Table 2 Summary of stepwise regression analyses on Schizophrenia Quality of Life Scale and Quality of Life Scale (N=99) (from Ref.13 Tomotake M, *et al.* Psychol Rep 99, 477-487, 2006)

	Dependent variables	Independent variables	Adjusted R^2	β
SQLS	Psychosocial	CDSS	.48***	.58***
		BPRS positive symptoms		.42***
		Dose of neuroleptics		-.22**
		BPRS negative Symptoms		-.18*
	Motivation and energy	CDSS	.23***	.48***
	Symptoms and side-effects	BPRS positive symptoms	.21***	.37**
		CDSS		.27**
		Dose of neuroleptics		-.20*
QLS	Total	BPRS negative symptoms	.46***	-.53***
		BPRS positive symptoms		-.24**
	Interpersonal relations	BPRS negative symptoms	.36***	-.60***
		Duration of illness		-.21*
	Instrumental role	BPRS negative symptoms	.28***	-.33**
		BPRS positive symptoms		-.31**
	Intrapsychic foundations	BPRS negative symptoms	.53***	-.59***
		BPRS positive symptoms		-.24**
	Common objects and activities	BPRS negative symptoms	.33***	-.58***
		Duration of illness		-.19*

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
SQLS=Schizophrenia Quality of Life Scale, QLS=Quality of Life Scale, CDSS=Calgary Depression Scale for Schizophrenia, BPRS=Brief Psychiatric Rating Scale.

BPRS positive symptoms score. The BPRS negative symptoms score and duration of illness contributed independently to the prediction of the Common objects and activities subscale.

In general, these findings seem to indicate that depressive symptom is the most important predictor of subjective QOL and negative symptom is the most important one of objective QOL.

RELATION BETWEEN LIFE SKILLS AND QUALITY OF LIFE

There are a few studies that investigated the relationship between life skill and QOL in people with schizophrenia. Norman *et al.* (16) reported the significant relationships among life skill, subjective QOL and objective QOL in subjects with schizophrenia or schizoaffective disorder. On the other hand, Parker *et al.* (21) reported no significant correlation between life skill and subjective QOL.

Recently, Aki *et al.* (22) investigated the relation between life skills and QOL in schizophrenia patients. In the study, they used the Life Skills Profile (LSP) to evaluate life skills of patients with schizophrenia, and subjective QOL and objective QOL were assessed the SQLS and the QLS, respectively. The LSP was designed by Rosen *et al.* (23) to assess survival and adaptation in the community by individuals with severe mental illness. The LSP is a thirty nine-item questionnaire. Each item is rated from 1 to 4 and a higher score indicates a greater level of life skills. The LSP has five subscales that are Self-care, Non-turbulance, Socialization, Communication, and Responsibility. Table 3 shows the results of correlation analyses between the SQLS, the QLS and the LSP in the study. The LSP total score correlated with scores of the SQLS and the

Table 3 Correlation among Schizophrenia Quality of Life Scale, Quality of Life Scale and Life Skills Profile (N=64) (from Ref.22 Aki H, *et al.* Psychiatry Res 158, 19-25, 2008)

	SQLS			QLS				
	Psychosocial	Motivation and energy	Symptoms and side-effects	Total	Interpersonal relations	Instrumental role	Intrapsychic foundation	Common objects and activities
LSP								
Total	-0.47**	-0.41*	-0.46**	0.55**	0.48**	0.56**	0.49**	0.47**
Self-care	-0.40*	-0.32	-0.43**	0.52**	0.46**	0.54**	0.45**	0.49**
Non-turbulence	-0.44**	-0.25	-0.43**	0.16	0.08	0.24	0.17	0.13
Socialization	-0.36	-0.44**	-0.28	0.63**	0.57**	0.57**	0.57**	0.50**
Communication	-0.33	-0.31	-0.37*	0.37	0.32	0.39*	0.33	0.27
Responsibility	-0.24	-0.17	-0.25	0.26	0.22	0.29	0.23	0.26

*p< 0.05, **p< 0.01 (Bonferroni correction).
SQLS=Schizophrenia Quality of Life Scale, QLS=Quality of Life Scale, LSP=Life Skills Profile.

QLS, which seems to indicate that basic life skills have some effects on schizophrenia patients' QOL. Especially, life skills about self-care and socialization are important factors.

From the findings, it is suggested that improving life skills may lead to enhancement of schizophrenia patients' QOL. However, a prospective research will be needed to clarify this.

RELATION BETWEEN COGNITIVE FUNCTION AND QUALITY OF LIFE

Cognitive problems have been considered a core component of schizophrenia. However, they have only recently been considered as potential treatment targets (24). Recently, it has become apparent that there are several aspects of impaired neurocognition that are consistently found in schizophrenia. Such cognitive dysfunctions are paid much more attention because they are thought to lead to poor social functioning.

Some research groups reported that functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalogram (EEG) show relations between neuroanatomical measures and cognitive deficits in schizophrenia patients, and these relations are particularly found in frontal regions, temporal cortex, and hippocampus (24). And it has been reported that cognitive functions of schizophrenia patients were of the order of one to two standard deviations below the mean of healthy controls in several cognitive dimensions, particularly memory, attention, verbal fluency, and executive function (25-28).

These cognitive dysfunctions are thought to be associated with lowered social activity, poor acquisition of social skills during the rehabilitation programme, and lowered QOL. Some previous research groups have investigated the relation between QOL and cognitive function in people with schizophrenia, and reported the significant correlations between QOL and some domains of cognitive function such as verbal memory, vocabulary, fluency performance, attention, social knowledge, and executive function (12, 28, 29-32).

From the results of previous studies, it seems to be clear that cognitive dysfunctions and some clinical symptoms are significantly correlated with lowered QOL in schizophrenia patients. However, it remains unclear how much impact these factors have on their QOL. Some studies demonstrated that cognitive dysfunction had a greater influence on schizophrenia patients' QOL than positive symptoms (33-35). On the other hand, some reported that neuropsychological function had a little impact on their QOL in the presence of some clinical symptoms (32, 36). The discrepancy among these studies might have been caused by differences of sample population, cognitive tests, and QOL scales (32-34, 36).

To elucidate the relation between cognitive function and QOL in schizophrenia patients, Yamauchi *et al.* (37) investigated the relations between the SQLS, the QLS, and the PANSS cognitive factor in 84 outpatients with schizophrenia. The results showed that although the PANSS cognitive factor was significantly correlated with both of the SQLS and the QLS, it seemed to have a greater influence on the QLS score than the SQLS score.

Recently, our research group (38) conducted a

strict study to elucidate the relation between cognitive function and QOL by using the Brief Assessment of Cognition in Schizophrenia (BACS) (39, 40) that is a newly developed neuropsychological battery for assessing cognitive function of schizophrenia patient. The BACS has been developed for clinical trials with a brief battery of tests for measuring cognition. It assesses the aspects of cognition that were found to be most impaired and most strongly correlated with outcome in patients with schizophrenia. The domains of cognitive function evaluated by the BACS are Verbal memory (List learning), Working memory (Digit sequencing task), Motor speed (Token motor task), Verbal fluency (Category instances and Controlled oral word association test), Attention and speed of information processing (Symbol coding), and Executive function (Tower of London) (39).

In our study (40), Z-score for Verbal memory was -1.68 (SD=1.28), that for Working memory -1.23 (SD=1.78), that for Motor speed -1.81 (SD=1.64), that for Attention and speed of information processing -1.66 (SD=1.19), that for Verbal fluency -0.82 (SD=1.11), and that for Executive function -1.20 (SD=1.95), showing that cognitive performance of schizophrenia patients were much disturbed than healthy controls. The correlations between the QLS scores and the BACS scores are shown in Table 4. The BACS Composite score, Attention and speed of information processing score, and Verbal memory score showed significant and positive correlations with the QLS total and all or some subscale scores. In the study, stepwise regression analyses when using several clinical variables including the BACS scores as independent variables showed that the QLS total score was significantly predicted by the PANSS negative syndrome scale score, the CDSS score, and the BACS Attention and speed of information processing score. The results were rather consistent with those of previous researches in terms of that cognitive dysfunction was on the whole related to lowered objective QOL (28, 30, 37).

In addition, we also investigated the relation between subjective QOL and cognitive function and reported that there was no significant correlation between them (41).

CONCLUSIONS

Subjective and objective QOL measures have different predictors in people with schizophrenia. Depressive symptom is most related to subjective QOL, negative symptom is most associated with objective one, and basic life skills are related to both. Cognitive dysfunctions in some neurocognitive domains are associated with lowered objective QOL, but the effects of them are much smaller than negative and depressive symptoms. It is suggested that improving depressive and negative symptoms and basic life skills may contribute to enhancement of QOL of schizophrenia patients.

REFERENCES

1. Awad AG, Voruganti LN, Heslegrave RJ : A conceptual model of quality of life in schizophrenia : description and preliminary clinical validation. Qual Life Res 6 : 21-26, 1997

Table 4 Correlation between Quality of Life Scale and Brief Assessment of Cognition in Schizophrenia (N=61) (from Ref.38 Ueoka Y, *et al.* Prog Neuropsychopharmacol Biol Psychiatry 35, 53-59, 2011)

	QLS				
	Total	Interpersonal relations	Instrumental role	Intrapsychic foundation	Common objects and activities
BACS					
Verbal memory	0.419**	0.415**	0.311	0.422**	0.295
Working memory	0.281	0.283	0.142	0.290	0.259
Motor speed	0.196	0.175	0.126	0.222	0.228
Attention and speed of information processing	0.515**	0.495**	0.372*	0.541**	0.418**
Verbal fluency	0.203	0.200	0.154	0.206	0.170
Executive function	0.168	0.174	0.103	0.131	0.175
Composite score	0.341*	0.346*	0.205	0.341*	0.305

*p< 0.05, **p< 0.01 (Bonferroni correction).
BACS=Brief Assessment of Cognition in Schizophrenia, QLS=Quality of Life Scale.

2. Lehman AF : A quality of life interview for the chronically mental ill. Eval Program Plann 11 : 51-62, 1988
3. Meltzer HY : Outcome in schizophrenia : beyond symptom reduction. J Clin Psychiatry 60 (Suppl 3) : 3-7, 1999
4. Attikisson C, Cook J, Karno M : Caring for people with severe mental disorders : clinical services research. Schizophr Bull 18 : 561-626, 1992
5. Fitzgerald PB, Williams CL, Corteling N, Filia SL, Brewer K, Adams A, de Castella AR, Rolfe T, Davey P, Kulkami J : Subject and observer-rerated quality of life in schizophrenia. Acta Psychiatr Scand 103 : 387-392, 2001
6. Taniguchi T, Sumitani S, Aono M, Iga J, Kinouchi S, Aki H, Matsushita M, Taniguchi K, Tsuno M, Yamanishi K, Tomotake M, Kaneda Y, Ohmori T : Effect of antipsychotic replacement with quetiapine on the symptoms and quality of life of schizophrenic patients with extrapyramidal symptoms. Hum Psychopharmacol 21 : 439-445, 2006
7. Saxena S, Orley J : Quality of life assessment : the world health organization perspective. Eur Psychiatry 12 (Suppl 3) : 263-266, 1997
8. Voruganti L, Heslegrave R, Awad AG, Seeman MV : Quality of life measurement in schizophrenia : reconciling the quest for subjectivity with the question of reliability. Psychol Med 28 : 165-172, 1998
9. Heinrichs DW, Hanlon TE, Carpenter WT : The Quality of Life Scale : an instrument for rating the schizophrenic deficit symptoms. Schizophr Bull 10 : 388-398, 1984
10. Wilkinson G, Hesdon B, Wild D, Cookson R, Farina C, Sharma V, Fitzpatrick R, Jenkinson C : Self-report quality of life measure for people with schizophrenia : the SQLS. Br J Psychiatry 177 : 42-46, 2000
11. Kaneda Y, Imakura A, Fujii A, Ohmori T : Schizophrenia quality of life scale : validation of the Japanese version. Psychiatry Res 113 : 107-113, 2002
12. Dickerson FB, Ringel NB, Parente F : Subjective quality of life in out-patients with schizophrenia : clinical and utilization correlates. Acta Psychiatr Scand 98 : 124-127, 1998
13. Tomotake M, Kaneda Y, Iga J, Kinouchi S, Tayoshi S, Motoki I, Sumitani S, Yamauchi K, Taniguchi T, Ishimoto Y, Ueno S, Ohmori T : Subjective and objective measures of quality of life have different predictors in people with schizophrenia. Psychol Rep 99 : 477-487, 2006
14. Huppert JD, Weiss KA, Lim R, Pratt S, Smith TE : Quality of life in schizophrenia : contribution of anxiety and depression. Schizophr Res 51 : 171-180, 2001
15. Reine G, Lancon C, Di Tucci S, Sapin C, Auquier P : Depression and subjective quality of life in chronic phase schizophrenic patients. Acta Psychiatr Scand 108 : 297-303, 2003
16. Norman RMG, Malla AK, McLean T, Voruganti LPN, Cortese L, McIntosh E, Cheng S, Rickwood A : The relationship of symptoms and level of functioning in schizophrenia to general wellbeing and the Quality of Life Scale. Acta Psychiatr Scand 102 : 303-309, 2000
17. Bow-Thomas CC, Velligan DI, Miller AL, Olsen J : Predicting quality of life from symptomatology in schizophrenia at exacerbation and stabilization. Psychiatry Res 86 : 131-142, 1999
18. Browne S, Garavan J, Gervin M, Roe M, Larkin C, O'callaghan E : Quality of life in schizophrenia : insight and subjective response to neuroleptics. J Nerv Ment Dis 186 : 74-78, 1998
19. Browne S, Roe M, Lane A, Gervin M, Morris M, Kinsella A, Larkin C, Callaghan EO : Quality of life in schizophrenia : relationship to sociodemographic factors, symptomatology and tardive dyskinesia. Acta Psychiatr Scand 94 : 118-124, 1996
20. Meltzer HY, Burnett S, Bastani B, Ramirez LF : Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. Hosp Community Psychiatry 41 : 892-897, 1990
21. Parker G, O'Donnell M, Hadzi-Pavlovic D, Proberts M : Assessing outcome in community mental health patients : a comparative analysis of measures. Int J Soc Psychiatry 48 : 11-19, 2002
22. Aki H, Tomotake M, Kaneda Y, Iga J, Kinouchi S, Tayoshi S, Tayoshi S, Moriguchi K, Motoki I, Sumitani S, Yamauchi K, Taniguchi T, Ishimoto Y, Ueno S, Ohmori T : Subjective and objective quality of life, levels of life skills, and their clinical determinants in outpatients with schizophrenia. Psychiatry Res 158 : 19-25, 2008
23. Rosen A, Hadzi-Pavlovic D, Parker G : The life skills profile : a measure assessing function and disability in schizophrenia. Schizophr Bull 15 : 325-337, 1989

24. Targum SD, Keefe RSE : Cognition and schizophrenia : is there a role for cognitive assessments in diagnosis and treatment? Psychiatry 5 : 55-59, 2008
25. Heinrichs RW, Zakzanis KK : Neurocognitive deficits in schizophrenia : a quantitative review of the evidence. Neuropsychology 12 : 426-445, 1998
26. Gold JM : Cognitive deficits as teatment targets in schizophrenia. Schizophr Res 72 : 21-28, 2004
27. Kraus MS, Keefe RSE : Cognition as an outcome measure in schizophrenia. Br J Psychiatry 191 (Suppl 50) : 46-51, 2007
28. Savilla K, Kettler L, Galletly C : Relationships between cognitive deficits, symptoms and quality of life in schizophrenia. Aust N Z J Psychiatry 42 : 496-504, 2008
29. Addington J, Addington D : Neurocognitive and social functioning in schizophrenia : a 2.5 year follow-up study. Schizophr Res 44 : 47-56, 2000
30. Bozikas VP, Kosmidis MH, Kafantari A, Gamvrula K, Vasiliadou E, Petrikis P, Fokas K, Karavatos A : Community dysfunction in schizophrenia : rate-limiting factors. Prog Neuropsychopharmacol Biol Psychiatry 30 : 463-470, 2006
31. Ritsner MS : Predicting quality of life impairment in chronic schizophrenia from cognitive variables. Qual Life Res 16 : 929-937, 2007
32. Matsui M, Sumiyoshi T, Arai H, Higuchi Y, Kurachi M : Cognitive functioning related to quality of life in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 32 : 280-287, 2008
33. Breier A, Schreiber JL, Dyer J, Pickar D : National Institute of Mental Health longitudinal study of chronic schizophrenia : prognosis and predictors of outcome. Arch Gen Psychiatry 48 : 239-246, 1991
34. Green MF : What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153 : 321-330, 1996
35. Ho BC, Nopoulos P, Flaum M, Arndt S, Andreasen NC : Two-year outcome in first-episode schizophrenia : predictive value of symptoms for quality of life. Am J Psychiatry 155 : 1196-1201, 1998
36. Wegener S, Redoblado-Hodge MA, Lucas S, Fitzgerald D, Harris A, Brennan J : Relative contributions of psychiatric symptoms and neuropsychological functioning to quality of life in first-episode psychosis. Aust N Z J Psychiatry 39 : 87-92, 2005
37. Yamauchi K, Aki H, Tomotake M, Iga J, Numata S, Motoki I, Izaki Y, Tayoshi S, Kinouchi S, Sumitani S, Tayoshi S, Takikawa Y, Kaneda Y, Taniguchi K, Ishimoto Y, Ueno S, Ohmori T : Predictors of subjective and objective quality of life in outpatients with schizophrenia. Psychiatry Clin Neurosci 62 : 404-411, 2008
38. Ueoka Y, Tomotake M, Tanaka T, Kaneda Y, Taniguchi K, Nakataki M, Numata S, Tayoshi S, Yamauchi K, Sumitani S, Ohmori T, Ueno SI, Ohmori T : Quality of life and cognitive dysfunction in people with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 35 : 53-59, 2011
39. Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L : The Brief Assessment of Cognition in Schizophrenia : reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 68 : 283-297, 2004
40. Kaneda Y, Sumiyoshi T, Keefe RSE, Ishimoto Y, Numata S, Ohmori T : Brief Assessment of Cognition in Schizophrenia : validation of the Japanese version. Psychiatry Clin Neurosci 6 : 602-609, 2007
41. Tomotake M, Ueoka Y, Tanaka T, Kaneda Y, Ohmori T : Effect of cognitive dysfunction on subjective quality of life in people with schizophrenia. British Association of Behavioral and Cognitive Psychotherapies 38th Annual Conference, Manchester, 2010

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Effect of blonanserin on cognitive function in antipsychotic-naïve first-episode schizophrenia

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Objective The purpose of this study was to evaluate the effects of blonanserin, a novel antipsychotic, on cognitive function in first-episode schizophrenia.
Methods Twenty-four antipsychotic-naïve patients with first-episode schizophrenia participated in the study. Blonanserin was given in an open-label design for 8 weeks. The Brief Assessment of Cognition in Schizophrenia—Japanese language version (BACS-J) was administered as the primary outcome measure at baseline and 8 weeks. Clinical evaluation included the Positive and Negative Syndrome Scale (PANSS), the Schizophrenia Quality of Life Scale—Japanese language version (SQLS-J), and the Clinical Global Impression—Severity of Illness Scale (CGI-S). To exclude the possibility of retest effects on the BACS-J, 10 age-matched patients with chronic schizophrenia treated with blonanserin were tested at baseline and after an 8-week interval.
Results Twenty first-episode patients completed the study. Repeated measures analysis of covariance revealed a significant group-by-time interaction effect on the letter fluency task due to better performance in the first-episode group, but not in the control group. Main effect of time or group-by-time interaction effect on the Tower of London task was not significant; however, the first-episode group, but not the control group, showed substantial improvement with a moderate effect size. All items on the PANSS, SQLS-J, and CGI-S significantly improved after 8 weeks of treatment.
Conclusions These results suggest that blonanserin improves some types of cognitive function associated with prefrontal cortical function.

KEY WORDS—blonanserin; cognition; quality of life; schizophrenia; letter fluency

INTRODUCTION

Cognitive impairment is a core feature of schizophrenia (Gold and Harvey, 1993; Green *et al.*, 2000) and is present early in the course of the illness (Mesholam-Gately *et al.*, 2009; Bozikas and Andreou, 2011). A number of studies have reported a 1–2 standard deviation (SD) decline in the performance on tests of multiple cognitive domains, including attention, executive function, memory, and processing speed, compared with healthy volunteers (Saykin *et al.*, 1994; Bilder *et al.*, 2000; Wolwer *et al.*, 2008; Mesholam-Gately *et al.*, 2009). These cognitive deficits have been shown to largely determine social and occupational functioning (Green, 1996; Meltzer *et al.*, 1996), as well as quality of life (QOL) in patients with schizophrenia (Matsui *et al.*, 2008; Tomida *et al.*, 2010; Woon *et al.*, 2010). Given that cognitive deficits are among the strongest predictors of functional outcome in schizophrenia (Green *et al.*, 2000), treatments for these symptoms are most urgently needed (Sumiyoshi *et al.*, 2008; Miyamoto *et al.*, in press).

A renewed interest in the amelioration of cognitive impairment associated with schizophrenia arose with the introduction of new antipsychotic drugs. Earlier reviews suggested that the second-generation antipsychotics (SGAs) may have more beneficial effects on cognition than the first-generation antipsychotics (FGAs) (Keefe *et al.*, 1999; Harvey and Keefe, 2001; Mishara and Goldberg, 2004). However, several confounding factors, such as incomparable antipsychotic doses, heterogeneous patient samples, effects of prior medication, lack of control for retest effects on cognitive measures, and adjunctive anticholinergic medication,

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limit the conclusions that can be drawn regarding the effects of different antipsychotic drugs on cognition (Carpenter and Gold, 2002; Goldberg *et al.*, 2007, 2010; Hill *et al.*, 2010; Andersen *et al.*, 2011). Recent large controlled studies have demonstrated significant cognitive improvement with both FGAs and SGAs from baseline, but neither class appeared to be clearly superior to the other, and the magnitude of cognitive improvement was modest at best (Keefe *et al.*, 2007a, 2007b; Davidson *et al.*, 2009).

Blonanserin, 2-(4-ethyl-1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahy-drocycloocta [b] pyridine, was developed as a novel antipsychotic drug in Japan (Noda *et al.*, 1993; Oka *et al.*, 1993) and was approved for the treatment of schizophrenia in Japan and Korea (Deeks and Keating, 2010). It has high affinity for dopamine $D_{2,3}$ and serotonin 5-HT_{2A} receptors but shows low affinity for $D_{1,4,5}$, adrenergic $\alpha_{1,2}$, β, 5-$HT_{1A,2B,2C,3-7}$ histamine H_1, and muscarinic M_1 receptors (Oka *et al.*, 1993; Deeks and Keating, 2010). A preclinical study demonstrated that blonanserin increased extracellular levels of dopamine and norepinephrine in the prefrontal cortex (Ohoyama *et al.*, 2011). In three randomized, 8-week, double-blind clinical trials, blonanserin was equal to haloperidol and risperidone in primary endpoints (final global improvement rate or improvement in total symptomatology) and was superior to haloperidol in improving negative symptoms in patients with schizophrenia (Murasaki, 2007a; Miura, 2008; Yang *et al.*, 2010). The overall tolerability profile of blonanserin was similar to that of haloperidol and risperidone (Murasaki, 2007a; Miura, 2008; Deeks and Keating, 2010; Yang *et al.*, 2010), but blonanserin was associated with a lower incidence of extrapyramidal symptoms (EPS) than haloperidol (Murasaki, 2007a). In our previous randomized, double-blind, 8-week study comparing blonanserin with risperidone, blonanserin significantly improved certain cognitive functions such as verbal memory, attention, and processing speed in patients with chronic schizophrenia (Miyake *et al.*, 2008).

To date, no study has examined the effects of blonanserin on clinical efficacy including cognitive function in first-episode schizophrenia. Given the above-mentioned observations from basic and clinical studies, it is hypothesized that treatment with blonanserin would improve some domains of cognitive function, probably those associated with prefrontal cortical function, in patients with first-episode schizophrenia. To test this hypothesis, this study was conducted to evaluate the effects of blonanserin on clinical symptoms and subjective QOL in patients with antipsychotic-naïve first-episode schizophrenia.

METHODS

This prospective, single-blind, open-label study was conducted at St. Marianna University School of Medicine Hospital and Ofuji Hospital from March 2009 to July 2011. It was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the St. Marianna University School of Medicine Bioethics Committee. All participants gave informed consent after the study procedures had been fully explained.

Study participants

Twenty-four subjects (13 male and 11 female) participated in this study. Eligible participants were inpatients and outpatients with a clinical diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000), who met the following inclusion criteria: (i) aged 16 to 40 years; (ii) experiencing their first episode of psychosis for at least 1 month and less than 5 years; and (iii) no history of antipsychotic exposure or, if previously treated, a total lifetime of antipsychotic treatment of less than 16 weeks and no antipsychotic administration for 12 weeks before participating in the study. Most of the inclusion criteria were based on previous first-episode studies (Keefe *et al.*, 2007b; McEvoy *et al.*, 2007; Perkins *et al.*, 2008). Diagnosis was performed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders.

Exclusion criteria were as follows: (i) patients who had been treated with blonanserin before study entry; (ii) comorbid central nervous system disorder; (iii) meeting the DSM-IV-TR criteria for current and/or past alcohol or other substance dependence or abuse; (iv) meeting the DSM-IV-TR criteria for mental retardation; (v) taking tricyclic antidepressants; (vi) treatment with electroconvulsive therapy in the 12 weeks preceding the study; (vii) patients who were not voluntarily hospitalized; (viii) active expression of suicidal or homicidal ideation; (ix) pregnancy or breast feeding; and (x) inability to understand the study protocol or if the subject was judged to be uncooperative by the rater.

To exclude possible retest effects on cognitive measures, 10 patients with chronic schizophrenia (five male and five female) who matched for age, sex, and education were recruited as a control group (Table 1). Inclusion criteria for the control group were as follows: (i) patients who have been treated with a stable dose of blonanserin as monotherapy for at least 12 weeks; (ii)

Table 1. Baseline demographic and clinical characteristics among first-episode schizophrenia and control group subjects

	First-episode group ($n=20$)	Control group ($n=20$)	Significance[c]
Gender (male/female)	10/10	5/5	NS[d]
Age[a] (years)	26.1 (6.2)	26.9 (6.6)	NS
Education level[a] (years)	13.8 (2.0)	13.2 (1.4)	NS
Duration of untreated psychosis[a] (months)	8.1 (11.8)	15.2 (13.8)	NS
Benzodiazepine dose[a] (mg/day)	0.7 (1.7)	0.8 (1.6)	NS
PANSS			
Positive score	23.8 (4.0)	15.4 (3.7)	NS
Negative score	29.5 (6.4)	18.2 (5.7)	NS
General psychopathology score	56.9 (8.1)	37.3 (10.5)	NS
Total score	109.7 (16.0)	70.9 (18.0)	NS

NS, no significant difference; PANSS, Positive and Negative Syndrome Scale.
[a]Values represent mean (SD).
[b]Lorazepam-equivalent dose.
[c]Independent *t*-test.
[d]Chi-squared test.

aged 16 to 40 years; (iii) having a history of psychotic relapses; and (iv) duration of illness of at least 2 years. Exclusion criteria for the control group were the same as those of the first-episode patients, except for blonanserin treatment.

Study design

Twenty-four subjects were initially recruited to the present study and assigned to the first-episode schizophrenia group (first-episode group). Subsequently, 10 subjects were recruited and assigned to the control group (control group).

In the first-episode group, blonanserin was orally administered for 8 weeks. The manufacturer recommends twice daily administration of blonanserin (Deeks and Keating, 2010). However, the half-life of blonanserin was reported to be 67.9 h after repeated administrations at 4 mg/day for 10 days in healthy individuals (Deeks and Keating, 2010). Thus, in this study, blonanserin was administered once or twice daily after meal intake. While the approved dose range of blonanserin is 8–24 mg/day, first-episode patients generally respond more to lower antipsychotic doses than do patients with recurrent episodes (Miyamoto *et al.*, 2008; Salimi *et al.*, 2009). Thus, patients initially received a low dose of blonanserin (2–6 mg/day), but the dosage was adjusted to between 2 and 24 mg/day according to the treating physician's discretion. In the control group, the dose of blonanserin was fixed during the trial.

Benzodiazepines, sedative-hypnotics, antidepressants except for tricyclic antidepressants, and/or mood stabilizers were allowed if clinically needed, but they were kept to a minimum during the study (Table 2). Whenever clinically significant EPS occurred, anticholinergic drugs were allowed. However, clinicians were encouraged to lower the dose of blonanserin to relieve EPS. There was no limit to the biperiden-equivalent dose that could be prescribed. Prophylactic administration of anticholinergic drugs and additional antipsychotics were not permitted. In the control group, the dose of concomitant psychotropic medications was not changed during the trial. Clinical assessments were undertaken at baseline and after 8 weeks.

It has been stated that short-term clinical trials in which patients undergo cognitive assessments with short intervals are particularly vulnerable to the effect

Table 2. Use of concomitant medications at endpoint

	First-episode group ($n=20$)		Control group ($n=10$)	
Concomitant medications	*n*	Mean daily dose (range) (mg/day)	*n*	Mean daily dose (range) (mg/day)
Anticholinergics	5	0.80 (1.0–2.0)[a]	7	1.70 (1.0–7.0)[a]
	5 (biperiden)		6 (biperiden)	
			1 (biperiden and promethazine)	
Daytime benzodiazepines	9	1.00 (0.4–7.2)[b]	4	0.88 (1.0–3.0)[b]
Hypnotics	2	0.12 (1.2)[b]	3	0.96 (1.2–4.8)[b]
Mood stabilizers			1 (carbamazepine)	600
			1 (lithium)	400
			1 (valproic acid)	600

[a]Biperiden-equivalent dose.
[b]Lorazepam-equivalent dose.

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of repeated exposure to the tests and/or assessment environment (i.e., retest effects) (Crespo-Facorro *et al.*, 2009; Goldberg *et al.*, 2010). To compare the retest effect on cognitive assessments, the control group was assessed at baseline and 8 weeks after the initial assessment. Treatment adherence was assessed by interview at each testing session.

Cognitive function, subjective quality of life, and clinical assessment

The primary outcome measure was the change in cognitive function from baseline to endpoint during blonanserin treatment. Secondary outcome measures were changes in psychiatric symptoms, subjective QOL, and severity of psychopathology.

Cognitive function was assessed by trained psychiatrists or psychologists using the Brief Assessment of Cognition in Schizophrenia—Japanese language version (BACS-J) (Kaneda *et al.*, 2007). The BACS-J has established reliability and validity and is designed to measure cognitive function in schizophrenia (Keefe *et al.*, 2004; Kaneda *et al.*, 2007). The BACS-J cognitive battery uses the following assessments in the respective targeted domains: list learning (verbal memory), digit sequencing task (working memory), token motor task (motor speed), category fluency and letter fluency (verbal fluency), symbol coding (attention and processing speed), and the Tower of London test (executive function). To reduce retest effects, subjects were randomized to receive either version A or B of the BACS-J at baseline and the other version at the endpoint session. For each assessment, a *z*-score was calculated using the mean raw scores and SD in pooled healthy controls ($n = 340$) from another study (Kaneda *et al.*, 2008).

Subjective QOL was assessed by the Schizophrenia Quality of Life Scale—Japanese language version (SQLS-J) (Kaneda *et al.*, 2002). The SQLS-J is a practical method of measuring self-reported QOL in people with schizophrenia and has established reliability and validity (Wilkinson *et al.*, 2000; Kaneda *et al.*, 2002). The 30 items on the SQLS-J are classified into three areas: (i) psychosocial conditions; (ii) motivation/energy; and (iii) symptoms/side effects. Each area scale was transformed to range from 0 (the best status) to 100 (the worst status). The "psychosocial conditions" area addresses various emotional conditions such as loneliness, hopelessness, difficulty in social situations, and worries about the future. The "motivation/energy" area addresses various problems of motivation and activity, such as the lack of will or drive to do things. The "symptoms/side effects" area addresses issues such as muscle twitches and dry mouth, which can be caused by medication (Wilkinson *et al.*, 2000; Kaneda *et al.*, 2002).

Other clinical evaluations were made by trained psychiatrists using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1987) and the Clinical Global Impression—Severity of Illness Scale (CGI-S) (Guy, 1976). Drug-induced EPS were assessed using the Drug-induced Extrapyramidal Symptoms Scale (DIEPSS) (Inada, 1996). The raters (S. M., S. O, and T. T.) were experienced clinicians who were extensively trained in the administration of outcome measures, including the PANSS and DIEPSS, before the beginning of the study to a minimum intraclass correlation of 0.80. The clinicians and psychologists who provided the clinical ratings were blinded to the assigned procedure of study patients.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Japan Inc., Tokyo, Japan). Differences between the first-episode group and the control group in demographic and baseline characteristics were assessed using independent sample *t*-tests, except for gender, which was assessed using the chi-squared test.

The primary aim of this study was to clarify the effects of blonanserin on cognitive function, as measured by BACS-J. A repeated measures analysis of covariance (ANCOVA) was performed for each cognitive variable with baseline data as covariate. For the primary analysis, the between-subject factor was the group (first-episode group and control group) and the within-subject factor was the time (baseline and endpoint). Effects of group, time, and group-by-time (interaction effect) were examined. Greenhouse–Geisser corrections were used when the assumption of sphericity was violated. Our main interest in the repeated measures ANCOVA was whether the group-by-time interaction reached significance for each cognitive variable. We also used a Bonferroni correction for multiple comparisons of BACS-J data. In a secondary analysis, within-group improvements in cognitive performance over time were evaluated using paired *t*-tests. Effect size (Cohen's *d*) was calculated as the within-group differences between the means divided by the pooled SD. In a third analysis, paired *t*-tests were used to assess changes in each SQLS-J subscale and other clinical assessment scores. Finally, Pearson's exploratory correlational analysis was used to determine potential associations between cognitive and clinical change scores. All statistical tests were two-tailed, and a *p*-value less than 0.05 was considered significant.

RESULTS

Demographic and clinical characteristics

A total of 24 first-episode patients were recruited and tested at baseline. Of these, 20 (10 male and 10 female) completed the study. The reasons for drop-out were unwillingness to undergo treatment at baseline ($n=2$), loss to follow-up at week 4 ($n=1$), and transfer to another hospital at week 4 ($n=1$). In the control group, 10 were retested on the cognitive measures after 8 weeks. Thus, data from these 20 patients in the first-episode group and 10 patients in the control group were used for a completer analysis. Two patients participated as inpatients, and they moved from inpatient to outpatient status during the study. The duration of hospitalization was 13 days for a patient in the first-episode group and 34 days for a patient in the control group. The DSM-IV-TR diagnostic distribution of the participating schizophrenic patients was paranoid type ($n=19$ in the first-episode group; $n=9$ in the control group), disorganized type ($n=1$ in the first-episode group), and schizoaffective disorder ($n=1$ in the control group).

Baseline demographic and clinical characteristics of subjects are shown in Table 1. There were no significant group differences in gender, age, education level, duration of untreated psychosis that was defined as the interval between the first onset of psychotic symptoms and the administration of the first adequate antipsychotic treatment (Larsen *et al.*, 1996), or each PANSS score (all $p > 0.05$). In the control group, mean duration of illness was 76.8 (±59.7; SD) months and mean duration of treatment with blonanserin was 27.1 (± 43.1) months. One patient in the control group had participated in a phase III clinical trial of blonanserin and a subsequent long-term follow-up study.

Dosage of blonanserin and concomitant drugs

In the first-episode group, the mean daily dose of blonanserin at starting after baseline assessment and at 8 weeks was 2.9 (± 1.5) and 7.2 (± 4.0) mg/day, respectively. In the control group, the mean daily dose of blonanserin during the study was 12.8 (± 7.8) mg/day. There was a significant difference between the two groups in mean dosage of blonanserin at 8 weeks ($t=-2.62$, d.f. = 28, $p=0.008$).

In the first-episode group, none of the patients had taken anticholinergics at baseline, but six patients had taken daytime benzodiazepines (mean lorazepam-equivalent dose: 0.7 [±1.7] mg/day) at baseline. Concomitant psychotropic medications used at endpoint are shown in Table 2. The difference between the two groups in mean dosage of anticholinergics (biperiden equivalents) at 8 weeks was not significant ($p > 0.05$). Furthermore, the difference between the two groups in mean dosage of daytime benzodiazepines or hypnotics (lorazepam equivalents) at 8 weeks was not significant ($p > 0.05$). None of the patients in either group had taken antidepressants.

Effect of blonanserin on cognitive function

Results of the BACS-J raw scores and *z*-scores at baseline and endpoint are shown in Table 3. Results of repeated measures ANCOVAs comparing the two groups in BACS-J *z*-scores are shown in Table 4. The analysis of between-group differences demonstrated no significant group effects for each BACS-J item (all $p > 0.05$). The analysis of within-group differences also demonstrated no significant time effects for each BACS-J item (all $p > 0.05$). Group-by-time interaction reached significance in the letter fluency task ($F=8.42$; d.f. = 1, 27; $p=0.007$), which remained so even after Bonferroni correction.

Results of paired *t*-tests demonstrated that *z*-scores of the letter fluency score and the Tower of London score were significantly increased after treatment with blonanserin in the first-episode group (all $p < 0.05$) (Table 3). The effect sizes for these changes were in a moderate range (Table 3). No BACS-J subscale scores showed a significant change in the control group during the 8-week interval (all $p > 0.05$).

Effect of blonanserin on other clinical assessments

Results of paired *t*-tests comparing changes in scores on the secondary measures from baseline to endpoint in the first-episode group are shown in Table 5. Significant improvements were found in all items on the PANSS, SQLS-J, and CGI-S (all $p < 0.01$). There was a significant difference in the DIEPSS total score between baseline and endpoint in the first-episode group ($p < 0.05$). Eleven patients (55.0%) in the first-episode group showed mild EPS during the study, and five patients (25.0%) required administration of low-dose anticholinergic biperiden (Table 2). There were no significant differences in each PANSS score between baseline and endpoint in the control group (Table 6).

Associations between cognitive test scores and changes in clinical assessments

There was a significant correlation between the changes in the *z*-score of the letter fluency task and motivation/energy score on the SQLS-J (correlation coefficient = −0.55; $p=0.041$). There were no significant correlations between changes in any of the other BACS-J scales and the PANSS, SQLS-J, CGI-S, or DIEPSS scores (all $p > 0.05$). Also, there were no

Table 3. BACS-J raw score and z-score at baseline and endpoint

		Baseline				Endpoint							
		First-episode group ($n=20$)		Control group ($n=10$)		First-episode group ($n=20$)				Control group ($n=10$)			
						Change		Within-group differences		Change		Within-group differences	
BACS-J[a]	Range of raw score	Raw score	z-score	Raw score	z-score	Raw score	z-score	Effect size[b]	p[c]	Raw score	z-score	Effect size[b]	p[c]
Verbal memory	0–75	41.10 (13.50)	−1.32 (1.68)	43.80 (10.61)	−0.87 (1.12)	1.85 (11.25)	0.22 (0.33)	0.15	0.48	1.80 (8.26)	0.21 (0.08)	0.46	0.28
Digit sequencing task	0–28	19.65 (3.44)	−0.62(0.90)	17.40 (4.38)	−1.27 (1.18)	−0.50 (4.49)	−0.13 (0.32)	0.12	0.61	0.90 (1.97)	0.24 (0.06)	0.30	0.31
Token motor task	0–100	60.10 (20.80)	−2.66 (1.88)	58.00 (17.61)	−3.06 (1.57)	−1.55 (10.52)	−0.14 (0.20)	0.08	0.53	2.00 (10.54)	0.21 (0.06)	0.02	0.94
Category fluency	0–	17.25 (5.48)	−0.66 (0.65)	16.40 (4.62)	−0.70 (0.50)	0.80 (4.69)	0.15 (0.16)	0.24	0.15	0.20 (2.49)	0.03 (0.11)	0.48	0.10
Letter fluency	0–	19.45 (7.55)	−1.06 (1.10)	22.20 (7.69)	−0.62 (1.05)	4.20 (1.05)	0.61 (0.10)	0.58	0.001	−1.00 (3.97)	−0.13 (0.28)	0.05	0.81
Symbol coding[d]	0–110	56.00 (13.83)	−1.12 (0.91)	46.50 (13.95)	−2.01 (1.17)	−1.30 (10.05)	−0.66 (1.44)	0.33	0.22	3.90 (5.78)	0.34 (0.06)	0.21	0.19
Tower of London	0–22	16.20 (2.57)	−1.05 (1.09)	16.40 (3.31)	−0.94 (1.40)	0.85 (2.78)	0.61 (0.18)	0.62	0.004	1.00 (3.13)	0.46 (0.62)	0.10	0.74

BACS-J, Brief Assessment of Cognition in Schizophrenia—Japanese language version.
[a]Values are mean (SD).
[b]Cohen's *d*.
[c]Paired *t*-tests were used to compare changes in z-score.
[d]$p < 0.05$, independent sample *t*-tests at baseline.

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Table 4. Repeated measures ANCOVA comparing first-episode schizophrenia and control group in BACS-J *z*-score

	Between-group differences (group effect)			Within-group differences (time effect)			Group × time interaction		
BACS-J[a]	*F*	d.f.	*p*	*F*	d.f.	*p*	*F*	d.f.	*p*
Verbal memory	2.57	1, 27	0.12	2.22	1, 27	0.15	0.96	1, 27	0.34
Digit sequencing task	0.01	1, 27	0.92	0.07	1, 27	0.80	0.85	1, 27	0.37
Token motor task	0.69	1, 27	0.41	1.27	1, 27	0.27	0.08	1, 27	0.78
Category fluency	0.85	1, 27	0.36	0.006	1, 27	0.94	1.13	1, 27	0.30
Letter fluency	2.43	1, 27	0.13	0.34	1, 27	0.57	8.42	1, 27	0.007
Symbol coding	0.73	1, 27	0.40	0.97	1, 27	0.33	0.73	1, 27	0.40
Tower of London	0.51	1, 27	0.48	0.71	1, 27	0.41	0.38	1, 27	0.54

ANCOVA, analysis of covariance; BACS-J, Brief Assessment of Cognition in Schizophrenia—Japanese language version.
[a]Baseline symbol coding task data were used as covariates.

Table 5. Change in scores of secondary measures from baseline to endpoint in first-episode schizophrenia group

	Baseline ($n=20$)	Endpoint ($n=20$)	Statistics		
	Score	Change	*t*	d.f.	*p*
PANSS[a]					
Positive score	23.8 (3.9)	−10.0 (0.5)	7.48	19	<0.001
Negative score	29.5 (6.4)	−9.0 (0.2)	6.06	19	<0.001
General psychopathology score	56.9 (8.1)	−18.0 (0.6)	8.00	19	<0.001
Total score	109.7 (16.0)	−36.6 (2.1)	7.77	19	<0.001
SQLS-J[a]					
Psychosocial conditions score	70.0 (16.5)	−21.4 (7.2)	4.18	19	0.001
Motivation/energy score	65.4 (15.7)	−11.4 (2.0)	3.09	19	0.006
Symptoms/side effects score	41.6 (16.1)	−11.6 (3.3)	2.94	19	0.008
CGI-S[a]	4.3 (0.8)	−1.6 (0.0)	10.1	19	<0.001
DIEPSS[a]	0.0 (0.0)	1.85 (2.5)	−3.29	19	0.004

CGI-S, Clinical Global Impression—Severity scale; DIEPSS, Drug-induced Extrapyramidal Symptoms Scale; PANSS, Positive and Negative Syndrome Scale; SQLS-J, Schizophrenia Quality of Life Scale—Japanese language version.
[a]Values are mean (SD).

Table 6. Change in scores of PANSS from baseline to endpoint in control group

	Baseline ($n=10$)	Endpoint ($n=10$)	Statistics		
	Score	Change	*t*	d.f.	*p*
PANSS[a]					
Positive score	15.4 (3.7)	2.3 (2.6)	−1.19	9	0.263
Negative score	18.2 (5.7)	1.2 (0.1)	−1.53	9	0.161
General psychopathology score	37.3 (10.5)	−2.5 (6.4)	0.65	9	0.535
Total score	70.9 (18.0)	3.8 (5.2)	−0.98	9	0.354

PANSS, Positive and Negative Syndrome Scale.
[a]Values are mean (SD).

significant correlations between changes in the PANSS total and subscale scores and the SQLS-J scores (all $p > 0.05$).

DISCUSSION

To the best of our knowledge, this is the first study that examined the effects of blonanserin on cognitive function in patients with first-episode schizophrenia, with a control group that was also included and retested to examine potential retest effects. There were three main findings in this study. First, treatment with blonanserin was associated with improvement in letter fluency in this group of patients, as revealed by comparison with age-matched and sex-matched chronic patients. Second, clinical symptoms and subjective QOL were significantly improved after 8 weeks of treatment with blonanserin in first-episode schizophrenia. Third,

improvement in letter fluency with blonanserin treatment was positively correlated with improvement in some domains of subjective QOL.

In this study, we used patients with first-episode schizophrenia who were antipsychotic-naïve before initial assessments. It was thus possible to delineate the profile of cognitive deficits early in the disease process and assess the direct impact of medication. Our sample appears to be representative of first-episode schizophrenia patients as it is similar to other first-episode studies in terms of severity of psychopathology scores and profile of cognitive impairments (Hill *et al.*, 2009; Mesholam-Gately *et al.*, 2009).

Effect of blonanserin on cognitive function

In this study, blonanserin improved letter fluency exclusively in the first-episode patients. Although group-by-time interaction was not significant for executive function, as represented by the Tower of London task, a modest effect size (0.62) was observed only for the first-episode subjects, but not the chronic group (0.10).

Previous studies have suggested that performance on letter fluency task is associated with functional activation in the left prefrontal cortex and the left inferior parietal cortex (Gourovitch *et al.*, 2000; Bokat and Goldberg, 2003; Kubota *et al.*, 2005). In addition, several brain imaging studies have reported activation of the prefrontal cortex, particularly the dorsolateral part during the Tower of London task (Morris *et al.*, 1993; Baker *et al.*, 1996; Owen *et al.*, 1996; Dagher *et al.*, 1999; Lazeron *et al.*, 2000). Taken together, blonanserin may improve letter fluency and executive function, which are probably associated with functional activation in the prefrontal cortex in patients with first-episode schizophrenia. This is consistent with a rodent study reporting the ability of blonanserin to enhance dopamine and norepinephrine release in the prefrontal cortex (Ohoyama *et al.*, 2011). In this context, the lack of a beneficial effect on working memory, as has also been observed with clozapine (Hagger *et al.*, 1993), may be due to an inadequate intensity of dopamine surge. Further studies on blonanserin treatment using functional brain imaging may be worthwhile in the future.

The present findings with regard to cognitive domains improved by blonanserin treatment are different from those reported in our previous study in which blonanserin improved verbal memory, attention, and processing speed in patients with chronic schizophrenia (Miyake *et al.*, 2008). These discrepancies may be due to several factors. First, subjects in the two studies differ in terms of baseline demographic and clinical characteristics such as age, illness chronicity, subtype of schizophrenia, and prior exposure to antipsychotic and/or anticholinergic medications (Miyake *et al.*, 2008). Second, there is a difference in the mean dosages of anticholinergics between the two patient groups. In the previous study, the mean doses of anticholinergics (biperiden-equivalent dose) at baseline and endpoint were 2.9 and 1.4 mg/day, respectively. In the current study, anticholinergic medications were used at a minimum. We have recently reported that discontinuation of long-term biperiden use significantly improved attention and processing speed, as measured by BACS-J, in patients with chronic schizophrenia treated with an SGA (Ogino *et al.*, 2011). Thus, the improvements in attention and processing speed observed in our previous study could be, at least in part, attributed to the reduction of concomitant anticholinergics. Third, we used different doses of blonanserin and cognitive batteries between the two studies. In our previous study, the mean doses of blonanserin at baseline and endpoint were 17.4 and 18.0 mg/day, respectively. We speculate that these methodological differences might have affected the results.

To assess retest effects, we included age-matched patients with chronic schizophrenia treated with blonanserin alone as a reference group. By contrast, several recent studies of SGAs on individuals in their first episode of schizophrenia included healthy comparison groups in which patients and healthy individuals were tested serially over equivalent intervals (Fagerlund *et al.*, 2004; Goldberg *et al.*, 2007; Crespo-Facorro *et al.*, 2009; Andersen *et al.*, 2011). Results of these studies suggest that the effects of practice can notably contribute to cognitive score improvements after treatment with SGAs. Recent data collected from a large clinical trial also show that practice effects are not restricted to a first-episode sample but can be observed in middle-aged chronic multi-episode patients (Keefe *et al.*, 2008; Goldberg *et al.*, 2010). In the present study, chronic patient controls did not show cognitive enhancement in any of the BACS-J subtests, suggesting that retest effects (likely practice effects) were absent in this sample. Although repeated measures ANCOVAs suggest that the observed cognitive score changes in letter fluency score in the first-episode group may likely reflect improvement rather than a retest effect, we cannot exclude the possibility that motivation and expectancy of the subjects confounded the results (Velligan *et al.*, 2006; Goldberg *et al.*, 2010). Although we used chronic patients as a control group, the poor changes in cognitive performance by chronic patients relative to first-episode patients might be due to more pronounced illness-related learning deficits or higher

dosing of blonanserin and anticholinergics. Future studies with a longer duration of blonanserin treatment and the inclusion of healthy controls as a comparator group are warranted to further reduce the possibility of practice effect.

The treatment interval in this study was 8 weeks, which is shorter than that used in other trials of SGAs in first-episode patients (Fagerlund *et al.*, 2004; Goldberg *et al.*, 2007; Crespo-Facorro *et al.*, 2009; Andersen *et al.*, 2011). It is possible that the ability of blonanserin to enhance cognitive functioning may have been greater if patients had been re-examined after a longer interval. However, Keefe *et al.* (2007b) suggested that most of the cognitive benefits of SGAs occur in the early phases (6–10 weeks) of treatment and that further benefits over longer periods may be small. Consistent with this notion, we found significant improvements only on the letter fluency task after 6-month treatment with blonanserin in first-episode schizophrenia patients (Miyamoto *et al.*, unpublished results).

Effect of blonanserin on clinical outcomes and subjective quality of life

In the present study, 8-week treatment with blonanserin significantly improved both positive and negative symptoms as well as subjective QOL. The significant effect on psychopathology in first-episode schizophrenia was in line with previous studies in patients with chronic schizophrenia (Murasaki, 2007a, 2007b; Kinoshita, 2008; Miura, 2008; Miyake *et al.*, 2008; Osada *et al.*, 2009; Yang *et al.*, 2010). Although changes in psychopathology and cognitive function were not significantly correlated, improvement in letter fluency showed a significant correlation with improvement on the SQLS-J motivation/energy score. It has been reported that execution of letter fluency is associated with negative symptoms in schizophrenia (Liddle and Morris, 1991; Allen *et al.*, 1993; Mahurin *et al.*, 1998; Howanitz *et al.*, 2000). In addition, some studies have suggested that negative symptoms, such as letter fluency performance, are related to prefrontal cortical activity (Howanitz *et al.*, 2000). The prefrontal cortex has been shown to be an area of dysfunction in never-medicated patients with first-episode schizophrenia (MacDonald *et al.*, 2005; Snitz *et al.*, 2005; van Veelen *et al.*, 2010). Although we could not find a significant relationship between change in letter fluency or executive function and negative symptoms, further studies are required to clarify the influence of blonanserin on the function of prefrontal cortex as well as social and vocational functions.

Effective dosage and safety of blonanserin in first-episode schizophrenia

In this study, the mean (±SD) daily dose of blonanserin at endpoint was 7.2 (±4.0) mg/day for first-episode patients, which was lower than usual doses. In fact, in three non-comparative, long-term trials of blonanserin in patients with chronic schizophrenia conducted in Japan, the average dose of blonanserin was approximately 13 mg/day (Murasaki, 2007b; Kinoshita, 2008; Osada *et al.*, 2009). It has been suggested that patients with first-episode schizophrenia are more responsive and sensitive to treatment with an antipsychotic drug in terms of efficacy and side effects than patients with chronic schizophrenia (McEvoy *et al.*, 1991; Salimi *et al.*, 2009). Thus, the average dose of antipsychotics in first-episode patients is usually lower than that used with multi-episode patients (Robinson, 2010). Supporting this notion, we observed relatively lower doses of blonanserin in first-episode patients than in patients with chronic schizophrenia (see Results section).

In this study, EPS were observed in 55.0% of first-episode patients, and 25.0% of these patients required anticholinergic drugs. However, the mean dose of anticholinergics at endpoint was very low, and no severe adverse effects were observed during the study. Data on the safety of blonanserin in our sample will be described in detail in another report (Miyamoto *et al.*, unpublished results).

Limitations

There are several limitations in the current study. First, the sample size was small, making the results of this study vulnerable to type I and type II errors. Also, we did not include subjects with severe agitation, suicidal ideation, or substance dependence. Moreover, most subjects had the paranoid type of schizophrenia. It is thus unclear whether the present results are potentially generalizable to patients with first-episode schizophrenia in real-world settings. Our results will require replication in a larger cohort and over a longer term.

Second, as already mentioned, it was difficult to distinguish practice effects from placebo effects in the present study, although inclusion of a placebo-treated group was not viable for ethical reasons (Andersen *et al.*, 2011). Moreover, this study was underpowered to detect a practice effect on cognitive functioning because of the small sample size of the control group. The inclusion of a comparator antipsychotic in a double-blind fashion could have strengthened the conclusions to be drawn.

Despite these limitations, this study provides the first evidence for the ability of blonanserin to improve

cognitive function, psychopathology, and subjective QOL in first-episode schizophrenia. It has been reported that much of the deterioration (e.g., advancement of negative symptoms) associated with schizophrenia may occur during 2 to 3 years after the onset of illness (Birchwood *et al.*, 1998). Thus, treating patients with an antipsychotic with superior efficacy across a broad range of symptoms in the early stage is expected to improve long-term outcome (Miyamoto *et al.*, 2008; Robinson, 2010). In view of the results obtained in this study, blonanserin may be a promising candidate for a first-line antipsychotic for patients with first-episode schizophrenia.

CONCLUSION

Blonanserin may improve some types of cognitive function associated with the frontal lobe activity in patients with first-episode schizophrenia. Moreover, blonanserin may have beneficial effects on psychiatric symptoms and subjective QOL. Further studies with a larger sample size and longer duration of treatment are needed to confirm our observations.

CONFLICTS OF INTEREST

Dr Miyamoto has served as a consultant for Dainippon Sumitomo Pharmaceutical. He has received advisory board honoraria from Chugai Pharmaceutical. No other authors have any conflicts of interest with any commercial or other associations in connection with the submitted manuscript.

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REFERENCES

Allen HA, Liddle PF, Frith CD. 1993. Negative features, retrieval processes and verbal fluency in schizophrenia. *Br J Psychiatry* **163**: 769–775.

American Psychiatric Association. 2000. *Diagnostic Criteria from DSM-IV-TR*. American Psychiatric Association: Washington, DC.

Andersen R, Fagerlund B, Rasmussen H, *et al.* 2011. Cognitive effects of six months of treatment with quetiapine in antipsychotic-naive first-episode schizophrenia. *Psychiatry Res* **187**: 49–54.

Baker SC, Rogers RD, Owen AM, *et al.* 1996. Neural systems engaged by planning: a PET study of the Tower of London task. *Neuropsychologia* **34**: 515–526.

Bilder RM, Goldman RS, Robinson D, *et al.* 2000. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry* **157**: 549–559.

Birchwood M, Todd P, Jackson C. 1998. Early intervention in psychosis. The critical period hypothesis. *Br J Psychiatry Suppl* **172**: 53–59.

Bokat CE, Goldberg TE. 2003. Letter and category fluency in schizophrenic patients: a meta-analysis. *Schizophr Res* **64**: 73–78.

Bozikas VP, Andreou C. 2011. Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. *Aust N Z J Psychiatry* **45**: 93–108.

Carpenter WT, Gold JM. 2002. Another view of therapy for cognition in schizophrenia. *Biol Psychiatry* **51**: 969–971.

Crespo-Facorro B, Rodriguez-Sanchez JM, Perez-Iglesias R, *et al.* 2009. Neurocognitive effectiveness of haloperidol, risperidone, and olanzapine in first-episode psychosis: a randomized, controlled 1-year follow-up comparison. *J Clin Psychiatry* **70**: 717–729.

Dagher A, Owen AM, Boecker H, *et al.* 1999. Mapping the network for planning: a correlational PET activation study with the Tower of London task. *Brain* **122**(Pt 10): 1973–1987.

Davidson M, Galderisi S, Weiser M, *et al.* 2009. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). *Am J Psychiatry* **166**: 675–682.

Deeks ED, Keating GM. 2010. Blonanserin: a review of its use in the management of schizophrenia. *CNS Drugs* **24**: 65–84.

Fagerlund B, Mackeprang T, Gade A, *et al.* 2004. Effects of low-dose risperidone and low-dose zuclopenthixol on cognitive functions in first-episode drug-naive schizophrenic patients. *CNS Spectr* **9**: 364–374.

Gold JM, Harvey PD. 1993. Cognitive deficits in schizophrenia. *Psychiatr Clin North Am* **16**: 295–312.

Goldberg TE, Goldman RS, Burdick KE, *et al.* 2007. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry* **64**: 1115–1122.

Goldberg TE, Keefe RS, Goldman RS, *et al.* 2010. Circumstances under which practice does not make perfect: a review of the practice effect literature in schizophrenia and its relevance to clinical treatment studies. *Neuropsychopharmacology* **35**: 1053–1062.

Gourovitch ML, Kirkby BS, Goldberg TE, *et al.* 2000. A comparison of rCBF patterns during letter and semantic fluency. *Neuropsychology* **14**: 353–360.

Green MF. 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* **153**: 321–330.

Green MF, Kern RS, Braff DL, *et al.* 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull* **26**: 119–136.

Guy W. 1976. *Clinical Global Impression*. US Department of Health and Human Services Publication (ADM): Rockville, MD.

Hagger C, Buckley P, Kenny JT, *et al.* 1993. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biol Psychiatry* **34**: 702–712.

Harvey PD, Keefe RS. 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry* **158**: 176–184.

Hill SK, Bishop JR, Palumbo D, *et al.* 2010. Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert Rev Neurother* **10**: 43–57.

Hill SK, Reilly JL, Harris MS, *et al.* 2009. A comparison of neuropsychological dysfunction in first-episode psychosis patients with unipolar depression, bipolar disorder, and schizophrenia. *Schizophr Res* **113**: 167–175.

Howanitz E, Cicalese C, Harvey PD. 2000. Verbal fluency and psychiatric symptoms in geriatric schizophrenia. *Schizophr Res* **42**: 167–169.

Inada T. 1996. Evaluation and diagnosis of drug-induced extrapyramidal symptoms: commentary on the DIEPSS and guide to its usage. Yagi G (ed.). Seiwa shoten: Tokyo.

Kaneda Y, Imakura A, Fujii A, *et al.* 2002. Schizophrenia Quality of Life Scale: validation of the Japanese version. *Psychiatry Res* **113**: 107–113.

Kaneda Y, Sumiyoshi T, Keefe R, *et al.* 2007. Brief assessment of cognition in schizophrenia: validation of the Japanese version. *Psychiatry Clin Neurosci* **61**: 602–609.

Kaneda Y, Sumiyoshi T, Nakagome K, *et al.* 2008. The brief assessment of cognition in schizophrenia Japanese version (BACS-J). *Seishin Igaku (Clinical Psychiatry)* **50**: 913–917.

Kay SR, Fiszbein A, Opler LA. 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* **13**: 261–276.

Keefe RS, Bilder RM, Davis SM, *et al.* 2007a. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry* **64**: 633–647.

Keefe RS, Malhotra AK, Meltzer HY, *et al.* 2008. Efficacy and safety of donepezil in patients with schizophrenia or schizoaffective disorder: significant placebo/practice effects in a 12-week, randomized, double-blind, placebo-controlled trial. *Neuropsychopharmacology* **33**: 1217–1228.

Keefe RS, Seidman LJ, Christensen BK, *et al.* 2004. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. *Am J Psychiatry* **161**: 985–995.

Keefe RSE, Silva SG, Perkins DO, *et al.* 1999. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr Bull* **25**: 201–222.

Keefe RS, Sweeney JA, Gu H, *et al.* 2007b. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry* **164**: 1061–1071.

Kinoshita T. 2008. Long-term clinical study of blonanserin for schizophrenia: a multicenter open study to determine safety and effectiveness in schizophrenic patients (Japan-wide study). *Jpn J Clin Psychopharmacol* **11**: 135–153.

Kubota Y, Toichi M, Shimizu M, *et al.* 2005. Prefrontal activation during verbal fluency tests in schizophrenia—a near-infrared spectroscopy (NIRS) study. *Schizophr Res* **77**: 65–73.

Larsen TK, McGlashan TH, Moe LC. 1996. First-episode schizophrenia: I. Early course parameters. *Schizophr Bull* **22**: 241–256.

Lazeron RH, Rombouts SA, Machielsen WC, *et al.* 2000. Visualizing brain activation during planning: the tower of London test adapted for functional MR imaging. *AJNR Am J Neuroradiol* **21**: 1407–1414.

Liddle PF, Morris DL. 1991. Schizophrenic syndromes and frontal lobe performance. *Br J Psychiatry* **158**: 340–345.

MacDonald AW, 3rd, Carter CS, Kerns JG, *et al.* 2005. Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. *Am J Psychiatry* **162**: 475–484.

Mahurin RK, Velligan DI, Miller AL. 1998. Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. *Psychiatry Res* **79**: 139–149.

Matsui M, Sumiyoshi T, Arai H, *et al.* 2008. Cognitive functioning related to quality of life in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **32**: 280–287.

McEvoy JP, Hogarty GE, Steingard S. 1991. Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry* **48**: 739–745.

McEvoy JP, Lieberman JA, Perkins DO, *et al.* 2007. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry* **164**: 1050–1060.

Meltzer HY, Thompson PA, Lee MA, *et al.* 1996. Neuropsychologic deficits in schizophrenia: relation to social function and effect of antipsychotic drug treatment. *Neuropsychopharmacology* **14**: 27S-33S.

Mesholam-Gately RI, Giuliano AJ, Goff KP, *et al.* 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. *Neuropsychology* **23**: 315–336.

Mishara AL, Goldberg TE. 2004. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biol Psychiatry* **55**: 1013–1022.

Miura S. 2008. Clinical evaluation of blonanserin for schizophrenia: a randomized controlled study comparing blonanserin with risperidone. *Jpn J Clin Psychopharmacol* **11**: 297–314.

Miyake N, Miyamoto S, Takeuchi A, *et al.* 2008. Effect of new-generation antipsychotic blonanserin on cognitive impairment in schizophrenia: A randomized double-blind comparison with risperidone. *Jpn J Clin Psychopharmacol* **11**: 1329–1336.

Miyamoto S, Fleischhacker WW, Lieberman JA. in press. Pharmacologic treatment of schizophrenia. In *Comprehensive Care of Schizophrenia*, 2nd edn, Murray R, Lieberman JA (eds). Oxford University Press: New York.

Miyamoto S, Merrill DB, Lieberman JA, *et al.* 2008. Antipsychotic drugs. In *Psychiatry*, 3rd edn, Tasman A, Kay J, Lieberman JA, *et al.* (eds). John Wiley & Sons: Chichester; 2161–2201.

Morris RG, Ahmed S, Syed GM, *et al.* 1993. Neural correlates of planning ability: frontal lobe activation during the Tower of London test. *Neuropsychologia* **31**: 1367–1378.

Murasaki M. 2007a. Clinical evaluation of blonanserin for schizophrenia: a randomized controlled study comparing blonanserin with haloperidol. *Jpn J Clin Psychopharmacol* **10**: 2059–2079.

Murasaki M. 2007b. Long-term clinical study of blonanserin for schizophrenia: a multicenter open study to determine safety and effectiveness in schizophrenic patients (Kanagawa Region Clinical Psychopharmacology Study Group). *Jpn J Clin Psychopharmacol* **10**: 2241–2257.

Noda Y, Kurumiya S, Miura Y, *et al.* 1993. Comparative study of 2-(4-ethyl-1-piperazinyl)-4-(fluorophenyl)-5,6,7,8,9, 10-hexahydrocycloocta [b]pyridine (AD-5423) and haloperidol for their pharmacological activities related to antipsychotic efficacy and/or adverse side-effects. *J Pharmacol Exp Ther* **265**: 745–751.

Ogino S, Miyamoto S, Tenjin T, *et al.* 2011. Effects of discontinuation of long-term biperiden use on cognitive function and quality of life in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **35**: 78–83.

Ohoyama K, Yamamura S, Hamaguchi T, *et al.* 2011. Effect of novel atypical antipsychotic, blonanserin, on extracellular neurotransmitter level in rat prefrontal cortex. *Eur J Pharmacol* **653**: 47–57.

Oka M, Noda Y, Ochi Y, *et al.* 1993. Pharmacological profile of AD-5423, a novel antipsychotic with both potent dopamine-D2 and serotonin-S2 antagonist properties. *J Pharmacol Exp Ther* **264**: 158–165.

Osada K, Miyamoto S, Maruta S, *et al.* 2009. Long-term clinical study of blonanserin for schizophrenia: a multicenter open study to assess the safety and efficacy in patients with schizophrenia (continuation of two long-term studies by request from patients). *Jpn J Clin Psychopharmacol* **12**: 2337–2351.

Owen AM, Doyon J, Petrides M, *et al.* 1996. Planning and spatial working memory: a positron emission tomography study in humans. *Eur J Neurosci* **8**: 353–364.

Perkins DO, Gu H, Weiden PJ, *et al.* 2008. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. *J Clin Psychiatry* **69**: 106–113.

Robinson D. 2010. First-episode schizophrenia. *CNS Spectr* **15**: 4–7.

Salimi K, Jarskog LF, Lieberman JA. 2009. Antipsychotic drugs for first-episode schizophrenia: a comparative review. *CNS Drugs* **23**: 837–855.

Saykin AJ, Shtasel DL, Gur RE, *et al.* 1994. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry* **51**: 124–131.

Snitz BE, MacDonald A, 3rd, Cohen JD, *et al.* 2005. Lateral and medial hypofrontality in first-episode schizophrenia: functional activity in a medication-naive state and effects of short-term atypical antipsychotic treatment. *Am J Psychiatry* **162**: 2322–2329.

Sumiyoshi T, Bubenikova-Valesova V, Horacek J, *et al.* 2008. Serotonin1A receptors in the pathophysiology of schizophrenia: development of novel cognition-enhancing therapeutics. *Adv Ther* **25**: 1037–1056.

Tomida K, Takahashi N, Saito S, *et al.* 2010. Relationship of psychopathological symptoms and cognitive function to subjective quality of life in patients with chronic schizophrenia. *Psychiatry Clin Neurosci* **64**: 62–69.

van Veelen NM, Vink M, Ramsey NF, *et al.* 2010. Left dorsolateral prefrontal cortex dysfunction in medication-naive schizophrenia. *Schizophr Res* **123**: 22–29.

Velligan DI, Kern RS, Gold JM. 2006. Cognitive rehabilitation for schizophrenia and the putative role of motivation and expectancies. *Schizophr Bull* **32**: 474–485.

Wilkinson G, Hesdon B, Wild D, *et al.* 2000. Self-report quality of life measure for people with schizophrenia: the SQLS. *Br J Psychiatry* **177**: 42–46.

Wolwer W, Brinkmeyer J, Riesbeck M, *et al.* 2008. Neuropsychological impairments predict the clinical course in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* **258**(Suppl 5): 28–34.

Woon PS, Chia MY, Chan WY, *et al.* 2010. Neurocognitive, clinical and functional correlates of subjective quality of life in Asian outpatients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **34**: 463–468.

Yang J, Bahk WM, Cho HS, *et al.* 2010. Efficacy and tolerability of blonanserin in the patients with schizophrenia: a randomized, double-blind, risperidone-compared trial. *Clin Neuropharmacol* **33**: 169–175.

Chapter Number

Serotonin-1A Receptors and Cognitive Enhancement in Schizophrenia: Role for Brain Energy Metabolism

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1. Introduction

Disturbances of cognitive function, evaluated by psychological and neurophysiological methods, have been shown to predict outcome in patients with schizophrenia (Green et al. 2000, Javitt et al. 2008, Sumiyoshi T. et al. 2011). In view of the paucity of treatment options to improve cognition for these patients, efforts to identify novel strategies are needed.

The prefrontal cortex (PFC) has been considered to regulate various aspects of cognitive abilities, e.g. working memory, memory organization, executive function, and attention (Sumiyoshi T. et al. 2011). Atypical antipsychotic drugs (AAPDs), eliciting cognitive benefits to some extent, enhance dopamine (DA) release in the medial PFC (mPFC), as demonstrated by in vivo microdialysis (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005, Ichikawa et al. 2001). The ability of AAPDs to enhance DA in mPFC has been found to depend on serotonin (5-HT)-5-HT_{1A} receptors, irrespective of direct in vitro affinity, based on observations from mutant mice lacking these receptors (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005). This is consistent with behavioral observations that 5-HT_{1A} partial agonists (e.g. tandospirone) and AAPDs with agonist actions on 5-HT_{1A} receptors (e.g. perospirone, aripiprazole, ziprasidone, lurasidone) ameliorate memory deficits in rodent models of schizophrenia (Hagiwara et al. 2008, Horiguchi et al. 2011, Meltzer et al. 2011, Nagai et al. 2009). Findings from electrophysiological studies suggest these cognitive benefits of 5-HT_{1A} agonism are mediated by Glu and GABA neurons (Higuchi et al. 2010, Llado-Pelfort et al. 2011).

In this chapter, the authors discuss the role for the key 5-HT receptor subtypes, i.e., 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, and 5-HT_7 receptors, in cognitive function in schizophrenia. Specifically, we will focus on several psychotropic/antipsychotic compounds stimulating 5-HT_{1A} receptors, considered as one of the most promising candidates for cognitive enhancers (Meltzer et al. 2011, Newman-Tancredi and Kleven 2011, Newman-Tancredi and Albert in press). A hypothesis is presented on the relationship between cognition and lactate that provides an important energy substrate and reflects neural activity in the brain.

2. Neurocognitive deficits of schizophrenia

Schizophrenia has been characterized by positive symptoms (delusions, hallucinations and thought disorder) and negative symptoms (psychomotor retardation, affective flattening, social withdrawal, and alogia). Patients with the illness also exhibit a wide range of disturbances of cognitive function, e.g. several types of memory, executive function (e.g. planning, monitoring, inhibition), vigilance, motor speed, and verbal fluency, with more than 1SD below the average of normal controls (Harvey and Keefe 1997).

Generally, they are considered to be independent of the psychotic symptoms. The cognitive deficits of schizophrenia have been investigated extensively as a determinant of functional outcome (Addington and Addington 2000, Green 1996, Green et al. 2000).

Several instruments to comprehensively assess cognitive function in schizophrenia have been developed. In particular, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Nuechterlein et al. 2008) (Fig 1) and the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al. 2004) (Fig 2) are regarded to be qualified as international-standard neuropsychological tools in this respect. The authors have developed the Japanese versions of these cognitive test batteries (Kaneda et al. 2007, Sato et al. 2010), and have confirmed their sensitivity and validity to detect cognitive deficits in patients (Fig 3).

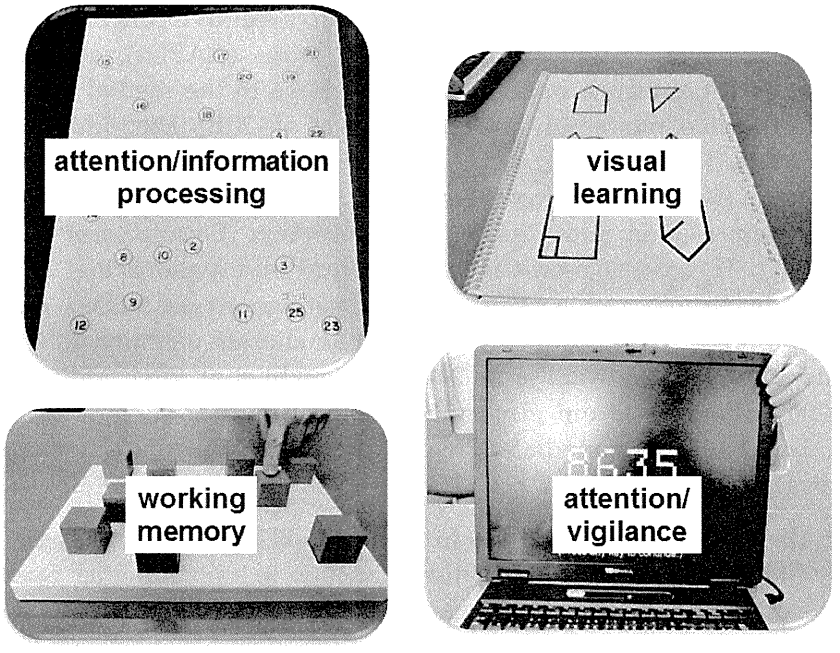

Fig. 1. Examples of tests from the MATRICS Consensus Cognitive Battery

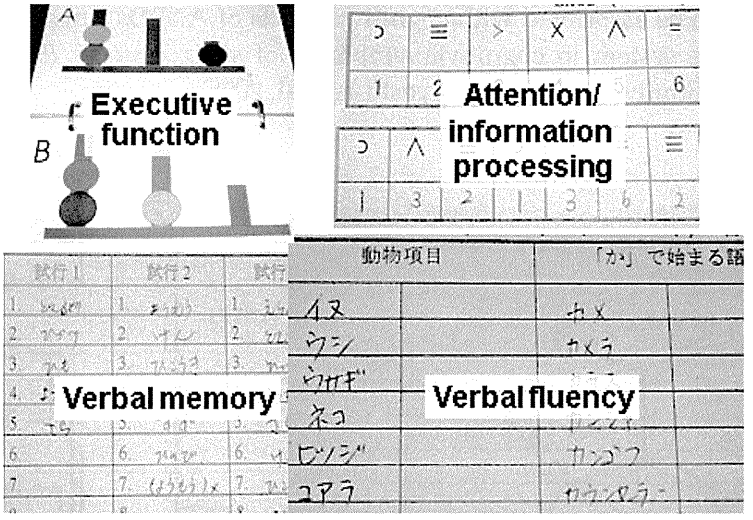

Fig. 2. Examples of tests from the Brief Assessment of Cognition in Schizophrenia

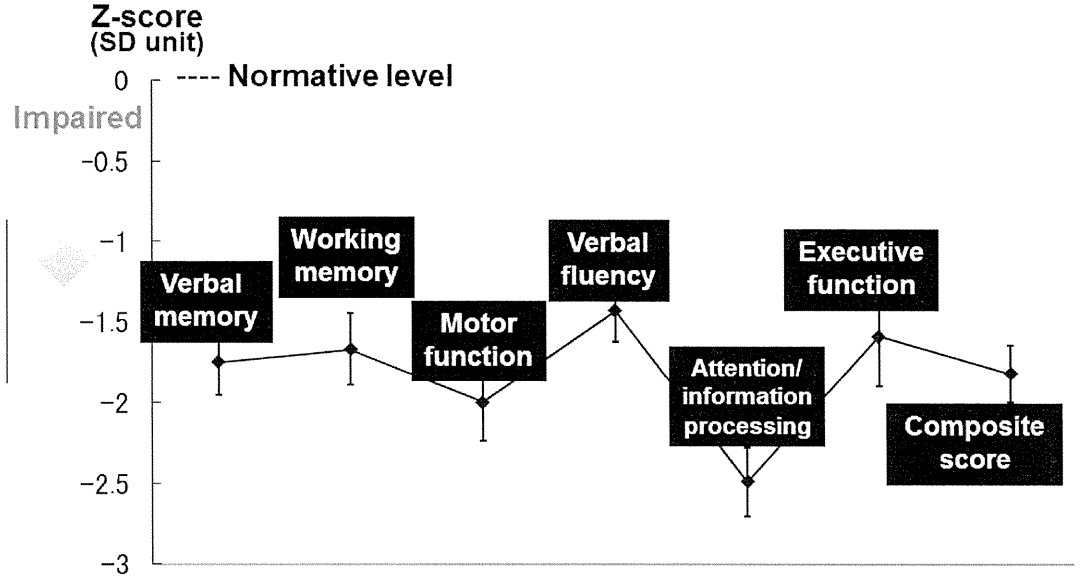

Fig. 3. Impaired cognitive function in schizophrenia as evaluated by the Brief Assessment of Cognition in Schizophrenia -Japanese Version (Kaneda et al. 2007)

3. 5-HT receptors and cognitive function

The role for several subtypes of 5-HT receptors in cognitive function has attracted interest, based, partly, on the distinct pharmacological properties of AAPDs, such as clozapine, risperidone, and olanzapine. For example, the ability of these agents to enhance DA and acetylcholine release in the mPFC, demonstrated by in vivo microdialysis, has been reported (Bortolozzi et al. 2010, Diaz-Mataix et al. 2005, Ichikawa et al. 2002, Ichikawa et al. 2001). Among the subtypes of 5-HT receptors (Fig. 4), 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, and 5-HT_7 receptors

have been shown to be associated with cognitive effects of AAPDs, suggesting pivotal roles for the serotonergic system in cognitive symptoms of schizophrenia (Sumiyoshi T. et al. 2007a, Meltzer and Sumiyoshi 2008, Sumiyoshi T. et al. 2008).

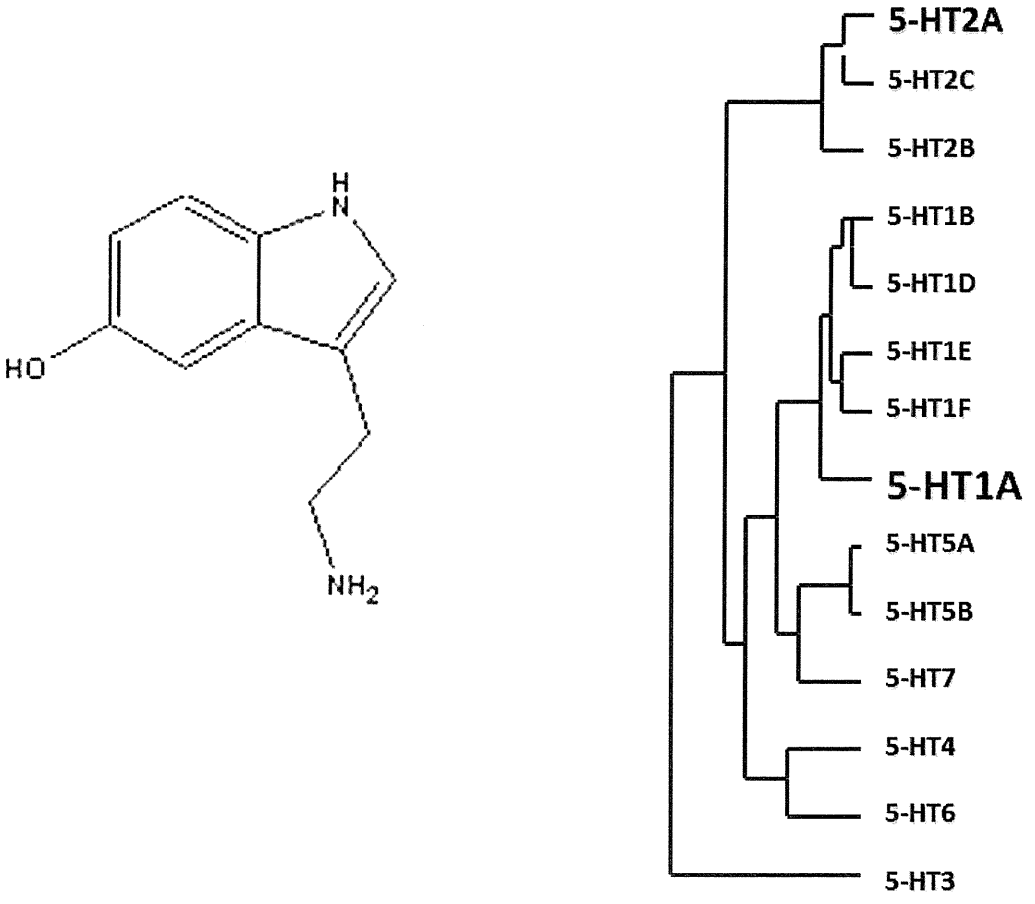

Fig. 4. Chemical structure of serotonin (5-HT) and its receptor subtypes

Table 1. summarizes the mode of actions (agonism or antagonism) and specific compounds related to the above-mentioned 5-HT receptor subtypes. Among them, 5-HT_{1A} receptor stimulation is currently considered as the most promising approach (Llado-Pelfort et al. 2011, Newman-Tancredi and Kleven 2011, Newman-Tancredi and Albert in press, Sumiyoshi C. et al. 2006, Sumiyoshi T. et al. 2008, Sumiyoshi T. et al. 2007a, Sumiyoshi T. et al. 2000, Sumiyoshi T. et al. 2007b, Sumiyoshi T. et al. 2001a, Sumiyoshi T. et al. 2001b, Sumiyoshi T. et al. 2009), as discussed in the next section. This is followed by 5-HT_{2A} antagonism, as elicited by certain (although not satisfactory) efficacy of a series of AAPDs whose principal pharmacologic feature is blockade of 5-HT_{2A} receptors (Meltzer et al. 1989, Meltzer et al. 2011, Meltzer and Massey 2011, Stockmeier et al. 1993, Sumiyoshi T. et al. 1995). Recent evidence from animal models of schizophrenia suggests the advantage of agonists at 5-HT_6 or 5-HT_7 receptors for ameliorating memory impairment, as revealed by behavioral experiments using antagonist at the N-methyl-D-aspartate (NMDA) type of Glu receptors (Horiguchi et al. 2011, Meltzer et al. 2011, Meltzer and Massey 2011).