychosocial treatment designed to improve functional outcome and quality of life (Gold, 2004).

There are no medications at present that are specifically designed and approved for cognitive enhancement in schizophrenia. On the other hand some research suggests that atypical antipsychotics (McGurk et al., 2005; Meltzer and McGurk, 1999), as well as cholinergic (e.g. cholinesterase inhibitors) (Buchanan et al., 2003) and serotonergic agents (partial 5-HT$_{1A}$ agonists and 5-HT$_{2}$ antagonists) (Sumiyoshi et al., 2000; Sumiyoshi et al., 2001a; Sumiyoshi et al., 2006) have a modest effect on cognitive improvement in schizophrenia. As an increase in dopamine (DA) activity in the prefrontal cortex (PFC) is considered to be beneficial for the treatment of cognitive dysfunction...
The 5-HT$_{1A}$ receptor is often considered in relation to cognitive function, which is most likely due to its wide distribution in the hippocampus, cortex and thalamus (regions thought to mediate cognition and memory) and its interactions with other receptor systems. Serotonin agonist effects, through the 5-HT$_{1A}$ receptor, have been suggested to contribute to enhancement of DA release in the PFC (Ichikawa and Meltzer, 1999; Ichikawa et al., 2001). Partial agonist at 5-HT$_{1A}$ receptors by some atypical antipsychotics (e.g. clozapine, olanzapine and ziprazidone) has been reported to preferentially augment DA and NA in the PFC relative to subcortical areas, which may be related to their modest efficacy to improve negative and cognitive symptoms of schizophrenia (Li et al., 1998).

In previous investigations, an adjunctive treatment with 5-HT$_{1A}$ agonists to atypical antipsychotic medication produced inconsistent results with regards to clinical improvements in schizophrenia. In an open 6-week trial with an adjunct of buspirone (up to 30 mg/day) to stable doses of typical antipsychotics Goff et al. (1991) reported a modest decrease of clinical ratings of psychopathology in 20 patients with schizophrenia, while measures of akathisia did not change from baseline. In a similar study of 13 patients with schizophrenia who were receiving haloperidol, (Sirota et al., 2001) reported a decrease in the mean PANSS score, as well as in all three subscales (positive, negative and general), after a 6-week add-on treatment with buspirone (up to 100 mg/day).

With regards to cognitive function Sumiyoshi and colleagues (Sumiyoshi et al., 2000; Sumiyoshi et al., 2001a, 2001b) were the first to investigate the effects of adjunctive therapy with 5-HT$_{1A}$ agonist tandospirone on memory function. In a double-blind, placebo controlled 6-week study, they (Sumiyoshi et al., 2001b) administered a fixed dose of tandospirone or placebo to 26 patients with schizophrenia who were on stable doses of atypical antipsychotics. Tandospirone reportedly improved scores on tests of executive function (e.g. Wisconsin Card Sort Test- WCST categories) and verbal memory (e.g. Wechsler memory scale—Revised—WMS-R) in the absence of changes to psychopathology and extrapyramidal symptom (EPS) ratings (Sumiyoshi et al., 2001b). The lack of change in psychopathology was proposed to indicate primary effects of tandospirone on cognition, and not secondary effects through reduction in positive or negative symptomatology (Sumiyoshi et al., 2001b). In a more recent study of buspirone adjunct to atypical antipsychotics over a period of 3 and 6 months, Sumiyoshi (Sumiyoshi et al., 2007) reported improvements in attention (as assessed by the digit symbol substitution test, DSST) in patients with schizophrenia. Based on the whole series of adjunct studies with the 5-HT$_{1A}$ agonist tandospirone and buspirone, Sumiyoshi et al. (2007) proposed that these agents can be used as safe and effective cognitive enhancers in treatment of schizophrenia.

The current study assessed changes in performance on tests of memory and executive function, as well as negative symptomatology in a 6-week, double-blind, placebo-controlled trial of buspirone in patients with schizophrenia and schizoaffective disorder receiving atypical antipsychotic medications. Compared to administration of placebo, a 6-week administration of buspirone (15–30 mg) is expected to reduce negative symptoms and improve performance on tests of executive function (e.g. spatial WM, stroop colour and word test), verbal memory, attention and psychomotor speed in these patients.

We hypothesised that buspirone’s mechanism of action in improving executive function, as assessed by the n-back spatial WM task, would be via a preferential increase in the PFC DA release through 5-HT$_{1A}$ receptors in the dorsal raphe nuclei (DRN), which provides a major input to PFC (Millan, 2000). In other words, by preventing the direct inhibitory actions of 5-HT via serotonergic projections from the DRN to the substantia nigra (SN), buspirone is hypothesised to disinhibit DA system in the midbrain, and subsequently increase DA levels in the PFC (Kapur and Remington, 1996). Given the preferential role of PFC DA in executive functions (e.g. WM) our choice of the n-back task was to assess potential changes in WM function as a result of pharmacological manipulation of dopaminergic system. In addition to improvements in executive functions following increased prefrontal DA release, we predicted that 5HT$_{1A}$ agonist buspirone would improve verbal learning in patients with schizophrenia, through its potential actions on presynaptic SHT$_{1A}$ autoreceptors in the DRN. Further, inhibition of 5-HT synthesis and release will result in inhibition of postsynaptic 5-HT$_{1A}$ receptors on pyramidal neurons in the hippocampus, whose activity is thought to exert inhibitory influence on human explicit memory function (Yasuno et al., 2003).
METHOD

Participants

Patients suitable to enrol in the study were recruited from outpatient clinics through a direct contact with their treating doctors and case-managers. Potential subjects who met all inclusion and exclusion criteria, as determined by their clinician and the principal investigator, were approached directly and invited to participate in the trial. A total of 62 patients meeting the DSM-IV criteria for a diagnosis of schizophrenia or schizoaffective disorder were approached and invited to take part in the study. Of those, 19 persons satisfied study criteria, but were not interested in taking part in the trial; 24 persons withdrew their consent prior to its commencement; and the remaining 19 people took a part in this research trial. Participants were male (n = 15) and female (n = 4) persons with the DSM-IV diagnosis of schizophrenia (n = 17) or schizoaffective disorder (n = 2) who were recruited over a 3 year period. Participants were randomised to either placebo (n = 9) or buspirone (n = 9) arm. Further, all participants were on a stable dose of atypical antipsychotics (e.g. clozapine, risperidone, olanzapine, quetiapine and amisulpride) for at least 2 months prior to taking part in the study. Demographics characteristics of the patient population are shown in Table 1. The patients’ diagnoses were supported by a structured clinical interview, the mini international neuropsychiatric interview ([MINI] Sheehan, Lecrubier, Sheehan, Amorim, Janavs et al., 1998).

Neurocognitive measures

Hopkins verbal learning test. Two different lists of the Hopkins verbal learning test (HVLT) (see Brandt, 1991 for details of test design and administration) were used to assess verbal memory at baseline and at week 6 of the study. The primary outcome measures were the total number of words recalled across three trials (Part A), the total number of recognised words (Part B) and the total number of words recalled after a delay (Part C).

Cogstate cognitive function test battery. The CogState test engine has high timing accuracy, and was presented using a laptop computer. The CogState battery has been shown to be sensitive to subtle changes in cognitive function across different settings, such as fatigue, stress, mild intoxication, mild head injury, concussion and post-operative cognitive decline (Falleti et al., 2003; Silbert et al., 2004; Darby et al., 2002). For the purpose of the current study, three tasks were selected from this testing battery to assess psychomotor speed, visual attention and spatial WM.

Simple reaction time (SRT) task consisted of a playing card displayed face down at the centre of the computer screen. It was used to assess psychomotor speed. Subjects were required to press ‘yes’ key (‘D’ key on the computer keyboard) as soon as a card turned face up, which was repeated multiple times at randomly different intervals. Duration of the task was 2 min, and the primary outcome measure was the speed of performance;

Choice reaction time (CRT) task, a test of visual attention, followed the presentation of the SRT task. Similarly, this task consisted of a playing card displayed face down at the centre of the computer

<table>
<thead>
<tr>
<th>Table 1. Demographic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
</tr>
<tr>
<td>Age (years)- M (SD)</td>
</tr>
<tr>
<td>Duration of illness (years)- M (SD)</td>
</tr>
<tr>
<td>Educational status</td>
</tr>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Secondary</td>
</tr>
<tr>
<td>Tafe/trade</td>
</tr>
<tr>
<td>Tertiary</td>
</tr>
<tr>
<td>Occupational status</td>
</tr>
<tr>
<td>Unemployed</td>
</tr>
<tr>
<td>Part-time</td>
</tr>
<tr>
<td>Full-time</td>
</tr>
<tr>
<td>Antipsychotic medication</td>
</tr>
<tr>
<td>Clozapine/olanzapine</td>
</tr>
<tr>
<td>Quetiapine/risperidone</td>
</tr>
<tr>
<td>Amisulpride</td>
</tr>
</tbody>
</table>

Participants were given written information about the study prior to undergoing an assessment with the principal investigator and a senior consulting psychiatrist J.O. Participants gave written informed consent prior to any study procedures being conducted, and after the nature, as well as any potential consequences of participation, were explained. All participants were screened by the principal investigator for other major Axis 1 diagnoses, major medical/neurological disorders, history of head injury, current substance abuse/dependence and the ability to provide written, informed consent. Females of childbearing age were required to have a negative urine pregnancy test at screening and were advised to use adequate contraception. Further, this study was approved by the Human Research Ethics Committees of the Austin Health Network and the Melbourne Clinic.
Subjects were required to make a decision in response to a question: ‘Is the face-up card red?’ by pressing either ‘yes’ or ‘no’ key. As with the SRT, this procedure was repeated multiple times at randomly different intervals over the 2 min testing period, and the primary outcome measure was speed of performance.

Spatial working memory (SWM) was assessed using the spatial n-back paradigm. For this task playing cards were arranged in the centre of the computer screen. The number of cards (locations) displayed on the screen was fixed to two cards (this aspect of the task was termed ‘spatial load’). The playing cards on the screen were presented face down, making the object that marked each location identical in all trials. On each trial, one of the playing cards turned face up to show its value in colour (red or black) and number (2,3,4,5,6,7,8,9 or 10), and both possible locations were marked by a different playing card. These aspects of the card were varied in order to add a distraction component to the task. Participants were, however, instructed to ignore all descriptive qualities of target cards (e.g. colour, number and suit) and only focus on spatial position of cards on the screen.

The n-back component of the task varied between 1-back and 2-back conditions, such that the 1-back condition was used as a control task while the 2-back condition was used as a spatial WM task. Duration of each test condition was 2.5 min. The playing card on every trial was displayed face up for 3000 ms during which time the response had to be instigated, followed by a period of 1500 ms; each subsequent trial was initiated at the end of the 1500 ms period. The computer software was designed to record the primary outcome measures from each condition that encompassed the number of correct responses made (expressed as a function of the total trials) and the mean reaction time (RT) for correct responses.

For each spatial WM task condition, participants were presented with 50 trials, and at each presentation, they were required to answer the following question: ‘Does the location of the face-up card exactly match the location of the one you saw 1/2 cards back?’ Participants responded to each presentation selecting either ‘yes’ answer or ‘no’ answer to this question by pressing either the ‘K’ key or ‘D’ key on the computer keyboard as quickly as possible. The spatial mapping of responses to keys was constant in that participants’ always answered ‘yes’ with their dominant hand.

Stroop colour and word test. The Stroop Colour and word test was used to assess executive function, more specifically cognitive flexibility and selective attention, or the ability to resist interference from irrelevant stimuli (see Golden and Freshwater, 2002 for detailed description of the test).

Symptom ratings

The presence and severity of schizophrenia symptoms was investigated using the positive and negative syndrome scale (PANSS, Kay et al., 1987), scale for the assessment of negative symptoms (SANS, Andreasen, 1983) and the brief psychiatric rating scale (BPRS, Overall and Gorham, 1962). Assessment of extrapyramidal symptoms was performed using the Simpson–Angus scale (SAS, Simpson and Angus, 1970) abnormal involuntary movements scale (AIMS) and barnes akathisia rating scale (BARS, Barnes, 1989). Patients’ mean scores on all three measures are shown in Table 2.

Table 2. Clinical psychopathology symptom measures

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo M (SD)</th>
<th>Buspirone M (SD)</th>
<th>Repeated-measures ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W0</td>
<td>W2</td>
<td>W4</td>
</tr>
<tr>
<td>PANSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>11.6(3.6)</td>
<td>12.6(5.2)</td>
<td>11.8(4.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>16.9(6.1)</td>
<td>16.6(6.0)</td>
<td>16.3(4.9)</td>
</tr>
<tr>
<td>General</td>
<td>28.0(7.3)</td>
<td>26.8(5.8)</td>
<td>27.6(6.6)</td>
</tr>
<tr>
<td>Total</td>
<td>55.4(14.9)</td>
<td>55.9(13.5)</td>
<td>55.7(13.1)</td>
</tr>
<tr>
<td>SANS</td>
<td>32.7(14.6)</td>
<td>31.1(11.9)</td>
<td>31.8(12.7)</td>
</tr>
<tr>
<td>BPRS</td>
<td>36.2(6.7)</td>
<td>36.2(5.7)</td>
<td>36.4(6.1)</td>
</tr>
<tr>
<td>AIMS</td>
<td>1.8(2.2)</td>
<td>2.3(3.3)</td>
<td>2.8(3.8)</td>
</tr>
<tr>
<td>SAS</td>
<td>13.2(1.8)</td>
<td>13.3(1.6)</td>
<td>13.8(2.1)</td>
</tr>
<tr>
<td>BARS</td>
<td>1.0(1.8)</td>
<td>1.0(1.8)</td>
<td>1.3(1.9)</td>
</tr>
</tbody>
</table>

Note: W0, baseline; PANSS, positive and negative syndrome scale; SANS, scale for the assessment of negative symptoms; BPRS, brief psychiatric rating scale; AIMS, abnormal involuntary movements scale; SAS, Simpson–Angus scale; BARS, barnes akathisia rating scale.
**TREATMENT OF COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA**

*Treatments*

Participants took part in a double-blind, independent groups design study, receiving either placebo (3 × 28 mg saccharin tablets, Booths Healthcare, Sydney) or a minimum of 15 mg/day and a maximum of 30 mg/day dose of buspirone (Buspar tablets, Bristol Myers Squibb Company, Melbourne) during the 6-week period. Selection of buspirone dosing range was based on reports that smaller doses induce serotonergic effects, whereas high doses (e.g. > 30 mg) may induce postsynaptic dopaminergic antagonism, which may result in reversal of a therapeutic effect and incurrence of EPS (Goff et al., 1991). Additionally, augmentation therapy with another azapirone agent tandospirone (30 mg/day), which has similar affinity for 5-HT\textsubscript{1A} receptors to buspirone (27 and 20 nM respectively) enhanced cognition in patients with schizophrenia (Sumiyoshi et al., 2001b; Sumiyoshi et al., 2007). Both placebo and buspirone tablets were encapsulated in a hard, opaque gelatin capsules in order to maintain the double blind. All other medications remained unchanged during the 6-week testing period, and compliance with study medication was monitored by pill count.

Randomisation was performed by the central pharmacy at the Austin Health. Neither the investigator nor the subject had knowledge of the code of the double-blind, placebo randomisation. Randomisation was in the ratio of 1:1 buspirone to placebo, and the treatment assignments were carried out in accordance with a computer-generated randomisation schedule. Buspirone dose was averaged across the duration of the study for each participant in the buspirone arm, and it ranged between 15 and 25 mg (the mean dose of buspirone across all subjects was M = 21.6, SD = 3.75 mg).

**Procedure**

Each participant was required to attend eight separate study visits including a screening and a baseline visit. Treatment visits (3–6) were conducted each week for 6 weeks to ensure treatment adherence and patients’ safety, and to monitor for potential changes in illness symptoms. All participants underwent a neuropsychological assessment at week 0 (baseline) and again at week 6 (final visit). Symptom rating scales were administered at testing weeks 0, 2, 4 and 6 by the same trained rater. Scheduled clinical assessments of adverse events and vital signs were performed weekly at every visit for 6 weeks. Based on the outcome of those assessments, a decision was made regarding participants’ continuation in the study, or to change the dose of buspirone/placebo (e.g. increase or decrease by 5 mg) for the following testing week.

Vital Signs, such as arterial systolic and diastolic blood pressure and radial pulse in the sitting position were measured at screening and each assessment visit. Body weight was also recorded at baseline and each assessment visit. Adverse events (AEs) were recorded on AE case report forms and were elicited by asking the patient ‘Have you experienced any problems or symptoms since last evaluation?’ Each complaint was further characterised by direct questioning and graded as mild, moderate or severe. Status of previous AEs were also monitored at each assessment and graded.

**Statistical analysis**

Analysis of data was undertaken using an independent samples t-test, descriptive statistics and the repeated measures analyses of variance (ANOVA; SPSS version 13). Homogeneity of the co-variance matrix was evaluated by using Box’s M. Data from the Cogstate battery (SRT, CRT and spatial WM) were normalised using logarithmic base 10 (log 10) transformation for the RT data (SRT, CRT and spatial WM) and arsine transformation for the proportion accuracy data (spatial WM) (Maruff, Werth, Giordani, Caveney, Feltner et al., 2006) before statistical analysis.

Demographic data were analysed using a t-test (e.g. age and duration of illness) and \( \chi^2 \) test for categorical data. These analyses revealed no significant differences between the groups on any of the demographic variables. Clinical as well as cognitive data were analysed using separate 2 (treatment) × 2 (time) repeated measures ANOVAs.

**RESULTS**

Of nine participants in the placebo arm, one person was withdrawn at week 4 of the trial due to need for hospitalisation, while one person withdrew after 1 week due to complaints of adverse events. In the buspirone arm, three people withdrew from the study in weeks 2, 3 and 5 respectively, due to reports of medication side-effects (e.g. nausea, worsening in symptoms of psychopathology and erectile dysfunction, respectively). One person was withdrawn from the trial by the principal investigator prior to commencement of any procedures due to unsatisfactory liver function as indicated by blood test results. Thus, the data analysed statistically comprise the results of 18 participants who received at least one dose of medication. For those
participants who withdrew prior to week 6, either an early exit interview was conducted ($n = 3$), or the last observation carried forward technique (LOCF; $n = 2$) was used for the purpose of data analysis.

Clinical psychopathology symptom measures

Group means and standard deviations for PANSS, SANS and BPRS scales at baseline, week 2, week 4 and week 6 are presented in Table 2. Based on the results from the repeated measures ANOVA, there was no main interaction between time of testing and treatment condition on any of the psychopathology symptom measures.

Clinical EPS measures

Means and standard deviations for the AIMS, the SAS and the BAS at baseline, week 2, week 4 and week 6 for both groups are displayed in Table 2. The repeated-measures ANOVA revealed no significant interaction between time of testing and the treatment condition on the AIMS or the BAS ratings. Conversely, there was a significant main interaction between the time of testing and treatment condition for the SAS scores, with indications of a small decrease in the SAS scores from baseline in the buspirone treatment arm. This however was unlikely to be clinically significant given that the main effect of treatment on SAS scores was non-significant.

Hopkins verbal learning test

Means and standard deviations for the three IVR trials, the average IVR, recognition and delayed recall, at the two time points (pre- and post-treatment) for both treatment groups, are represented in Table 3. Repeated measures ANOVA showed no significant interactions between time of testing and treatment for any of the HVLT measures.

Selective attention performance

The means and standard deviations for the stroop colour and word test measures are shown in Table 3. A series of separate repeated measures ANOVAs were conducted for each individual Stroop measure, revealing no significant interaction between time of testing and treatment condition.

Psychomotor speed and visual attention

Table 3 shows means and standard deviations for both RT measures across the two time points (e.g. pre- and

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Buspirone</th>
<th>Repeated-measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-</td>
<td>Post-</td>
<td>Pre-</td>
<td>Post-</td>
</tr>
<tr>
<td>HVLT</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>IVR-trial 1</td>
<td>5.4 (2.4)</td>
<td>5.2 (2.9)</td>
<td>5.7 (1.4)</td>
<td>4.6 (1.4)</td>
</tr>
<tr>
<td>IVR-trial 2</td>
<td>8.3 (1.9)</td>
<td>7.9 (2.5)</td>
<td>6.8 (3.2)</td>
<td>5.9 (2.1)</td>
</tr>
<tr>
<td>IVR-trial 3</td>
<td>8.6 (2.4)</td>
<td>8.9 (2.6)</td>
<td>8.1 (2.4)</td>
<td>7.2 (2.0)</td>
</tr>
<tr>
<td>IVR-averaged</td>
<td>7.4 (2.1)</td>
<td>7.3 (2.5)</td>
<td>6.8 (2.2)</td>
<td>5.9 (1.7)</td>
</tr>
<tr>
<td>Recognition</td>
<td>11.4 (1.3)</td>
<td>11.22 (1.4)</td>
<td>11.2 (1.1)</td>
<td>11.0 (1.3)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>7.7 (2.3)</td>
<td>7.0 (2.8)</td>
<td>6.6 (2.3)</td>
<td>5.8 (3.1)</td>
</tr>
<tr>
<td>Colour/Words</td>
<td>81.8 (10.2)</td>
<td>82.6 (12.4)</td>
<td>76.9 (12.3)</td>
<td>70.2 (15.5)</td>
</tr>
<tr>
<td>Interference</td>
<td>56.5 (11.6)</td>
<td>57.0 (11.9)</td>
<td>55.0 (17.6)</td>
<td>51.5 (11.6)</td>
</tr>
<tr>
<td>Interference</td>
<td>31.7 (10.7)</td>
<td>35.4 (9.1)</td>
<td>28.1 (13.4)</td>
<td>28.7 (9.5)</td>
</tr>
<tr>
<td>SRT</td>
<td>2.5 (0.1)</td>
<td>2.5 (0.1)</td>
<td>2.6 (0.2)</td>
<td>2.6 (0.2)</td>
</tr>
<tr>
<td>CRT</td>
<td>2.7 (0.1)</td>
<td>2.7 (0.0)</td>
<td>2.8 (0.1)</td>
<td>2.6 (0.6)</td>
</tr>
<tr>
<td>1-back Speed</td>
<td>2.9 (0.1)</td>
<td>2.9 (0.1)</td>
<td>2.9 (0.1)</td>
<td>2.9 (0.2)</td>
</tr>
<tr>
<td>1-back Accuracy</td>
<td>1.2 (0.4)</td>
<td>1.2 (0.2)</td>
<td>1.1 (0.4)</td>
<td>1.3 (0.2)</td>
</tr>
<tr>
<td>2-back Speed</td>
<td>2.9 (0.1)</td>
<td>2.9 (0.1)</td>
<td>3.0 (0.2)</td>
<td>3.0 (0.1)</td>
</tr>
<tr>
<td>2-back Accuracy</td>
<td>0.8 (0.3)</td>
<td>0.8 (0.4)</td>
<td>0.9 (0.3)</td>
<td>0.7 (0.3)</td>
</tr>
</tbody>
</table>

Note: M, mean; SD, standard deviation; HVLT, Hopkins verbal learning test; IVR, immediate verbal recall; SRT, simple reaction time; CRT, choice reaction time.
post-treatment). Repeated measures ANOVA revealed no significant interaction between time of testing and treatment on SRT and CRT performance.

**Spatial WM performance**

Table 3 displays averaged values for speed and accuracy on the n-back task. Statistical analysis of the data showed no significant interaction between time of testing and treatment on either speed or accuracy of spatial WM performance (Table 3).

**DISCUSSION**

Improvement of cognitive dysfunction in schizophrenia is considered to be a crucial part in the overall treatment plan for the disorder. Extensive research is now directed towards development of so-called ‘cognitive enhancers’, given that cognitive symptoms are viewed as major contributors to poor level of psychosocial functioning of patients with schizophrenia. Pharmacological approaches to remediation of cognitive dysfunction have concentrated on augmentation or accessory treatment strategies (e.g. add-on treatment) rather than on a single treatment method.

The current study investigated changes in cognitive function following an adjunctive buspirone regimen in patients treated with atypical antipsychotics for schizophrenia. While it was anticipated that buspirone would improve negative symptoms and cognitive function, it was not expected to produce any effects on positive symptoms or EPS. Contrary to the predictions, 6-week adjunct of buspirone to standard treatment with atypical antipsychotics failed to produce any statistically or clinically significant improvements in negative or cognitive symptoms in the current patient sample. As hypothesised however, there were no significant changes on measures of positive symptoms and EPS as a result of buspirone treatment.

This is in agreement with a recent double blind, placebo controlled study by Sumiyoshi et al. (2007) who reported no cognitive enhancement in the sample of 59 patients (29 in placebo and 30 in buspirone group) after add-on treatment with buspirone. They did, however, report a small improvement in attention (e.g. measured by the DSST) at 3 but not 6 months following the adjunct treatment. Consistent with the current results, no favourable effects of buspirone over placebo were reported for further improvements of the positive and negative symptoms of schizophrenia (Brody et al., 1990; Sumiyoshi et al., 2007). In an open trial of buspirone adjunct however (e.g. mean dose 23.8 mg/day), Goff et al. (1991) reported a significant reduction in the positive but not the negative symptoms (as measured with the BPRS) in 20 patients with schizophrenia who were treated with haloperidol. In a similar study of buspirone adjunct (e.g. 100 mg/day) to haloperidol, Sirota and associated (2001) also reported a reduction in scores on all three subscales of the PANSS. This may be due to buspirone’s affinity for D2 receptors where it acts as an antagonist. Administration of high doses of buspirone, such as the case in Sirota et al’s study (2001), may therefore account for an improvement in positive symptomatology, and thus, reduction in PANSS scores. Furthermore it is recognised that buspirone may enhance plasma concentrations of haloperidol, thus giving a ‘pseudo’ dose increase of the antipsychotic, which may also partially explain the findings.

Current results indicate that duration of treatment, treatment dose (e.g. between 10 and 100 mg/day), study design (e.g. open trial vs. double blind) and concomitant medications (e.g. typical antipsychotics vs. atypical antipsychotics) may therefore account for differences between the current and previous research findings. The effect of buspirone, when used alone, takes 2–3 weeks to become evident and reach its maximal efficacy (Sadock and Sadock, 2007). Semiacute adjunct treatment (e.g. 6 weeks) may be too short to be clinically efficacious in patients with schizophrenia, whereas more chronic administration in the duration of 3 or 4 months may prove beneficial. Prolonged administration beyond 3 or 4 months however may reverse buspirone induced cognitive improvements (e.g. Sumiyoshi et al., 2006) by altering serotonergic tone. The exact mechanism of action by which chronic buspirone administration may affect availability of 5-HT (e.g. via presynaptic autoreceptors or post-synaptic 5-HT1A receptors) is not clear. It is possible that chronic stimulation of 5-HT1A post-synaptic receptors in the hippocampus results in an increased inactivation or diminished sensitivity of these receptors. Prolonged administration of buspirone may cause adaptive changes in the 5-HT1A receptor function leading to altered response of 5-HT1A receptors to intrinsic 5-HT or 5-HT1A receptor agonist (Sumiyoshi and Meltzer, 2004).

In the current study, buspirone was given in combination with atypical antipsychotics that have differential pharmacological profiles and receptor affinities, including those for 5-HT1A/D2 receptors (see Miyamoto et al., 2005; Jarskog et al., 2007 for more detail on receptor affinities). This indicates that there may be a desirable balance of affinity for different receptor types, as well as the optimal efficacy at
5-HT<sub>1A</sub> receptors (Newman-Tancredi et al., 2005). It is possible that 5-HT<sub>1A</sub>/D<sub>2</sub> receptor affinities need to be at their optimal levels so that the beneficial properties of 5-HT<sub>1A</sub> receptor activation (e.g. reduction of EPS, improvement in negative and cognitive symptoms) and D<sub>2</sub> receptor blockade (e.g. reduction of psychotic symptoms) are permitted (Newman-Tancredi et al., 2005). Newman-Tancredi and colleagues (2005) therefore suggested that ‘the contribution of 5-HT<sub>1A</sub> receptor activation to the pharmacological profile of action of the antipsychotics will depend on the relative 5-HT<sub>1A</sub>/D<sub>2</sub> affinities and on 5-HT<sub>1A</sub> agonist efficacy of the drugs’ (p. 341).

Finally, given that administration of buspirone, both in the current and in previous studies, failed to improve executive and memory functions (thought to rely on cortical DA and hippocampal 5-HT system respectively) whilst resulting in small improvements on a test of attention warrants possible explanations. First, it may be that intrinsic activation of 5-HT<sub>1A</sub> receptors by atypical antipsychotics hinders the ability of buspirone to further improve cognitive functions in question. It is possible that the effect of buspirone on cognitive and negative symptoms depends on its pharmacokinetic interaction with other medications. The value of combined treatment with buspirone may be limited by the combination of intrinsic stimulation of 5-HT<sub>1A</sub> receptors by atypical antipsychotics in addition to that of buspirone, given that the ability of atypical antipsychotics to improve cognition may rely on the relative balance between 5-HT<sub>1A</sub> agonism and D<sub>2</sub> antagonism (Newman-Tancredi et al., 2005; Sumiyoshi et al., 2007). If this theory is proved to be correct, disruption of balance in receptor affinities therefore may help explain the lack of cognitive effects seen in the current and other similar studies. Newman-Tancredi and associates (2005) proposed a framework within which to address these issues by exploring the affinity and efficacy (e.g. determining the G-protein activation at 5-HT<sub>1A</sub> receptors and adenylyl cyclase activity) of 5-HT<sub>1A</sub> agonists, and a potential implication that this may have for treatment of schizophrenia (see Newman-Tancredi et al., 2005 for details).

Second, the ability of buspirone to enhance cortical DA release may in part be due to its antagonist activity on D<sub>2</sub> and α<sub>2</sub> adrenoceptors (Sakaue et al., 2000; Gobert et al., 1999; Tanda et al., 1994), which may contribute to buspirone’s effect on cognition (Sumiyoshi et al., 2007). As suggested by Sumiyoshi et al. (2007), the relatively small improvement in performance on the DSST test of attention in their study may partly be due to deterioration of performance in patients who received placebo. Another possibility is that buspirone, through its metabolite 1-PP, antagonised cortical α<sub>2</sub> receptors, and through this mechanism, mediated attentional function via PFC (Coull, 1998). A blockade of α2 receptor results in decrease of noradrenaline (NA) uptake and hence an increase in concentration of NA in the PFC. Therefore, improvements in attention following buspirone in Sumiyoshi et al.’s study may reflect stimulation of noradrenergic system in the PFC. Additionally, activation of 5-HT<sub>1A</sub> autoreceptors has been reported to disinhibit LC-derived frontocortical adrenergic projections (Millan et al., 2000). In parallel with the activation of mesocortical DA projection, 5-HT<sub>1A</sub> autoreceptor agonism may thus result in reinforcement of frontocortical adrenergic input, and hence improvements in cognition (Millan, 2000). The absence of attentional improvement in the current study however may reflect: (a) the small sample size; (b) dosage of treatment; (c) duration of treatment or (d) buspirone’s level of efficacy on 5-HT<sub>1A</sub> autoreceptors versus 5-HT<sub>1A</sub> post-synaptic receptors. Given that the effect of buspirone on NA system is more theoretical than empirical, it may be that it is not strong enough (possibly as a result of dosages used in the current study) to induce observable changes in attention.

LIMITATIONS AND FUTURE DIRECTIONS

The obvious shortcoming of our study is the small sample size (n = 19) which weakened the statistical power to detect a modest effect (e.g. d = 0.5) of treatment on cognitive function. According to the post hoc power analysis, the power to detect a significant effect (e.g. α = 0.05, two-tail) in the current study was very low (power = 0.17). To increase the power to 80% chance (α = 0.05, two-tail) of detecting a modest effect (d = 0.5), we would require a sample of 128 patients. Given the challenges in recruitment and testing phases of the study, any future research in this direction would need to be designed as multi-centre, collaborative project in order to generate an appropriate sample of subjects. Similarly, relatively short administration of buspirone might not have been enough to potentiate any effects, given that Sumiyoshi’s group found a positive effect (d = 0.38) of buspirone on attention (e.g. DSS) only after 3 months of administration (Sumiyoshi et al., 2006).

As buspirone plasma concentrations were not measured in the current study, data from previous reports using buspirone and other similar agents was used to determine dosage. This is not regarded as a major flaw in the study design, given that previous studies, which used varying doses of buspirone...
similarly reported no advantageous effects of buspirone on cognition in schizophrenia. This leads to the conclusion that perhaps buspirone is not the most appropriate choice of agent for enhancement of executive function and memory. However, it may be worth exploring its potential use for improvements in attentional processes in schizophrenia following Sumiyoshi et al’s (2007) findings.

In terms of the role of 5-HT1A receptors in cognitive function, studies with more selective 5-HT1A agonists, used in combination with neuroendocrine techniques, will be required to resolve this issue. The molecular mechanisms and structural events that occur at the receptor leading to pre- and post-synaptic activity however are not understood. Additional information regarding these mechanisms is crucial for design of drugs that can act selectively at pre- or post-synaptic 5-HT1A receptors (Strzelczyk et al., 2004).

ACKNOWLEDGEMENTS

This research was supported by a grant (02T-135) from the Stanley Medical Research Foundation.

REFERENCES

Andreasen NC. 1983. The Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa: Iowa City, Iowa.


