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Effect of buspirone, a serotonin$_{1A}$ partial agonist, on cognitive function in schizophrenia: A randomized, double-blind, placebo-controlled study

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Abstract

In previous studies, we demonstrated that tandospirone, a serotonin-5-HT$_{1A}$ partial agonist, added to ongoing treatment with small to moderate doses of typical antipsychotic drugs, improved executive function and verbal learning and memory. However, tandospirone is not available in most countries, and atypical antipsychotic drugs (AAPDs) have largely replaced typical antipsychotic drugs as the primary treatment for schizophrenia. Therefore, the goal of this randomly assigned placebo-controlled double-blind study was to determine if the addition of buspirone, a widely available 5-HT$_{1A}$ partial agonist, would enhance cognitive function, in subjects with schizophrenia treated with AAPDs. Seventy-three patients with schizophrenia, who had been treated with an AAPD for at least three months, were randomly assigned to receive either buspirone, 30 mg/day, or matching placebo. All other medications remained unchanged. Attention, verbal fluency, verbal learning and memory, verbal working memory, and executive function, as well as psychopathology, were assessed at baseline, and 6 weeks, and 3 and 6 months after baseline. A significant Time × Group interaction effect was noted on the Digit Symbol Substitution Test, a measure of attention/speeded motor performance, due to better performance of the buspirone group compared to the placebo group at 3 months. No significant interaction effects were noted for other domains of cognition. Scores on the Brief Psychiatric Rating Scale (Total, Positive) were improved during treatment with buspirone but not placebo, but the effects did not reach statistical significance. The results of this study showed a possible benefit of buspirone augmentation of AAPDs to enhance attention. However, we did not replicate the results of the previous study with tandospirone, which may be due to the differences between tandospirone and buspirone, between typical antipsychotics and AAPDs, or a combination of the above. Further study to determine the usefulness of 5-HT$_{1A}$ agonist treatment in schizophrenia is indicated.

Keywords: Buspirone; 5-HT$_{1A}$ receptor; Cognition; Attention; Antipsychotic drugs; Augmentation therapy; Tandospirone

1. Introduction

Impairment in neurocognitive functions, such as attention, memory, and executive function, is characteristic

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of most patients with schizophrenia (Heaton et al., 2001; Keefe et al., 2005; Mohamed et al., 1999; Saykin et al., 1991), and has been reported to affect long-term outcome measures, including work and social function (Green et al., 2000; Kern et al., 1999; Meltzer and McGurk, 1999; Sharma, 1999). Treatment with the atypical antipsychotic drugs (AAPDs), e.g. clozapine, risperidone, olanzapine, quetiapine, ziprasidone, melperone, and perospirone, has been shown to be associated with improvement in specific types of cognitive deficits in patients with schizophrenia (Araki et al., 2006; Harvey and Keefe, 2001; Keefe et al., 1999; Meltzer and McGurk, 1999; Meltzer and Sumiyoshi, 2003; Sumiyoshi et al., 2003; Woodward et al., 2005). The AAPDs may ameliorate cognitive impairment in schizophrenia, possibly via enhancement of dopaminergic and cholinergic output in the cortex and hippocampus (Chung et al., 2004; Ichikawa et al., 2002, 2001; Kuroki et al., 1998; Parada et al., 1997), which is linked to the serotonin-5-HT_{2A} antagonist/dopamine-D_2 antagonist property of these agents (Kuroki et al., 1998; Meltzer et al., 1989; Stockmeier et al., 1993; Sumiyoshi et al., 1995). However, the cognitive benefit of AAPDs has been found to be small-to-moderate (Woodward, 2006; Woodward et al., 2005; Keefe et al., 2007). Therefore, additional means to improve cognition in schizophrenia are needed.

A role for the 5-HT_{1A} receptor in cognitive enhancement is supported by postmortem studies which report that 5-HT_{1A} receptor density is increased in frontal and temporal cortices in schizophrenia (Burnet et al., 1996, 1997; Gurevich and Joyce, 1997; Hashimoto et al., 1991; Simpson et al., 1996; Sumiyoshi et al., 1996). Subsequent PET studies (Kasper et al., 2002; Tauscher et al., 2002) confirmed an increase in cortical 5-HT_{1A} receptor binding in schizophrenia. The increased density of 5-HT_{1A} receptors may represent up-regulation secondary to diminished 5-HT_{1A}-receptor stimulation (Hashimoto et al., 1991; Sumiyoshi et al., 1996).

We have previously conducted a series of pilot studies of the effects of the addition of tandospirone, a 5-HT_{1A} partial agonist and azapirone derivative (Hamik et al., 1990; Miller et al., 1992), to ongoing treatment with small to moderate doses of typical antipsychotic drugs (mainly haloperidol), on cognitive function in patients with schizophrenia (Sumiyoshi et al., 2000, 2001a,b). The addition of tandospirone (30 mg/day), but not placebo, to ongoing treatment with typical antipsychotic drugs for 4 to 6 weeks, was found to improve executive function (Sumiyoshi et al., 2001a) and verbal learning and memory (Sumiyoshi et al., 2000, 2001a,b). However, these studies did not address the important issue of whether tandospirone would improve cognition in patients treated with AAPDs, or whether other 5-HT_{1A} agonists more widely available than tandospirone, e.g. buspirone, would enhance any domains of cognition in patients with schizophrenia. As to the former point, we have recently reported a case of schizophrenia in which adjunctive use of tandospirone with perospirone, an AAPD with partial agonist activity at 5-HT_{1A} receptors (Araki et al., 2006), was effective for further enhancement of verbal learning and memory (Sumiyoshi et al., 2007). Subsequent clinical trials, prompted by our findings, have found that switching to ziprasidone (Sumiyoshi et al., 2006) or perospirone (Araki et al., 2006), two AAPDs having high affinity for 5-HT_{1A} receptors, from typical antipsychotics, improved some aspects of verbal memory in subjects with schizophrenia.

Buspirone, another azapirone derivative, is a partial agonist at 5-HT_{1A} receptors with weak D_2 receptor blocking properties compared to typical antipsychotic drugs, but more so than tandospirone (Meltzer et al., 1983; Taylor et al., 1982). A few open trials studied the effect of addition of buspirone on psychopathology in patients with schizophrenia receiving typical antipsychotic drugs, such as haloperidol (Brody et al., 1990; Goff et al., 1991; Sirota et al., 2001; Sovner and Parnell-Sovner, 1989). However, there has been, to our knowledge, no clinical study on the effects of addition of buspirone to treatment with AAPDs. Moreover, no previous study has investigated whether the adjunctive treatment with buspirone affects cognitive function in patients with schizophrenia.

The goal of this randomized, double-blind, placebo-controlled study was to test the hypothesis that the addition of buspirone would improve various domains of cognition and psychopathology in subjects with schizophrenia treated with AAPDs. We also sought to test the hypothesis that buspirone would produce improvement in the same domains of cognition in patients that had previously been reported in tandospirone-augmented patients treated with typical antipsychotic drugs.

2. Method

2.1. Subjects

The protocol of this study was approved by the Institutional Review Board of Vanderbilt University. Subjects for this study were outpatients meeting DSM-IV criteria for schizophrenia (19–63 yr), who had been treated with a stable dose of an AAPD for at least three months, which is suggested to attain the stable cognitive status (Lee et al., 1994; Woodward et al., 2005). They were interviewed with the Schedule for Affective Disorders and Schizophrenia Lifetime and Change (SADS-C) versions (Endicott and Spitzer, 1978). A psychiatric and anitpsychotic treatment history was obtained from the patient,

informants, and medical records. Subjects were excluded from the study if they 1) were pregnant or lactating, 2) were taking a mood stabilizer, antidepressants, anticholinergic or anxiolytic drugs, 3) had been cognitively tested with this or a similar neuropsychological test battery within the last 6 months, 4) had unstable medical conditions, brain damage and/or severe neurological disorders, or 5) had current substance dependence. Standard laboratory testing was normal. Clinical staff explained the nature of the study to the subjects, the risks and benefits, and the option not to participate in research. If the mental status of a subject was impaired to the point where s/he could not understand these issues, the subject was not approached to be in the research. After complete description of the study to the subjects, written informed consent was obtained.

Seventy-three subjects participated in the study. The demographic data of these subjects are shown in Table 1. Male/female ratio, age, age of onset of illness, duration of illness, race, employment status, and antipsychotic dose (risperidone equivalent; Kane et al., 2003) did not differ between the patients allocated to the placebo and buspirone arms. The co-administered antipsychotic drugs were: risperidone (N=19), olanzapine (N=11), clozapine (N=4), and ziprasidone (N=3) for the placebo group; and risperidone (N=19), olanzapine (N=12), clozapine (N=4), and ziprasidone (N=1) for the buspirone group. The mean (SD) duration of AAPD treatment before baseline assessment was 92.3 (170.4) months (range 13–832 months) for the placebo group and 52.8 (100.1) months (13–541 months) for the buspirone group, which did not differ significantly by Mann–Whitney U-test (z=−1.16, p=0.25).

Table 1
Demographic data of participants

	Patients allocated to placebo	Patients allocated to buspirone	Group difference (t-test/chi-square)
	(N=37)	(N=36)	p
Male/female	22/15	19/17	ns
Age, yr	39.7 (12.5)	40.5 (11.8)	ns
Age at onset of illness, yr	21.5 (9.3)	21.3 (9.7)	ns
Duration of illness, yr	19.0 (13.5)	19.0 (11.2)	ns
Race (Caucasian/ afroamerican/others)	23/12/2	19/16/1	ns
Employment status (full or partial employment/ unemployed)	7/30	9/26	ns
Antipsychotic drug dose[a] (mg/day)	3.9 (2.0)	4.2 (1.9)	ns

Values represent mean (SD).
ns, no significant difference.
[a]Risperidone equivalent dose (mg/day).

2.2. Drug treatment

Patients were randomly assigned to receive either buspirone 30 mg/day (b.i.d.), or identically appearing placebo (provided by Bristol–Meyeres Squibb Co.) with the following titration regimen. On Day 1–3, patients were given one 10 mg buspirone tablet or placebo for the evening dose. On Day 4–6, a second 10 mg tablet or placebo was added for the morning dose. On Day 7 and thereafter, an additional 10 mg tablet or placebo was added for the evening. The test dose of buspirone (30 mg/day; small-to-moderate dose) was chosen based on the findings that augmentation therapy with tandospirone 30 mg/day (small-to-moderate dose) enhanced cognition in patients with schizophrenia, as discussed above, and that these two 5-HT_{1A} agonists share similar affinities for 5-HT_{1A} receptors (Ki values=20 nM for buspirone and 27 nM for tandospirone) (Hamik et al., 1990). All other medications remained unchanged during the 6-month study period. Subjects were considered treatment failure if additional psychotropic drugs were needed, and dropped from the study. Compliance with study medication as well as antipsychotic medication was monitored by pill counts.

2.3. Clinical assessments

The following cognitive tests (Delis et al., 1987; Sumiyoshi et al., 2003) were administered by Master's level psychologists who were blinded to medication status at baseline and 6 weeks, and 3 and 6 months after baseline.

Attention/Speeded motor performance	Digit Symbol Substitution Test (DSST) from the Wechsler Adult Intelligence Scale-Revised (WAIS-R)
Verbal fluency	Controlled Word Association Test Category Instance Generation Test
Verbal learning and memory	California Verbal Learning Test (CVLT)—List A Trial 1–5 (immediate recall) CVLT—Long-Delay Free Recall (delayed recall)
Verbal working memory	Auditory Consonants Trigram (ACT)
Executive function,	Wisconsin Card Sorting Test (WCST)—Number of Category WCST—Percent Perseverations

At baseline, subjects were administered the Wide Range Achievement Reading Test-III (WRAT-III) (Wilkinson, 1993), a measure of premorbid intelligence. In addition, subjects were administered the Vocabulary

and Information subtests from the WAIS-R (Wechsler, 1981) to measure the current intellectual level. Psychopathology was quantified by means of the Brief Psychiatric Rating Scale (BPRS), 18-item version (Overall and Gorham, 1962) (0–6 scale) by trained research assistants, who were not informed of medication status. Intraclass correlation coefficients were more than 0.8 (Sumiyoshi et al., 2006).

2.4. Statistical analysis

Statistical analyses were performed using Statistical Analysis System (SAS). Changes in the clinical measures were analyzed by mixed model analysis of variance (ANOVA) with Time (baseline, 6 wk, 3 month, 6 month) as within-subject factor and Group (buspirone, placebo) as between-subject factor. The main interest was whether the Time × Group interaction effect was significant for each clinical variable. When interaction effects of Group over Time were found significant, subsequent post-hoc tests were conducted. Demographic data of the two treatment groups were compared by two-tailed *t*-test or chi-square test. Effect sizes (ES) were calculated by the method of Cohen (1977). Significance was considered when the p value was <0.05.

3. Results

Fifty-nine patients (29 for placebo group and 30 for buspirone group) completed the baseline assessment and at least one follow-up assessment (Table 2), whereas 14 dropped out after baseline assessment. The reasons for drop-out for these 14 subjects were: lost to follow-up ($N=2$), incarcerated ($N=2$), refusal to have further cognitive testing ($N=1$), non-compliance with treatment ($N=1$), and withdraw of consent for other reasons ($N=2$) for the placebo group; and headache ($N=3$), lost to follow-up ($N=2$), and not wanting to continue research ($N=1$) for the buspirone group.

Data from these 59 subjects were used for analyses. The male/female ratio, age, age of onset of illness, duration of illness, dose of antipsychotic drugs, the WAIS-R Vocabulary and Information, and the WRAT-III-Reading score did not differ between the patients receiving placebo and those receiving buspirone. Co-administered antipsychotic drugs were: risperidone ($N=13$), olanzapine ($N=11$), clozapine ($N=2$), and ziprasidone ($N=3$) for the placebo group; and risperidone ($N=15$), olanzapine ($N=10$), clozapine ($N=4$), and ziprasidone ($N=1$) for the buspirone group.

Mixed model ANOVA revealed a significant Time × Group interaction effect on the DSST with an effect size (ES) of 0.32. Subsequent analysis indicated that this was due to better performance on this test for the buspirone group compared to the placebo group at 3 months (ES = 0.38) (Table 3). There was a slight decrease in the placebo-treated group compared to an improvement in the buspirone-treated group at 3 months. At 6 months, there was no significant difference between the placebo- and buspirone-treated groups. No significant interaction effect was noted for other measures of cognition. There was also a significant main Time effect on the performance on the List A—Immediate Free Recall and Long-Delay Free Recall from the CVLT, as well as the WCST—Percent Perseverations, indicating improved performance over time in both placebo group and buspirone group. The Time × Group interaction effect on the DSST and main Time effect on the WCST—Percent Perseverations were no more significant if Bonferroni correction was applied.

No significant Time × Group interaction effect or main Time effect was noted for scores of the Total, Positive, and Withdrawal–Retardation (Blunted Affect, Emotional Withdrawal, Motor Retardation) subscales from the BPRS. Although not statistically significant, the BPRS Total and Positive scores in subjects receiving buspirone decreased by about 17–19%, while no such changes were found in the placebo group (Table 3).

A separate analysis was conducted on 49 subjects (24 for placebo group and 25 for buspirone group) treated with

Table 2
Baseline clinical data of subjects who completed at least one follow-up assessment

	Patients given placebo	Patients given buspirone	Group difference (*t*-test/chi-square)
	($N=29$)	($N=30$)	p
Male/female	16/13	16/14	ns
Age, yr	41.6 (12.7)	41.6 (11.7)	ns
Age at onset of illness, yr	22.0 (9.4)	22.0 (10.0)	ns
Duration of illness, yr	19.5 (14.6)	19.4 (11.2)	ns
Antipsychotic drug dose[a]	4.0 (2.1)	4.3 (1.8)	ns
WAIS-R Vocabulary (raw score)	35.2 (13.9)	36.6 (17.8)	ns
WAIS-R Information (raw score)	13.7 (5.8)	15.6 (6.6)	ns
WRAT-III	41.7 (6.9)	40.2 (9.3)	ns

Values represent mean (SD).
BPRS, Brief Psychiatric Rating Scale; WAIS-R, Wechsler Adult Intelligence Scale—Revised.
WRAT-III, Wide Range Achievement Test-III-Reading Score.
ns, no significant difference.
[a]Risperidone equivalent dose (mg/day).

Table 3
Effect of augmentation therapy with buspirone or placebo on cognition and psychopathology

	Patients given placebo	Patients given buspirone	Time effect		Time × group interaction	
	(*N*=29)	(*N*=30)	*F*	*p*	*F*	*p*
Digital Symbol Substitution Test						
Baseline	39.1 (8.9)	39.8 (17.5)				
6 week	40.0 (11.0)	40.9 (17.7)				
3 month	37.5 (12.8)	42.9 (17.5)[a]				
6 month	41.4 (8.9)	42.9 (15.0)	1.15	ns	3.37	0.02
Controlled Word Association Test						
Baseline	26.9 (7.6)	27.9 (14.5)				
6 week	26.4 (9.3)	30.1 (14.3)				
3 month	27.7 (10.0)	29.5 (13.3)				
6 month	28.1 (8.9)	28.3 (13.7)	0.43	ns	0.85	ns
Category Instance Generation Test						
Baseline	14.7 (5.3)	14.9 (6.3)				
6 week	14.5 (5.0)	16.4 (4.9)				
3 month	14.5 (5.9)	16.9 (5.4)				
6 month	14.7 (4.5)	16.5 (6.0)	0.92	ns	1.32	ns
California Verbal Learning Test						
List A Immediate Free Recall Trials 1–5						
Baseline	37.5 (10.8)	38.0 (15.0)				
6 week	42.5 (12.1)	40.7 (12.4)				
3 month	47.0 (14.1)	45.9 (14.6)				
6 month	46.2 (13.7)	46.9 (15.2)	20.07	<0.001	0.43	ns
Long-Delay Free Recall						
Baseline	6.9 (2.9)	7.1 (4.1)				
6 week	9.1 (3.1)	7.4 (3.7)				
3 month	9.6 (3.9)	9.1 (3.9)				
6 month	9.8 (3.2)	9.2 (3.2)	21. 80	<0.001	2.66	ns
Auditory Consonant Trigram						
Baseline	35.8 (9.2)	36.0 (11.3)				
6 week	38.7 (9.9)	36.1 (11.9)				
3 month	36.6 (9.3)	37.3 (10.3)				
6 month	37.1 (9.3)	38.8 (11.5)	1.23	ns	1.59	ns
Wisconsin Card Sorting Test						
Category number						
Baseline	3.1 (2.2)	3.2 (2.6)				
6 week	3.0 (2.0)	2.8 (2.3)				
3 month	3.0 (2.3)	3.3 (2.6)				
6 month	3.7 (2.4)	3.2 (2.5)	2.12	ns	1.33	ns
Percent perseverations						
Baseline	24.3 (16.5)	24.5 (19.7)				
6 week	20.0 (14.5)	27.6 (19.3)				
3 month	19.6 (9.2)	24.5 (22.2)				
6 month	18.4 (11.2)	19.7 (13.1)	3.08	0.03	1.97	ns
BPRS						
Total						
Baseline	20.0 (8.6)	20.6 (8.0)				
6 week	19.9 (8.4)	17.9 (7.1)				
3 month	20.7 (9.7)	18.8 (9.1)				
6 month	19.2 (9.4)	17.2 (8.6)	2.22	ns	1. 10	ns
Positive						
Baseline	6.0 (4.0)	6.2 (4.2)				
6 week	5.7 (3.8)	5.5 (3.7)				
3 month	6.2 (3.7)	5.6 (4.5)				
6 month	6.1 (3.7)	5.0 (3.3)	0.92	ns	1.09	ns
Withdrawal–Retardation						
Baseline	3.8 (2.6)	4.0 (3.0)				

Table 3 (*continued*)

	Patients given placebo	Patients given buspirone	Time effect		Time × group interaction	
	(*N*=29)	(*N*=30)	*F*	*p*	*F*	*p*
6 week	4.2 (2.7)	3.9 (3.1)				
3 month	4.4 (2.7)	4.1 (3.3)				
6 month	4.0 (2.5)	4.3 (3.0)	0.57	ns	0.52	ns

Values represent mean (SD).
ns, no significant difference.
BPRS, Brief Psychiatric Rating Scale.
[a]Significantly larger than the placebo group ($t=-3.23$, $p<0.01$).

either olanzapine ($N=21$) or risperidone ($N=28$), who completed the baseline assessment and at least one follow-up assessment. Age [43.7 (12.4) vs. 42.6 (10.6) yr], age of onset of illness [21.4 (9.4) vs. 21.6 (10.4) yr], duration of illness [23.3 (14.3) vs. 20.9 (11.2) yr], dose of antipsychotic drugs [3.7 (1.3) vs. 4.1 (1.7) mg/day], the WAIS-R Vocabulary [36.8 (14.6) vs. 34.1 (18.1)] and Information [14.2 (6.0) vs. 14.8 (6.3)], and the WRAT-III-Reading score [41.7 (6.9) vs. 40.2 (9.3)] did not differ between the patients receiving placebo and those receiving buspirone. Co-administered antipsychotic drugs for these subjects were; risperidone ($N=13$) and olanzapine ($N=11$) for the placebo group, and risperidone ($N=15$) and olanzapine ($N=10$) for the buspirone group. The results from this subgroup analysis were similar to those from the whole sample ($N=59$), i.e. Time × Group interaction effect was significant only on the DSST ($F=3.37$; $p=0.023$), while a significant main Time effect was noted for the performance on the List A—Immediate Free Recall ($F=14.05$; $p<0.001$) and Long-Delay Free Recall ($F=16.45$; $p<0.001$) from the CVLT, as well as the WCST—Percent Perseverations ($F=3.53$; $p=0.018$).

4. Discussion

The addition of buspirone to ongoing treatment with AAPDs was found to improve attention/speeded motor performance, as indicated by performance on the DSST, in schizophrenia patients. This advantage for buspirone was evident at 3 months, and was no longer present at 6 months. On the other hand, we could not confirm the hypothesis that buspirone outperformed placebo for the same cognitive domains as previously shown to be responsive to augmentation with tandospirone in typical neuroleptic-treated patients, i.e. executive function and verbal learning and memory. Scores on the BPRS (Total, Positive) were improved during treatment with buspirone but not placebo, but the effects did not reach statistical significance.

Significant improvements in performance on immediate and delayed recall, as measured by the CVLT, as well as on the WCST—Percent Perseverations were, observed. This is unlikely to be due to practice effects, even though the changes were noted across the patients treated with buspirone and those with placebo. There is controversial evidence for practice effects in these two measures at this prolonged interval (Woodward et al., 2007). Evidence for improvement on repeated testing in verbal learning and attention/speeded motor performance in haloperidol treated patients was noted. Improvements in verbal memory performance over repeated assessments have been reported in subjects with schizophrenia (e.g. Beglinger et al., 2003; Fiszdon et al., 2003). Fiszdon et al. (2003) administered the CVLT to 28 outpatients with schizophrenia on five occasions, 3 months apart, and found a significantly improved performance on the Trials 1–5 sum scores over time, similar to the results presented here. A significant repeated measure effect has also been noted in performance on the WCST—Percent Perseverations in patients allocated to a control arm (e.g. Bellack et al., 1996). Taken together, the results of the present study indicate repeated measure effects even in paradigms that provide relatively lengthy intervals between assessments, i.e. 6 weeks to 3 months, as has been suggested (Fiszdon et al., 2003). The lack of significant Time × Group interaction effects in the indices of the CVLT and WCST (Table 3) indicate a minimal influence of the addition of buspirone on repeated measure effects in patients treated with AAPDs.

Some previous animal studies have indicated that 5-HT_{1A} *ant*agonism, as opposed to agonism, has beneficial effects on cognition. Thus, Wedzony et al. (2000) reported that WAY 100135 attenuated the effect of MK-801, a non-competitive NMDA antagonist, on working memory and selective attention in rats. Similarly, administration of WAY 100635 has been shown to prevent the learning deficits induced by AMPA receptor blockade (Schiapparelli et al., 2006). On the other hand, Carli et al. (2000, 2001) found that stimulation of 5-HT_{1A} receptors in dorsal raphe by 5-

HT_{1A} agonists ameliorates the impairment of spatial learning caused by hippocampal damage. Schechter et al. (2002) suggested that 5-HT_{1A} antagonists may be effective in the treatment of cognitive dysfunction associated with Alzheimer's disease. This is based on the assumption that stimulation by intrinsic 5-HT on postsynaptic 5-HT_{1A} receptors located on cortical or hippocampal pyramidal neurons would be blocked by 5-HT_{1A} antagonists, which would enhance cholinergic and glutamatergic neurotransmission (Schechter et al., 2002). However, the same results would also be expected by administration of partial 5-HT_{1A} agonists, such as buspirone, which stimulate 5-HT_{1A} autoreceptors and attenuate the action of intrinsic 5-HT on postsynaptic 5-HT_{1A} receptors (Sumiyoshi and Meltzer, 2004). 5-HT_{1A} agonists have been shown to also facilitate cortical acetylcholine (Ach) release (Hirano et al., 1999; Katsu, 2001; Somboonthum et al., 1997).

In the present study, buspirone selectively enhanced performance on the DSST, although this may be partly due to deterioration in performance in the patients augmented with placebo. In the patients given placebo at 3 months, similar slight and transient exacerbation was noted in the BPRS Positive and Withdrawal–Retardation subscale scores, although these were not significant (Table 3). Thus, it is possible that such deterioration in positive and negative symptoms may, at least in part, have affected attention and processing speed in the placebo group. Keefe et al. (2006) has recently reported the neurocognitive data from 1493 patients who participated in the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) schizophrenia trial. By analyzing data from a comprehensive test battery that included 11 neurocognitive tests assessing a range of cognitive domains, the authors have found that the DSST by itself accounted for most of the test variance (Keefe et al., 2006). Their observations indicate the usefulness of the DSST as an index of general cognitive function. Performance on the DSST represents attention and processing speed, cognitive abilities associated with frontal lobe function. As discussed before, the increased 5-HT_{1A} receptor density in schizophrenia has been most consistently reported in prefrontal cortex (Hashimoto et al., 1991; Simpson et al., 1996; Sumiyoshi et al., 1996). Therefore, it is possible that the advantage of addition of buspirone was evident in some of the cognitive domains related to brain areas where impaired 5-HT_{1A} receptor-mediated transmission is most pronounced. The relatively small effects of buspirone, reported here, may be explained by previous findings that risperidone and olanzapine, two AAPDs most used in clinical practice and also in this study, also have the ability to improve the performance on the DSST in patients with schizophrenia (Rossi et al., 1997). In sum, the distinct cognition-enhancing ability of buspirone suggests its usefulness for patients who have large deficits in attention in spite of treatment with AAPDs.

Unlike the results of previous studies with tandospirone (Sumiyoshi et al., 2001a), buspirone did not outperform placebo in enhancing other cognitive domains, e.g. verbal learning and memory and executive function. This discrepancy can be explained in several ways. Firstly, patients who participated in the present study were already treated with AAPDs, i.e. clozapine, risperidone, olanzapine, or ziprasidone, for more than 3 months, while the previous trials concerned the addition of tandospirone to ongoing treatment with typical antipsychotic drugs, mainly haloperidol (Sumiyoshi et al., 2000, 2001a,b). It is possible that intrinsic 5-HT_{1A} agonist activity of the AAPDs, by causing an increase in DA and/or Ach release, may have limited the ability of augmentation with buspirone to improve specific cognitive functions, such as verbal learning memory and executive function. In support of this view, the 5-HT_{1A} antagonist WAY 100635 inhibits the increase in DA release produced by AAPDs, such as clozapine and ziprasidone which are themselves 5-HT_{1A} partial agonists (Ichikawa et al., 2001; Chung et al., 2004), as well as olanzapine and risperidone, which do not directly interact with 5-HT_{1A} receptors (Ichikawa et al., 2001; Diaz-Mataix et al., 2005). In fact, the analysis of data from the subgroup of patients co-administered with either olanzapine or risperidone yielded the same results as those from the whole subjects (see Results).

Secondly, there is a difference in the relative affinities of buspirone and tandospirone for 5-HT_{1A} and D_2 receptors, with Ki values of 20 nM and 240 nM vs. 27 nM and 1700 nM, respectively (Hamik et al., 1990). This indicates a relatively strong D_2 receptor blocking effect of buspirone compared to tandospirone. Buspirone differs from other 5-HT_{1A} agonists, including ipsapirone, tandospirone, flesinoxan, and 8-OH-DPAT whose ability to increase cortical DA efflux in the rat is blocked by the 5-HT_{1A} antagonist WAY 100635, while that of buspirone is not (Gobert et al., 1999; Sakaue et al., 2000; Tanda et al., 1994; Wedzony et al., 1996; Yoshino et al., 2002). The effect on DA release of these other 5-HT_{1A} agonists is most likely due to stimulation of 5-HT_{1A} receptors in the cortex, since local application of WAY 100635 via a microdialysis probe antagonized the increase in DA release in the medial prefrontal cortex induced by systemic injection of tandospirone (Yoshino et al., 2002). Gobert et al. (1999) speculated that the effect of buspirone to enhance cortical DA release may be due, in part, to its D_2/D_3 receptor blockade, and that the formation of its metabolite, 1-PP, a potent α_2-adrenoceptor antagonist, is able to markedly stimulate cortical DA release by blockade of tonically

active α_2-heteroceptors on the terminals of dopaminergic neurons in the medial prefrontal cortex. These microdialysis studies do not permit a direct comparison of their efficacy nor their interactions with specific AAPDs with regard to enhancement of cortical DA efflux. This difference in the mechanism by which buspirone stimulates cortical DA efflux may contribute to the differences in cognitive enhancement produced by it and tandospirone. In man, the ability of buspirone to increase plasma prolactin levels has been shown to be mediated by D_2 receptor blockade rather than 5-HT_{1A} stimulation effect (Meltzer et al., 1983). Tandospirone, on the other hand, acts more like a full agonist compared to buspirone (Hirose et al., 1990; Tanaka et al., 1995).

Thirdly, although the subjects studied here had been treated with a stable dose of an AAPD for a relatively lengthy period before entering the study, the possibility that they had not reached the stable cognitive status after starting the co-administered AAPDs may not totally be excluded.

Whether the ability of tandospirone to improve cognition is limited to patients treated with typical antipsychotics requires further study. As discussed before, we have reported the usefulness of the adjunctive use of tandospirone for further improving verbal learning and memory even in a case of schizophrenia who had already been treated with perospirone, an AAPD having high affinity for 5-HT_{1A} receptors (Sumiyoshi et al., 2007). On the other hand, the combination of intrinsic 5-HT_{1A} stimulating effect of the AAPDs plus that of buspirone may limit the value of combining buspirone with AAPDs, as the relative balance between 5-HT_{1A} agonism and D_2 antagonism may be a determining factor in the ability of AAPDs to improve cognition (Bruins Slot et al., 2005; Newman-Tancredi et al., 2005).

Although slight improvements in the BPRS Total and Positive scores were noticed (Table 3), the present randomized, controlled trial did not identify a significant advantage of buspirone over placebo in treating psychotic symptoms. Brody et al. (1990) also observed no improvement in positive and negative symptoms in seven patients who received adjunctive treatment with buspirone, 10–60 mg/day, for four weeks. However, a larger study by Goff et al. (1991) found a significant reduction in positive but not negative symptoms, as assessed with the BPRS, following the addition of buspirone, in 20 patients with schizophrenia who had been treated with haloperidol. A subsequent open trial of buspirone augmentation (100 mg/day) of haloperidol found an improvement in the Positive Symptoms, the Negative Symptoms, and the General Psychopathology subscales, as assessed by the Positive and Negative Syndrome Scale in 13 patients with schizophrenia (Sirota et al., 2001). The discrepancy between our current findings and the results of some of these previous studies may be explained by the difference in the dose of buspirone, study design (open trials vs. RCT), concomitant medications (typical antipsychotics vs. AAPDs), and/or some other factors.

In conclusion, the results of this randomized, double-blind, placebo-controlled study showed a possible benefit of buspirone augmentation of AAPDs to enhance attention, with minimal influence on other domains of cognition, in patients with schizophrenia. Further study of various 5-HT_{1A} agonists with specific antipsychotic drugs, both typical and atypical, is indicated, based on the totality of our studies with both buspirone and tandospirone.

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Contributors

Tomiki Sumiyoshi designed the study, wrote the protocol and the first draft of the manuscript. Sohee Park designed the neuropsychological test battery. Karu Jayathilake undertook the statistical analysis. Ajanta Roy, Aygun Ertugrul, and Herbert Y. Meltzer managed data collection and the literature searches. All authors contributed to and have approved the final manuscript.

Conflicts of Interest

None.

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