Table 2. Variables significantly associated with the log of the risperidone:9-hydroxyrisperidone concentration ratio (R:9-OHR) and the concentration:dose ratio (C:D) ($n = 73$)

Predicting variables for R:9-OHR ratio	Regression coefficient	95% Confidence interval	*p*-value
Homozygosity of CYP2D6*10	0.761	(0.110, 1.412)	0.023
Intake of CYP2D6-dependent drugs	2.043	(1.639, 2.447)	<0.001
Predicting variables for C:D ratio	**Regression coefficient**	**95% Confidence interval**	***p*-value**
Homozygosity of CYP2D6*10	0.371	(0.012, 0.729)	0.043
Intake of CYP2D6-dependent drugs	0.297	(0.071, 0.522)	0.011
Age	0.019	(0.007, 0.031)	0.002
Weight	−0.011	(−0.020, −0.002)	0.015

A total of 73 patients were included in these regression models. Natural logarithmic transformations of the R:9-OHR and C:D ratio were used as dependent variables. Biologically plausible predictors (CYP2D6 genotype, presence of co-medication with CYP2D6-dependent drugs, age, weight, and sex) were used as independent variables. The stepwise method was performed for variable selection. The presence of more predictors increases the value of the regression coefficient, thus implying a greater effect upon the R:9-OHR and C:D. The CYP2D6-dependent drugs are levomepromazine, chlorpromazine, bromperidol, haloperidol, olanzapine, paroxetine, fluvoxamine, amitriptyline, maprotiline, terbinafine, cimetidine, and mexiletine.

influence of the CYP2D6*10 alleles was more prominent in the co-medication group than in the non-co-medication group (Figure 1b). Based on the results of a previous report, which demonstrated that the efficacy of 9-hydroxyrisperidone might be comparable to that of risperidone (Huang *et al.*, 1993), we inferred that the same dose of risperidone would have a stronger pharmacologic effect in individuals with a higher number of *10 alleles. Our study shows that co-administration of risperidone and other CYP2D6-dependent drugs leads to a significant effect that warrants consideration in clinical practice. Since CYP2D6 metabolizes a wide variety of drugs, competitive inhibition of CYP2D6 with risperidone is relatively common (Murray, 2006). Our findings should be widely relevant in clinical settings, for about half of the populations of some ethnic groups including East Asians have one or more CYP2D6*10 alleles. Here, we wish to state that the above interpretation is based on the assumption that the efficacy of risperidone and 9-hydroxyrisperidone is equivalent *in vivo*. However, at least one previous report has suggested that plasma risperidone and 9-hydroxyrisperidone may not be equally potent *in vivo*, since the greater affinity of 9-hydroxyrisperidone for *p*-glycoprotein might limit the access of this metabolite to the brain, compared with that of the mother compound (Wang *et al.*, 2004).

A potential limitation of our study is that only East Asian samples were used. Hence, PMs, who are common among Caucasian populations, were not included in our study samples. Furthermore, we did not evaluate the presence of hypomorphic alleles other than CYP2D6*10 (i.e., *4, *5, *14, *41). Because of the small number of such patients in our study population, either heterozygous or homozygous for those alleles, formal statistical evaluation was not possible. Yet, the potential impact of hypomorphic alleles such as CYP2D6*4 and *5 on the pharmacokinetics of risperidone is much greater than that of CYP2D6*10, 10, since the CYP2D6*4 and *5 alleles represent biologically inactive alleles, whereas *in vitro* analyses have demonstrated that the enzyme transcribed from the CYP2D6*10 alleles retains residual activity (Fukuda *et al.*, 2000; Ramamoorthy *et al.*, 2001; Yu *et al.*, 2002). Indeed, it was recently demonstrated that American homozygotes or compound heterozygotes of CYP2D6 null alleles (*3, *4, *5, *6, and *52) were likely to have an increased C:D ratio with the same comprehensive CYP2D6 genotyping kit (de Leon *et al.*, 2007). In addition, patients who were found to have "wild type alleles" (i.e., *1 and *2) might have actually had hypomorphic alleles that could not be detected using the AmpliChip. The presence of the extremely high C:D ratio in one patient with CYP2D6*1/*2 might be accounted for by the possession of such an "undetected" hypomorphic allele if the abnormal phenotype were to be observed reproducibly using repeated measures. A follow-up study involving larger populations of various ethnic groups is required in order to clarify the pharmacokinetic profiles of carriers of such hypomorphic alleles.

Another limitation of the present study is that neither the dosage nor the quantitative and qualitative natures of inhibition by CYP2D6-dependent drugs was taken into account in the statistical evaluation. Obviously, the degree of inhibition by competitive inhibitors depends on the dosage. The unexpectedly high concentration in the patient with a CYP2D6*1/*2 genotype who was described above might be explained by the concomitant administration of high-dose bromperidol (15 mg; bromperidol is a butyrophenone that is often used in Japan) and chlorpromazine (75 mg). Also of note, some CYP2D6-inhibitors, including paroxetine and fluoxetine, are regarded as mechanism-based inhibitors and

DOI: 10.1002/hup

are more potent than competitive inhibitors (Fontana *et al.*, 2005). For the C:D ratio to be predictable in a given patient based on his CYP2D6 genotype and co-administered CYP2D6-dependent drugs, a mathematical model needs to be developed that incorporates the dose and relative inhibitory activity of all the CYP2D6-dependent drugs being prescribed together with the CYP2D6 genotype. Previously reported variables that could affect risperidone pharmacokinetics include weight, gender, and age (Balant-Gorgia *et al.*, 1999; de Leon *et al.*, 2007). As shown in Table 2, in a model that included weight as a predictive variable, female gender was not found to be significant. However, in a model that did not include weight, female gender was found to be significant (data not shown). Based on these statistical results, we inferred that a female gender increases the risperidone concentration because women tend to weight less than men.

We documented that the genotype at the CYP2D6 locus significantly affects the pharmacokinetics of risperidone. However, we have not evaluated whether the CYP2D6 genotype affects pharmacodynamics of risperidone. According to several reports, higher concentrations might be associated with an increased incidence of adverse reactions. Llerena described a patient with acute severe extrapyramidal side effects that were associated with an extremely high concentration of risperidone when it was taken in conjunction with haloperidol and levomepromazine (Llerena *et al.*, 2003). If indeed patients with higher concentrations tend to develop extrapyramidal side effects, patient with hypomorphic CYP2D6 allele(s), who have increased concentrations of risperidone and 9-hydroxyrisperidone, would be prone to develop such adverse reactions. The retrospective study in which PMs (i.e., null allele homozygotes) receiving risperidone tended to have adverse drug reactions support such hypothesis (de Leon *et al.*, 2005). We need to evaluate whether patients with one or more CYP2D6*10 alleles are more likely to develop adverse reactions than patients with wild type allele.

If one could identify through CYP2D6 genotyping those individuals at risk of developing such adverse reactions, necessary measures could be taken in advance, e.g., adjusting the dose of risperidone. The United States Food and Drug Administration has recently approved AmpliChip CYP450, the comprehensive CYP2D6 genotyping kit used in the present study, for clinical diagnostic use (http://www.fda.gov/cdrh/mda/docs/k042259.html). This approval may contribute to personalized medicine by enabling genotype analysis for clinical use. An algorithm that incorporates clinical parameters including co-medication with CYP2D6-dependent drugs, age and weight together with the patient's CYP2D6 genotype, needs to be developed to predict an appropriate dose for individual patients.

ACKNOWLEDGEMENTS

We appreciate the technical support of S. Shirahama, SRL, INC., Hachioji, Japan and the financial support provided by Roche Diagnostics K.K., Tokyo, Japan.

REFERENCES

Balant-Gorgia AE, Gex-Fabry M, Genet C, Balant LP. 1999. Therapeutic drug monitoring of risperidone using a new, rapid HPLC method: reappraisal of interindividual variability factors. *Ther Drug Monit* **21**: 105–115.

Bertilsson L, Dahl ML, Dalen P, Al-Shurbaji A. 2002. Molecular genetics of CYP2 D6: clinical relevance with focus on psychotropic drugs. *Br J Clin Pharmacol* **53**: 111–122.

Brachtendorf L, Jetter A, Beckurts KT, Holscher AH, Fuhr U. 2002. Cytochrome P450 enzymes contributing to demethylation of maprotiline in man. *Pharmacol Toxicol* **90**: 144–149.

Bradford LD. 2002. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. *Pharmacogenomics* **3**: 229–243.

Castberg I, Helle J, Aamo TO. 2005. Prolonged pharmacokinetic drug interaction between terbinafine and amitriptyline. *Ther Drug Monit* **27**: 680–682.

Cho HY, Lee YB. 2006. Pharmacokinetics and bioequivalence evaluation of risperidone in healthy male subjects with different CYP2D6 genotypes. *Arch Pharm Res* **29**: 525–533.

Chouinard G, Arnott W. 1993. Clinical review of risperidone. *Can J Psychiatry* **38** (Suppl 3): S89–S95.

Dahl ML, Johansson I, Bertilsson L, Ingelman-Sundberg M, Sjoqvist F. 1995. Ultrarapid hydroxylation of debrisoquine in a Swedish population. Analysis of the molecular genetic basis. *J Pharmacol Exp Ther* **274**: 516–520.

D'Arrigo C, Migliardi G, Santoro V, *et al.* Effect of fluvoxamine on plasma risperidone concentrations in patients with schizophrenia. *Pharmacol Res* **52**: 497–501.

de Leon J, Susce MT, Pan RM, Fairchild M, Koch WH, Wedlund PJ. 2005. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. *J Clin Psychiatry* **66**: 15–27.

de Leon J, Susce MT, Pan RM, Wedlund PJ, Orrego ML, Diaz FJ. 2007. A study of genetic (CYP2D6 and ABCB1) and environmental (drug inhibitors and inducers) variables that may influence plasma risperidone levels. *Pharmacopsychiatry* **40**: 93–102.

DeVane CL, Nemeroff CB. 2001. An evaluation of risperidone drug interactions. *J Clin Psychopharmacol* **21**: 408–416.

Ereshefsky L. 1996. Pharmacokinetics and drug interactions: update for new antipsychotics. *J Clin Psychiatry* **57** (Suppl 11): 12–25.

Fang J, Bourin M, Baker GB. 1999. Metabolism of risperidone to 9-hydroxyrisperidone by human cytochromes P450 2D6 and 3A4. *Naunyn Schmiedebergs Arch Pharmacol* **359**: 147–151.

Fontana E, Dansette PM, Poli SM. 2005. Cytochrome P450 enzymes mechanism based inhibitors: common sub-structures and reactivity. *Curr Drug Metab* **6**: 413–454.

Fukuda T, Nishida Y, Imaoka S, *et al.* 2000. The decreased *in vivo* clearance of CYP2D6 substrates by CYP2D6*10 might be caused not only by the low-expression but also by low affinity of CYP2D6. *Arch Biochem Biophys* **380**: 303–308.

Gossen D, de Suray JM, Vandenhende F, Onkelinx C, Gangji D. 2002. Influence of fluoxetine on olanzapine pharmacokinetics. *AAPS PharmSci* **4**: E11.

Hara Y, Nakajima M, Miyamoto KI, Yokoi T. 2005. Inhibitory effects of psychotropic drugs on mexiletine metabolism in human liver microsomes: prediction of *in vivo* drug interactions. *Xenobiotica* 35: 549–560.
Heller T, Kirchheiner J, Armstrong VW, *et al.* 2006. AmpliChip CYP450 GeneChip: a new gene chip that allows rapid and accurate CYP2D6 genotyping. *Ther Drug Monit* 28: 673–677.
Heykants J, Huang ML, Mannens G, *et al.* 1994. The pharmacokinetics of risperidone in humans: a summary. *J Clin Psychiatry* 55 (Suppl): 13–17.
Huang ML, Van Peer A, Woestenborghs R, *et al.* 1993. Pharmacokinetics of the novel antipsychotic agent risperidone and the prolactin response in healthy subjects. *Clin Pharmacol Ther* 54: 257–268.
Iwashima K, Yasui-Furukori N, Kaneda A, *et al.* 2007. No association between CYP2D6 polymorphisms and personality trait in Japanese. *Br J Clin Pharmacol* 64: 96–99.
Janssen PA, Niemegeers CJ, Awouters F, Schellekens KH, Megens AA, Meert TF. 1988. Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S2 and dopamine-D2 antagonistic properties. *J Pharmacol Exp Ther* 244: 685–693.
Johansson I, Oscarson M, Yue QY, Bertilsson L, Sjoqvist F, Ingelman-Sundberg M. 1994. Genetic analysis of the Chinese cytochrome P4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation. *Mol Pharmacol* 46: 452–459.
Leysen JE, Gommeren W, Eens A, de Chaffoy de Courcelles D, Stoof JC, Janssen PA. 1988. Biochemical profile of risperidone, a new antipsychotic. *J Pharmacol Exp Ther* 247: 661–670.
Llerena A, Berecz R, Dorado P, *et al.* 2003. Determination of risperidone and 9-hydroxyrisperidone in human plasma by liquid chromatography: application to the evaluation of CYP2D6 drug interactions. *J Chromatogr B Analyt Technol Biomed Life Sci* 783: 213–219.
Madeira M, Levine M, Chang TK, Mirfazaelian A, Bellward GD. 2004. The effect of cimetidine on dextromethorphan O-demethylase activity of human liver microsomes and recombinant CYP2D6. *Drug Metab Dispos* 32: 460–467.
Mihara K, Kondo T, Yasui-Furukori N, *et al.* 2003. Effects of various CYP2D6 genotypes on the steady-state plasma concentrations of risperidone and its active metabolite, 9-hydroxyrisperidone, in Japanese patients with schizophrenia. *Ther Drug Monit* 25: 287–293.
Murray M. 2006. Role of CYP pharmacogenetics and drug-drug interactions in the efficacy and safety of atypical and other antipsychotic agents. *J Pharm Pharmacol* 58: 871–885.
Nakagami T, Yasui-Furukori N, Saito M, *et al.* 2005. Thioridazine inhibits risperidone metabolism: a clinically relevant drug interaction. *J Clin Psychopharmacol* 25: 89–91.
Prior TI, Baker GB. 2003. Interactions between the cytochrome P450 system and the second-generation antipsychotics. *J Psychiatry Neurosci* 28: 99–112.
Ramamoorthy Y, Tyndale RF, Sellers EM. 2001. Cytochrome P450 2D6.1 and cytochrome P450 2D6.10 differ in catalytic activity for multiple substrates. *Pharmacogenetics* 11: 477–487.
Regenthal R, Kunstler U, Hesse S, Sabri O, Preiss R. 2005. D2 dopamine receptor occupancy, risperidone plasma level and extrapyramidal motor symptoms in previously drug-free schizophrenic patients. *Int J Clin Pharmacol Ther* 43: 370–378.
Remmerie BM, Sips LL, de Vries R, *et al.* 2003. Validated method for the determination of risperidone and 9-hydroxyrisperidone in human plasma by liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 783: 461–472.
Roh HK, Kim CE, Chung WG, Park CS, Svensson JO, Bertilsson L. 2001. Risperidone metabolism in relation to CYP2D6*10 allele in Korean schizophrenic patients. *Eur J Clin Pharmacol* 57: 671–675.
Scordo MG, Spina E, Facciola G, Avenoso A, Johansson I, Dahl ML. 1999. Cytochrome P450 2D6 genotype and steady state plasma levels of risperidone and 9-hydroxyrisperidone. *Psychopharmacology (Berl)* 147: 300–305.
Spina E, Avenoso A, Facciola G, Scordo MG, Ancione M, Madia A. 2001. Plasma concentrations of risperidone and 9-hydroxyrisperidone during combined treatment with paroxetine. *Ther Drug Monit* 23: 223–227.
Spina E, Martines C, Caputi AP, *et al.* 1991. Debrisoquine oxidation phenotype during neuroleptic monotherapy. *Eur J Clin Pharmacol* 41: 467–470.
Suzuki A, Otani K, Ishida M, *et al.* 1997. Increased plasma concentrations of bromperidol and its reduced metabolite with levomepromazine, but not with thioridazine. *Ther Drug Monit* 19: 261–264.
Suzuki Y, Someya T, Shimoda K, *et al.* 2001. Importance of the cytochrome P450 2D6 genotype for the drug metabolic interaction between chlorpromazine and haloperidol. *Ther Drug Monit* 23: 363–368.
Tateishi T, Chida M, Ariyoshi N, Mizorogi Y, Kamataki T, Kobayashi S. 1999. Analysis of the CYP2D6 gene in relation to dextromethorphan O-demethylation capacity in a Japanese population. *Clin Pharmacol Ther* 65: 570–575.
Wang JS, Ruan Y, Taylor RM, Donovan JL, Markowitz JS, DeVane CL. 2004. The brain entry of risperidone and 9-hydroxyrisperidone is greatly limited by p-glycoprotein. *Int J Neuropsychopharmacol* 7: 415–419.
Yasui-Furukori N, Saito M, Inoue Y, *et al.* 2007. Terbinafine increases the plasma concentration of paroxetine after a single oral administration of paroxetine in healthy subjects. *Eur J Clin Pharmacol* 63: 51–56.
Yu A, Kneller BM, Rettie AE, Haining RL. 2002. Expression, purification, biochemical characterization, and comparative function of human cytochrome P450 2D6.1, 2D6.2, 2D6.10, and 2D6.17 allelic isoforms. *J Pharmacol Exp Ther* 303: 1291–1300.

Psychiatry and Clinical Neurosciences 2009; 63: 521–528 doi:10.1111/j.1440-1819.2009.01995.x

Regular Article

Subjective assessments of the quality of life, well-being and self-efficacy in patients with schizophrenia

Bun Chino, MD, PhD,[1–3*†] Takahiro Nemoto, MD, PhD,[2†] Chiyo Fujii, MD, PhD[2] and Masafumi Mizuno, MD, PhD[3]

[1]*Department of Neuropsychiatry, Ginza Taimei Clinic,* [2]*Department of Neuropsychiatry, School of Medicine, Keio University and* [3]*Department of Neuropsychiatry, School of Medicine, Toho University, Tokyo, Japan*

Aim: The present study examined three kinds of subjective assessment scales in the same patient group with schizophrenia to analyze the correlations among scores obtained in relation to the background data.

Method: Thirty-six patients with schizophrenia were examined with the 26-item short form of the World Health Organization Quality of Life (WHO-QOL 26), Subjective Well-being under Neuroleptic drug treatment: Short Japanese version (SWNS) and Self-Efficacy for Community Life scale (SECL) for subjective assessment scales, five kinds of neurocognitive tests, Positive and Negative Syndrome Scale (PANSS) for clinical symptom, Social Functioning Scale (SFS), and Global Assessment of Functioning (GAF) scale for social functioning.

Result: The scores for delusions (components of positive syndrome), anxiety and depression (components of general psychopathology) on the PANSS significantly correlated with QoL and subjective well-being scores. In contrast, the scores for components of negative syndrome were not correlated with the subjective assessment scores. Furthermore, none of the clinical symptom scores were correlated with the score in self-efficacy scale. The SFS and GAF scores were significantly correlated with the subjective assessment scores. There were significant correlations among the scores on the three subjective assessment scales.

Conclusion: Each scale has different features and should be utilized depending upon the expected effect of treatment or the purpose of assessment. The treatments provided to patients must be directed at improving both psychological and social impairments, in order to enhance the social functioning and QoL of patients.

Key words: quality of life, schizophrenia, self-efficacy, subjective assessment, well-being.

SUBJECTIVE ASSESSMENTS, SUCH as of quality of life (QoL)[1] are commonly used in the field of psychiatry. Evaluation of QoL has attracted attention since the 1970s in Western countries, and since the 1980s in Japan.[2–4] At first, it was used only in treatment for physical ailments, such as in patients undergoing cancer surgery or receiving terminal care, in order to devise appropriate plans for clinical care and as an outcome parameter in health-care services. As for its use in the field of psychiatry, it was in the 1990s that it began to be used in research and clinical care for patients with schizophrenia.

As compared with patients with physical diseases, patients with mental disorders were regarded as being more difficult to assess. One of the reasons for this was because the concept of QoL was ambiguous, and direct comparison among studies was difficult. Another reason was that there was often an overlap between QoL items and psychological symptoms, and QoL by itself could not be assessed independently. In addition, there was the skepticism that

Correspondence: Bun Chino, MD, PhD, Ginza Taimei Clinic, da Vinci Ginza Annex, 6-2-3, Ginza, Chuo, Tokyo 104-0061, Japan. Email: gi026037@hotmail.com

Received 11 May 2008; revised 29 March 2009; accepted 2 April 2009.

†Both authors contributed equally to this article.

patients with severe schizophrenia, in particular, could not be assessed precisely. Lehman *et al.* found that psychiatric symptoms (anxiety and depression) affected QoL assessments among patients with chronic conditions.[5,6] Skantze *et al.* reported that outpatients with schizophrenia were able to complete self-report inventories, and were moreover able to participate in the interviews on QoL.[7] Tomotake *et al.* suggested that subjective and objective QoL had different predictors and should be considered as separate and complementary outcome variables.[8]

With the development of atypical antipsychotic drugs and psychosocial treatment modalities, subjective assessments, such as QoL, have been in high demand in the field of clinical psychiatry. Psychiatric policies such as de-institution and community-care have supported use of subjective assessments.[9,10] It is recommended that these new assessments should be commonly used for rehabilitation and treatment of patients with schizophrenia.

This study introduces three kinds of subjective assessments: QoL; subjective well-being; and self-efficacy. Subjective well-being is the major component of QoL. Awad defined subjective well-being as 'changed subjective state after just a few doses of neuroleptic',[11] and Haan defined it more generally as 'all experiences patients report, whether positive or negative, at the physical, emotional and cognitive levels related to treatment with antipsychotic medication'.[12] Naber developed the Subjective Well-being under Neuroleptic Treatment (SWN) scale to compare patient's subjective perceptions of conventional and atypical antipsychotic agents.[13]

Self-efficacy is the belief that one has the ability to perform a certain task or exhibit a certain behavior. Bandura suggested that decisions to enact most human behaviors depended on beliefs about self-efficacy, which mediates the relationship between coping skills and successful emotional adjustment.[14] Lieberman *et al.* developed the theoretical model that self-efficacy determined the coping effort and psychosocial functioning.[15] Ventura *et al.* indicated that self-efficacy and neurocognition, especially sustained attention, might underlie problem-focused coping.[16]

Whereas the three kinds of subjective assessment concepts, namely, QoL, subjective well-being and self-efficacy, have been well studied and documented, no studies have been conducted to compare the differences in results of assessment using the three scales in the same patient group, or to explore the validity of underlying concepts. Moreover, the interpretation of relationships between subjective assessment scores and cognitive functions is controversial. Fujii *et al.* indicated that neurocognition was the predictor of QoL in patients with schizophrenia.[17] In contrast, Hofer *et al.* reported that although cognitive function was the predictor of social functioning, it did not reliably predict the QoL in patients with schizophrenia.[18,19]

The aim of the present study was to examine correlations among the three kinds of subjective assessments and patient background, cognitive function, clinical symptoms and social functioning in patients with schizophrenia. We then discuss the uniqueness and characteristics of each of these assessments.

METHODS

The subjects consisted of 36 patients (21 male, 15 female) with schizophrenia. The mean age was 28.0 ± 5.0 years and the duration of illness was 5.5 ± 3.9 years. All were right-handed and none had any history of head injury or serious medical disease. They were diagnosed by trained psychiatrists using ICD-10 criteria[20] and were under treatment with antipsychotics, with the mean chlorpromazine-equivalent dose of 317.8 mg/day. The clinical symptoms were measured using the Positive and Negative Syndrome Scale (PANSS),[21] in which the scores for components of positive syndrome were low (12.3 ± 3.1) and those for components of negative syndrome were not so high (19.8 ± 4.4) compared to patients with chronic schizophrenia. The scores on Social Functioning Scale (SFS)[22,23] and Global Assessment of Functioning (GAF) scale[24] were relatively high (SFS, 118.2 ± 24.0; GAF, 62.1 ± 7.9). All the subjects provided verbal as well as written consent for participation in this research.

Subjective assessment

World Health Organization Quality of Life scale

The 26-item short form of the World Health Organization Quality of Life scale (WHO-QOL 26) is the brief version of the WHO-QOL 100, which was developed to assess subjects around the world, regardless of culture or civilization.[25,26] It consists of 26 items that are classified into five domains: physical domain, psychological domain, social relationship, environment domain, and general QoL.

Subjective Well-being under Neuroleptic drug treatment: Short Japanese version

The Subjective Well-being under Neuroleptic drug treatment: Short Japanese version (SWNS) is used to assess the subjective cognition and affect of patients with schizophrenia who are under treatment with antipsychotics.[13,27] The short version consists of 20 items that are classified into five categories: mental functioning, self control, emotional regulation, physical functioning and social integration.

Self-Efficacy for Community Life scale

The Self-Efficacy for Community Life scale (SECL) is used to assess the self-efficacy of patients with schizophrenia living in the community.[28] It consists of 18 items that are classified into five domains, as follows: daily living, behavior in relation to treatment, behavior in relation to symptoms, social life, and interpersonal relation.

Neurocognitive tests

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is the screening test used to assess general cognitive impairment, and consists of six domains of orientation, registration, attention, calculation, recall and language.[29]

Rey Auditory Verbal Learning Test

The Rey Auditory Verbal Learning Test (RAVLT) is the memory test in which subjects are asked to listen to a list of 15 common words and repeat as many of these words as they can remember, in any order.[30] This procedure is repeated four times. Then, an examiner asks the subjects to listen to another list of 15 common words and to repeat as many of these words as possible once only. The examiner then asks the subjects to recall as many words as possible again from the previous list of words.

Letter-Cancellation Test

Letter-Cancellation Test (LCT) is the attention test conducted using rows of letters randomly interspersed with the designated target letter.[31] Subjects are instructed to cross out all the target letters. Performance is scored according to the number of correct responses and the time taken to complete the test.

Letter and Category Fluency Test

In the Letter and Category Fluency Test subjects are asked to say as many words beginning with a given kana (syllable), 'shi', 'i', 're', as they can, for Letter Fluency test, and the names of animals, fruits, and transportations for the Category Fluency test within 60 s.[32] These tests are more useful to assess elemental fluency as compared with the Optional Thinking Test (OTT).

Optional Thinking Test

The OTT is one kind of fluency test that requires subjects to conceptualize options or alternatives to hypothetical, but typical real-life problems.[33] We translated this test version into Japanese with the permission of the original authors and used it to examine patients with schizophrenia and normal control subjects. High inter-rater reliability and validity were also confirmed.[34]

Statistical analysis

Statistical analyses were performed using Statcel2 (OMS Publishing, Saitama, Japan). Spearman rank correlation was calculated to evaluate the association between subjective assessments and neurocognition/symptoms/global functioning. For each comparison, $P < 0.05$ was considered to be statistically significant without any consideration for multiple comparisons.

RESULTS

The schizophrenia patients scored poorly on the subjective assessment scales (Table 1) and neurocognitive tests (Table 2. Patient background and neurocognitive test results were not correlated with any subjective assessment scores. In contrast, the scores for clinical symptoms (Table 3) were inversely correlated with the subjective assessment scores. In particular, the score for delusion 2.2 ± 0.5 (component of positive syndrome 12.3 ± 3.1), anxiety 2.2 ± 0.7 and depression 1.7 ± 0.8 (general psychopathology 33.4 ± 6.0) were correlated with the scores on WHO-QOL 26 and SWNS. In contrast, there were no sig-

Table 1. Subjective assessment scores

	Mean ± SD	Range
WHO-QOL 26	3.0 ± 0.6	1.5–4.1
SWNS	73.3 ± 16.3	37–104
SECL	114.1 ± 34.0	20–178

SECL, Self-Efficacy for Community Life scale; SWNS, Subjective Well-being under Neuroleptic drug treatment: Short Japanese version; WHO-QOL 26, 26-item short form of the World Health Organization Quality of Life.

nificant correlations between the scores for negative syndrome and the subjective assessment scores.

The SFS and GAF scores (Table 4) were significantly correlated with subjective assessment scores. There were significant correlations among the scores in three subjective assessment scales (WHO-QOL 26 and SWNS, 0.80; WHO-QOL and SECL, 0.62; and SWNS and SECL, 0.70).

DISCUSSION

All the schizophrenia patients who participated in this study were outpatients who were younger than 40 years of age and were psychologically stable. The inclusion criteria eliminated the influence of long duration of illness and of treatment with high doses of antipsychotics. The mean GAF score of these patients was >61, indicating that none of the patients had severe symptoms or difficulties in their life, and that therefore their global functions were reasonably preserved. The present results, however, showed that the schizophrenia patients had poor QoL and cognitive deficits. The QoL scores and cognitive function in the schizophrenia patients were generally low compared with those of the normal controls. This was consistent with previous reports of lower QoL scores in schizophrenia patients than in normal controls and patients with other mental disorders.[35]

The scores on QoL and other subjective assessment scales were not correlated with patient background. Previous studies showed that patient background significantly affected QoL. According to several studies, young female and married patients exhibited better QoL scores.[36,37] Although marital status was not checked, the sex and age of the patients were considered in the present study. There were no significant differences in the subjective assessment scores between male and female patients. As for age, all the patients were under 40 years old. This is one of the limitations of the present study and different results might be obtained in different age groups.

In addition, there were no correlations between neurocognitive test results and subjective assessment scores in the present study. Several studies have indicated that neurocognitive deficits affected subjective assessment scores. Fujii *et al.* indicated that neuropsychological parameters, including verbal memory, vocabulary, Digit Span, MMSE, and executive function, might be predictors of QoL in patients with schizophrenia.[17] In contrast, Lysaker *et al.* reported that poorer verbal memory, an executive function, was predictive of higher scores for hope and well-being.[38] Prouteau *et al.* reported that worse baseline attention predicted better QoL.[39] These paradoxical results may be explained by the contention that schizophrenia patients with neurocognitive deficits are unable to recognize their social condition as undesirable; in other words, neurocognitive deficits may shield patients with schizophrenia from the feeling of hopelessness that might accompany more realistic and accurate recognition of one's life condition. No consensus has been established as yet and the results may vary depending on the conditions of subjects. The present study did not find any correlation between neurocognitive test results and subjective assessment scores. The present patients were young and their symptoms were mild. This is also a limitation of the present study. The old or severe symptom patients might show different results. The next study should analyze patient background and conditions.

The clinical symptom scores in the present study were significantly correlated with the subjective assessment scores. Associations between depression, anxiety (PANSS General Psychopathology) and QoL have been noted several times. Karow *et al.* insisted

Table 2. Cognitive function scores

	Mean ± SD	Range
Mini-Mental State Examination	29.4 ± 0.7	28–30
Rey Auditory Verbal Learning Test	11.7 ± 2.4	6–15
Letter Cancellation Test (correct responses)	110.5 ± 4.1	96–114
Letter Cancellation Test (time)	110.5 ± 24.7	75–150
Letter Fluency Test	22.7 ± 7.8	6–41
Category Fluency Test	31.7 ± 6.7	18–48
Optional Thinking Test (total score)	14.0 ± 6.2	5–27

Table 3. Correlation between PANSS and subjective assessment in schizophrenia patients

	WHO-QOL 26	SWNS	SECL
PANSS Positive syndrome	−0.39*	−0.37*	−0.16
Delusion	−0.10*	−0.14*	−0.06
Conceptual disorganization	0.0009	−0.14*	−0.05
Hallucinatory behavior	0.03	−0.09	0.08
Excitement	−0.21*	−0.02	−0.03
Grandiosity	0.03	−0.13	0.18
Suspiciousness	−0.17	0.14	0.03
Hostility	0.07	0.12	0.23
PANSS Negative syndrome	−0.06	−0.06	−0.05
Blunted affect	0.24	0.22	0.18
Emotional withdrawal	0.12	0.13	0.07
Poor rapport	0.17	0.18	0.17
Passive/Apathetic social withdrawal	−0.14	−0.11	−0.18
Difficulty in abstract thinking	0.10	0.06	0.06
Lack of spontaneity and flow of conversation	0.18	0.09	0.03
Stereotyped thinking	−0.18*	−0.14	−0.09
PANSS General psychopathology	−0.43*	−0.49**	−0.28
Somatic concern	−0.35**	−0.30*	−0.32*
Anxiety	−0.27*	−0.30*	−0.29*
Guilt feeling	0.12	0.08	0.20
Tension	0.04	−0.03	−0.05
Mannerisms and posturing	0.27	0.11	0.09
Depression	−0.41**	−0.33**	−0.20
Motor retardation	−0.02	0.03	−0.06
Uncooperativeness	−0.32*	−0.20	−0.003
Unusual thought content	−0.19*	−0.24*	−0.07
Disorientation	0.34	0.31	0.41
Poor attention	−0.12	−0.25*	−0.16
Lack of judgment and insight	0.001	−0.05	0.09
Disturbance of volition	−0.15	−0.21*	−0.21
Poor impulse control	−0.01	−0.06	0.16
Preoccupation	−0.21*	−0.19*	−0.03
Active social avoidance	−0.22	−0.25*	−0.26*

*$P < 0.05$; **$P < 0.01$.

PANSS, Positive And Negative Syndrome Scale; SECL, Self-Efficacy for Community Life scale; SWNS, Subjective Well-being under Neuroleptic drug treatment: Short Japanese version; WHO-QOL 26, 26-item short form of the World Health Organization Quality of Life.

that anxiety was the most important symptom and it should be reduced in order to improve QoL.[40] Lehman *et al.* and Dickerson *et al.* indicated that depression was one of the symptomatic factors affecting QoL.[5,6,41] Consistent with previous reports, psychotic symptoms, delusion and excitement, as components of positive syndrome, were correlated with the subjective assessment scores.[42] In contrast, and not consistent with previous reports,[43] the scores for components of negative syndrome were not correlated with any of the subjective assessment scores. Green *et al.* suggested that cognitive and negative symptoms affected social functioning, leading to satisfaction in patients.[44] Patients in the present study were relatively young and their negative symptoms were not serious. Thus, the results might differ in old or severe symptom patients as well.

Regarding social functioning, the score for withdrawal, in particular, was significantly correlated with the subjective assessment scores. Similarly, a significant correlation was also found with GAF score. This implies that social functioning or activity contributes

Table 4. Correlations between SFS, GAF and subjective assessments in schizophrenia patients

	Mean ± SD	WHO-QOL 26	SWNS	SECL
Social Functioning Scale				
Withdrawal	10.4 ± 2.3	0.58**	0.68**	0.48**
Interpersonal	6.8 ± 2.5	0.44*	0.22	0.44*
Independence	23.3 ± 6.7	0.22	0.09	0.38*
Recreation	20.0 ± 6.8	0.40*	0.29	0.33
Pro-Social	15.2 ± 8.9	0.50**	0.22	0.51**
Independence	36.5 ± 2.6	0.56*	0.40*	0.63**
Employment	6.0 ± 3.2	0.44*	0.37*	0.42*
Total	118.2 ± 24.0	0.52**	0.30	0.55**
GAF	62.1 ± 7.9	0.53**	0.48**	0.50**

*$P < 0.05$; **$P < 0.01$.

GAF, Global Assessment of Functioning; SECL, Self-Efficacy for Community Life scale; SFS, Social Functioning Scale; SWNS, Subjective Well-being under Neuroleptic drug treatment: Short Japanese version; WHO-QOL 26, The 26-item short form of the World Health Organization Quality of Life.

significantly to the levels of satisfaction in patients. Furthermore, psychological symptoms also act as background factors. Aki *et al.* indicated that depressive symptoms predicted subjective QoL, negative symptoms predicted objective QoL, and each of them predicted the level of social skills.[45] Therefore, patients should be treated psychologically and socially at the same time in order to improve social functioning and QoL.

Finally, there were significant correlations among the scores in these subjective assessment scales. Although all were self-reporting questionnaires about feeling or cognition in daily life, there were slight differences. The score on WHO-QOL 26 was significantly correlated with both the scores on PANSS and SFS. The SWNS score was significantly correlated with that on the PANSS, but not with the SFS score. And the SECL score was significantly correlated with the SFS score but not the PANSS score. SWNS is used to assess subjective cognition and affect of patients with schizophrenia who are on antipsychotics, and it was developed to examine the effect of drug treatment. SECL is used to assess the self-efficacy of patients with schizophrenia who live in the community and it was developed to examine psychoeducation. Although SWNS assesses the psychological and subjective aspects, SECL assesses social and objective aspects in greater detail. Consequently, each scale should be utilized depending upon the effect of treatment and the objectives of assessment.

In conclusion, patient background and neurocognitive test results were not correlated with subjective assessment scores in the present study. In contrast, the scores for clinical symptoms such as depression or social withdrawal were correlated with scores for social functioning and the subjective assessment scores. The scores for social functioning were also correlated with the subjective assessment scores. Thus, the treatment provided to patients must be directed at improving both psychological and social impairments, in order to enhance social functioning and QoL.

REFERENCES

1 World Health Organization. *Constitution of the World Health Organization, Basic Documents*. WHO, Geneva, 1948.
2 Katschnig H, Freeman H, Sartorius N. *Quality of Life in Mental Disorders*. John Wiley & Sons, West Sussex, 2006.
3 Lambert M, Naber D. Current issues in schizophrenia: Overview of patient acceptability, functioning capacity and quality of life. *CNS Drugs* 2004; 18 (Suppl. 2): 5–17.
4 Kunitaka H, Mino Y. Quality of life and schizophrenia. A review of the literature. *Nippon Koshu Eisei Zasshi* 2003; 50: 377–388 (in Japanese).
5 Lehman AF. The effects of psychiatric symptoms on quality of life assessments among the chronic mentally ill. *Eval. Program Plann.* 1983; 6: 143–151.
6 Lehman AF, Postrado LT, Rachuba LT. Convergent validation of quality of life assessments for persons with severe mental illness. *Qual. Life Res.* 1993; 2: 327–333.
7 Skantze K, Malm U, Dencker SJ *et al.* Comparison of quality of life with standard of living in schizophrenic out-patients. *Br. J. Psychiatry* 1992; 161: 797–801.

8 Tomotake M, Kaneda Y, Iga J *et al.* Subjective and objective measures of quality of life have different predictors for people with schizophrenia. *Psychol. Rep.* 2006; 99: 477–487.
9 Mizuno M, Sakuma K, Ryu Y *et al.* The Sasagawa project: A model for deinstitutionalisation in Japan. *Keio J. Med.* 2005; 54: 95–101.
10 Ryu Y, Mizuno M, Sakuma K *et al.* Deinstitutionalization of long-stay patients with schizophrenia: The 2-year social and clinical outcome of a comprehensive intervention program in Japan. *Aust. N. Z. J. Psychiatry* 2006; 40: 462–470.
11 Awad AG. Subjective response to neuroleptics in schizophrenia. *Schizophr. Bull.* 1993; 19: 609–618.
12 Haan L. *Patient Perspectives, Subjective Experiences and Attitudes of Patients with Recent Onset Schizophrenia.* University of Amsterdam, Amsterdam, 2001.
13 Naber D. A self-rating to measure subjective effects of neuroleptic drugs, relationships to objective psychopathology, quality of life, compliance and other clinical variables. *Int. Clin. Psychopharmacol.* 1995; 10 (Suppl. 3): 133–138.
14 Bandura A. *Reflections on Human Agency. Contemporary Psychology in Europe.* Hogrefe & Huber Publishers, Seattle, 1966.
15 Lieberman RP, Mueser KT, Wallace CJ, Jacobs HE, Eckman T, Massel HK. Training skills in the psychiatrically disabled: Learning coping and competence. *Schizophr. Bull.* 1986; 12: 631–647.
16 Ventura J, Nuechterlein KH, Subotnik KL, Green MF, Gitlin MJ. Self-efficacy and neurocognition may be related to coping responses in recent-onset schizophrenia. *Schizophr. Res.* 2004; 69: 343–352.
17 Fujii DE, Wylie AM, Nathan JH. Neurocognition and long-term prediction of quality of life in outpatients with severe and persistent mental illness. *Schizophr. Res.* 2004; 69: 67–73.
18 Hofer A, Baumgartner S, Edlinger M *et al.* Patient outcomes in schizophrenia I: Correlates with sociodemographic variables, psychopathology, and side effects. *Eur. Psychiatry* 2005; 20: 386–394.
19 Hofer A, Baumgartner S, Bodner T *et al.* Patient outcomes in schizophrenia II: The impact of cognition. *Eur. Psychiatry* 2005; 20: 395–402.
20 World Health Organization. *The ICD-10 Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines.* World Health Organization, Geneva, 1992.
21 Kay SR, Opler LA, Fiszben A. *Positive and Negative Syndrome Scale (PANSS) Rating Manual.* Multi-Health Systems, Toronto, 1991.
22 Birchwood M, Smith J, Cochrane R, Wetton S, Copestake S. The social functioning scale. The development and validation of a new scale of social adjustment for use in family intervention programs with schizophrenic patients. *Br. J. Psychiatry* 1990; 157: 853–859.
23 Nemeto T, Fujii C, Miura Y *et al.* Reliability and validity of the social functioning scale Japanese version (SFS-J). *Jpn. Bull. Soc. Psychiatry* 2008; 17: 188–195.
24 American Psychiatric Association. *Diagnostic and Statistical Manual Disorders,* 4th edn. American Psychiatric Association, Washington DC, 1994.
25 WHO-QOL Group. Development of WHO QOL: Rational and current status. *Int. J. Ment. Health* 1994; 23: 24–56.
26 Tazaki M, Nakane Y. *WHO QOL-BREF Instrument.* Kaneko-shobo, Tokyo, 1997 (in Japanese).
27 Watanabe M. Reliability and validity of subjective well-being under neuroleptic drug treatment short form, Japanese version (SWNS-J). *Rinsho Seishin Yakuri* 2003; 6: 905–912 (in Japanese).
28 Okawa N, Oshima I, Cho N *et al.* Development of 'Self-Efficacy for Community Life Scale' for schizophrenia: Reliability and validity. *Seishinigaku* 2001; 43: 727–735 (in Japanese).
29 Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State' A practical method for grading the cognitive state for the clinician. *Psychiatry Res.* 1975; 12: 189–198.
30 Lezak MD. Auditory-verbal learning test. In: Lezak MD (ed.). *Neuropsychological Assessment,* 3rd edn. Oxford University Press, Oxford, 1995; 438–445.
31 Benton AL. Differential behavioral effects in frontal lobe disease. *Neuropsychologia* 1968; 6: 53–60.
32 Saito H. The reduction of fluency in patients with frontal lobe lesions: A neuropsychological investigation with fluency tests. *Keio J. Med.* 1996; 73: 399–409 (in Japanese).
33 Platt JJ, Spivack G. *Measures of Interpersonal Cognitive Problem-Solving for Adults and Adolescents.* Center for Addiction Research School of Osteopathic Medicine. Department of Psychiatry University of Medicine and Dentistry of New Jersey, New Jersey, 1981.
34 Chino B, Mizuno M, Nemoto T *et al.* Relation between social functioning and neurocognitive test results using the optional thinking test in schizophrenia. *Psychiatry Clin. Neurosci.* 2006; 60: 63–69.
35 Nakane Y. *A Study of QOL Assessment in Patients with Schizophrenia and Depression.* Ministry of Health and Welfare, Tokyo, 2001 (in Japanese).
36 Lehman AF, Ward NC, Linn LS. Chronic mental patients: The quality of life issue. *Am. J. Psychiatry* 1982; 139: 1271–1276.
37 Caron J, Mercier C, Diaz P *et al.* Socio-demographic and clinical predictors of quality of life in patients with schizophrenia or schizo-affective disorder. *Psychiatry Res.* 2005; 137: 203–213.
38 Lysaker PH, Clements CA, Wright DE, Evans J, Marks KA. Neurocognitive correlates of helplessness, hopelessness, and well-being in schizophrenia. *J. Nerv. Ment. Dis.* 2001; 189: 457–462.
39 Prouteau A, Verdoux H, Briand C *et al.* Cognitive predictors of psychosocial functioning outcome in schizophrenia: A

follow-up study of subjects participating in a rehabilitation program. *Schizophr. Res.* 2005; 77: 343–353.
40 Karow A, Moritz S, Lambert M, Schoder S, Krausz M. PANSS syndromes and quality of life in schizophrenia. *Psychopathology* 2005; 38: 320–326.
41 Dickerson FB, Ringel NB, Parente F. Subjective quality of life in out-patients with schizophrenia: Clinical and utilization correlates. *Acta Psychiatr. Scand.* 1998; 98: 124–127.
42 Ritsner M. Predicting changes in domain-specific quality of life of schizophrenia patients. *J. Nerv. Ment. Dis.* 2003; 191: 287–294.
43 Norman RMG, Malla AK, Mclean T *et al.* The relation of symptoms and level of functioning in schizophrenia to general wellbeing and the Quality of Life Scale. *Acta Psychiatr. Scand.* 2000; 102: 303–309.
44 Green MF, Kern RS, Braff DL. Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the right stuff? *Schizophr. Bull.* 2000; 26: 119–136.
45 Aki H, Tomotake M, Kaneda Y *et al.* Subjective and objective quality of life, levels of life skills, and their clinical determinants in outpatients with schizophrenia. *Psychiatry Res.* 2008; 158: 19–25.

Effects of Aripiprazole on Insight and Subjective Experience in Individuals With an At-Risk Mental State

Hiroyuki Kobayashi, MD,† Keiko Morita, MD,‡ Kiyoaki Takeshi, MD,‡ Hiroki Koshikawa, MD, PhD,§ Ryoko Yamazawa, MD, PhD,* Haruo Kashima, MD, PhD,* and Masafumi Mizuno, MD, PhD‡*

Introduction: Although medication with antipsychotic for the psychosis prodrome has often caused some ethical issues, recent studies have shown that some novel antipsychotics are safer and more tolerable for young people. This study aimed to investigate whether the administration of aripiprazole would not only relieve the prodromal symptoms but also be tolerable for prodromal subjects and to evaluate the effect of medication on improvements in insight and subjective well-being.

Methods: The Structured Interview for Prodromal Syndromes was performed for patients identified as having the psychosis prodrome. Psychiatric measures included the Scale of Prodromal Symptoms. Clinical insight was measured using the Scale to Assess Unawareness of Mental Disorder, and changes in subjective experience were assessed using the Subjective Well-being Under Neuroleptics, Short version. The time frame was the first 8 weeks after beginning study medication.

Results: Thirty-six treatment-seeking prodromal patients (men, 42%; mean [SD] age, 23.4 [5.6] years) were enrolled. At the 12-week follow-up point, 30 participants (83%) remained in the trial. Improvements on the Scale of Prodromal Symptoms and Scale to Assess Unawareness of Mental Disorder scores were statistically significant at end point. Although the Subjective Well-being Under Neuroleptics, Short version total scores improved significantly at 4 weeks, however, they did not change significantly from baseline at 8 weeks.

Conclusions: This trial suggests that aripiprazole not only produces a clinical benefit in prodromal subjects but also results in a high adherence to medication with immediate improvements in insight and subjective well-being. Although further placebo-controlled studies are needed, aripiprazole might be a first-line treatment for individuals at imminent risk for psychosis.

Key Words: prodrome, psychosis, subjective experience, insight, at-risk mental state

(*J Clin Psychopharmacol* 2009;29: 421–425)

Prepsychotic intervention has mainly 2 approaches: psychological intervention and medication.[1,2] Recent controlled studies have demonstrated that both approaches are effective for relieving prodromal symptoms and delaying the onset of psychosis.[3–5] From an ethical viewpoint, however, most researchers and clinicians consider psychological intervention to be a first-line treatment for the psychosis prodrome.[3,4]

From the *Department of Neuropsychiatry, School of Medicine, Keio University, Shinjuku-Ku; †Tokyo Musashino Hospital, Institute of Clinical Psychiatry, Itabashi-Ku; ‡Department of Neuropsychiatry, School of Medicine, Toho University, Ohta-Ku; and §Shakujii-Kouen Clinic, Nerima-Ku, Tokyo, Japan.

Received February 4, 2009; accepted after revision June 15, 2009.

Reprints: Hiroyuki Kobayashi, MD, Tokyo Musashino Hospital, Institute of Clinical Psychiatry, 4-11-11 Komone, Itabashi-Ku, Tokyo, Japan 173-0037 (e-mail: h-kobayashi@tmh.or.jp).

ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e3181b2fe22

Psychological interventions that are not usually associated with severe adverse effects pose little unnecessary risk to patients with false-positive test results. On the other hand, antipsychotic medication is often associated with adverse effects that are particularly undesirable for young subjects, such as pronounced weight gain and sexual dysfunction.[5,6] Such adverse effects not only pose a risk to subjects with false-positive test results but may also lead to poor adherence. Indeed, some randomized controlled trials have shown that the withdrawal rate in the medication group might be higher than that in the psychological intervention group[3,5]; therefore, adherence to antipsychotic treatment during the prodromal phase may be difficult to maintain.[7]

However, more recent studies on the psychosis prodrome have shown that some novel antipsychotics are safer and more tolerable for young people. Ruhrmann et al[8] demonstrated that the administration of amisulpride yielded both a marked symptomatic benefit and a high tolerability among subjects in a putatively late initial prodromal state. Woods et al[9] showed that aripiprazole resulted in not only a clinically beneficial treatment but also a high adherence to treatment among patients with the psychosis prodrome. Even if these antipsychotics are undoubtedly less harmful, however, individuals with an at-risk mental state may not easily agree to medication because they often do not have sufficient insight or understanding of the risk.[10] Given that patient nonadherence to medication depends on impaired insight[11,12] or subjective well-being[13–15] and adverse effects, the impact of medication on changes in insight or subjective experiences should be considered.

The aims of this study were to investigate whether the administration of aripiprazole for the treatment of psychotic prodrome would be effective and tolerable in a larger clinical sample and to evaluate the effect of medication on improvements in insight and subjective well-being.

METHODS

Participants

This study was performed at 3 sites: a university hospital (Toho University), a psychiatric hospital (Tokyo-Musashino Hospital), and a community mental health clinic (Shakujii-Kouen Clinic). Participants were eligible for enrollment in the study if they (1) were between the ages of 16 and 40 years; (2) lived in the Tokyo metropolitan area; and (3) met the Criteria of Prodromal Syndromes.[16] Patients were excluded from the study if they had (1) any lifetime *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of any psychotic disorder; (2) symptoms fully accounted for by an Axis I disorder or sequelae arising from drug/alcohol use; (3) abuse of alcohol or drugs; (4) antipsychotic medication use; or (5) change in the dosage of an antidepressant or mood stabilizer within 6 weeks. All the participants were help-seeking outpatients. Adult participants gave written informed consent and minors gave written informed assent with consent from a

TABLE 1. Demographic Characteristics of the Sample at Baseline

Characteristics	Data
Mean (SD) age, yr	23.4 (5.6)
Female patients, n (%)	21 (58.3)
First degree family history, n (%)	
Psychosis	4 (11.1)
Nonpsychosis	7 (19.4)
Medication use at baseline, n (%)	
Antipsychotics	10 (27.8)
Antidepressants	0 (0)
Benzodiazepine/hypnotics	13 (36.1)
Mood stabilizers	2 (5.6)
Lifetime substance abuse/dependence, n (%)	0 (0)

parent or guardian. Data were collected between October 2007 and September 2008.

Procedure

During the first week before beginning study medication, participants underwent eligibility and examinations. After beginning the study medication, participants were scheduled for 8 weekly visits.

Dosing followed a flexible schedule. Participants continued doses of antidepressant, mood stabilizer, or benzodiazepine prescribed before consent. Individuals and family psychosocial interventions with supportive and psychoeducational components were available to each participant. The institutional review board at each site approved this procedure.

MEASURES

Clinical Variables

The Structured Interview for Prodromal Syndromes (SIPS)[16] was performed for patients identified as having an at-risk mental state. We used the SIPS Japanese version, which we previously reported an excellent interrater reliability.[17] Psychiatric measures included the Scale of Prodromal Symptoms (SOPS) and the Global Assessment of Functioning (GAF). The SOPS items consist of 4 symptoms: positive, negative, disorganized, and general symptoms. The incidence of akathisia was recorded using the Barnes Akathisia Scale (BAS).[18] Transition to psychosis was operationally defined using the Presence of Psychotic Symptoms criteria. The SOPS and BAS were assessed at baseline, after 2, 4, and 8 weeks. The other measures were performed at baseline, after 4 and 8 weeks. Information on adherence to medication was collected from not only the participants but also their family or caregivers.

Subjective Experience Measure

Changes in subjective experience were assessed using the Subjective Well-being Under Neuroleptics, Short version (SWNS).[19] The SWNS is a 20-item and 6-point Likert-type self-rating scale. Naber et al[19] found a 5-factor solution of the scale, which was interpreted as emotional regulation, self-control, mental functioning, social integration, and physical functioning. We used the SWNS Japanese version, which showed good reliability and validity.[20]

Insight Measures

Current insight was measured with the Scale to Assess Unawareness of Mental Disorder (SUMD).[21] The SUMD rates awareness on 20 items based on a 5-point Likert scale. To assess current insight, we used the 3 global insight items (awareness of

TABLE 2. Mean Changes in SOPS, SUMD, SWNS, GAF, and BAS Scores From Baseline to Week 8 (LOCF Analysis)

	Mean (SD)			
	Baseline	End Point	Percentage Change	P
SOPS				
Total score	56.3 (12.1)	33.7 (11.2)	−40.2	<0.01
Positive symptoms	14.8 (4.1)	7.3 (3.2)	−50.8	<0.01
Negative symptoms	20.7 (5.7)	12.1 (4.6)	−41.5	<0.01
Disorganized symptoms	9.1 (4.1)	5.6 (3.5)	−37.7	<0.01
General symptoms	12.2 (3.7)	8.1 (3.8)	−33.6	<0.01
SUMD				
Current disorder				
Item 1–3 (global insight) awareness	2.81 (0.8)	2.24 (0.7)	−20.3	<0.01
Item 4–10 (symptom items) awareness	2.99 (0.4)	2.38 (0.3)	−20.4	<0.01
Item 4–10 (symptom items) attribution	3.20 (0.5)	2.42 (0.4)	−24.4	<0.01
SWNS				
Total score	54.6 (16.6)	55.9 (11.9)	2.4	NS
Physical functioning	11.1 (4.3)	10.1 (1.0)	−9.0	NS
Social integration	10.2 (4.7)	11.3 (6.3)	10.8	NS
Mental functioning	10.7 (3.8)	10.3 (1.6)	−3.7	NS
Self-control	12.1 (4.2)	11.6 (3.1)	−4.1	NS
Emotional regulation	10.6 (4.7)	11.4 (3.3)	7.5	NS
GAF total score	54.0 (8.3)	68.2 (7.5)	26.3	<0.01
BAS total score	0.0 (0.0)	0.13 (0.35)	2.7	NS

NS indicates not significant.

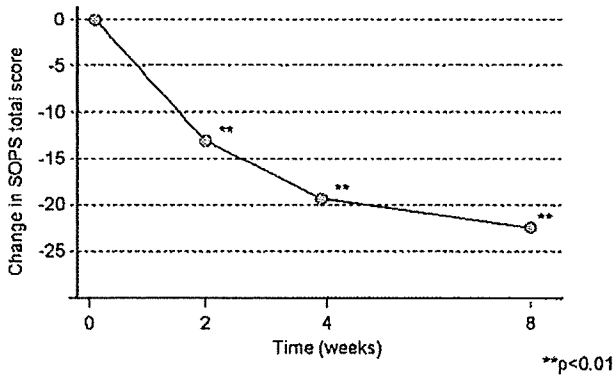

FIGURE 1. Mean changes in the SOPS total scores from baseline.

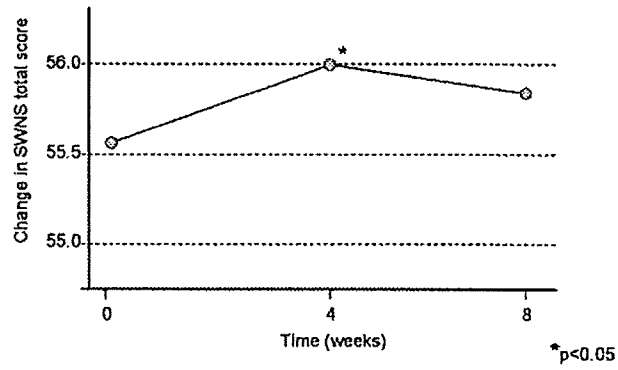

FIGURE 3. Mean changes in the SWNS total scores from baseline.

mental disorder, awareness of achieved medication effects, and awareness of social consequences of medications) and the 17 subscales (awareness of symptoms).

Statistical Analyses

For the present report, the time frame was the first 8 weeks after beginning study medication. All analyses were done on an intent-to-treat basis. In case of premature drop-out, last observation carried forward (LOCF) analysis was used. Treatment effects were calculated by paired t test. As for the SOPS total score, we used an alternative analysis using a mixed-effects likelihood-based repeated measures linear model on postbaseline change scores, using baseline scores as a covariate. Level of significance was set at 0.05 for all analyses. Statistical analyses were done with the SPSS 11.0 (SPSS Inc, Chicago, Ill).

RESULTS

Thirty-six treatment-seeking prodromal patients (men, 42%; mean [SD] age, 23.4 [5.6] years) were enrolled in this study (intent-to-treat sample). Demographic characteristics of the sample are presented in Table 1. Thirty-four (94%) of the 36 patients had the attenuated positive symptoms and 2 (6%) of the 36 patients had the brief intermittent positive symptoms according to the SIPS. Four (11%) of the 36 patients had a first degree family history of psychosis.

At the 12-week follow-up point, 30 participants (83%) remained in the trial. No participant converted to psychosis. The LOCF analyses revealed significant improvement from baseline on the SOPS (total score and all subscores), SUMD (both global insight and symptom subscales), and the GAF scales (Table 2). As Figure 1 shows, changes of the SOPS total score from baseline were statistically significant ($P < 0.01$) in a mixed-effect repeated measure. The SUMD scores also improved significantly at both 4 and 8 weeks (Fig. 2). On the other hand, the SWNS total scores did not change significantly from baseline at 8 weeks (mean [SD], 55.9 (11.9); $t = -0.63$; $df = 29$; $P = 0.55$; Fig. 3; Table 2), although they improved significantly at 4 weeks (mean [SD], 56.0 (6.2); $t = 2.24$; $df = 31$; $P < 0.05$).

The mean (SD) daily dose of aripiprazole at baseline was 7.1 (3.4) mg; the mean (SD) maximum dose, 11.1 (6.0) mg; and the mean (SD) dose at end point, 10.7 (5.4) mg. During treatment, 4 participants experienced emergent akathisia, which could be managed by slowing dose titration and prescribing anticholinergic medication or benzodiazepine. Mean BAS total scores consequently returned to baseline by the end-point evaluation (Table 2). No one experienced severe adverse events, and 2 patients discontinued aripiprazole because of adverse events. Treatment-emergent adverse events reported with a frequency of more than 5% were irritability (17%), headache (14%), nervousness (8%), insomnia (8%), increased appetite (6%), and sedation (6%); no serious adverse events occurred during the study.

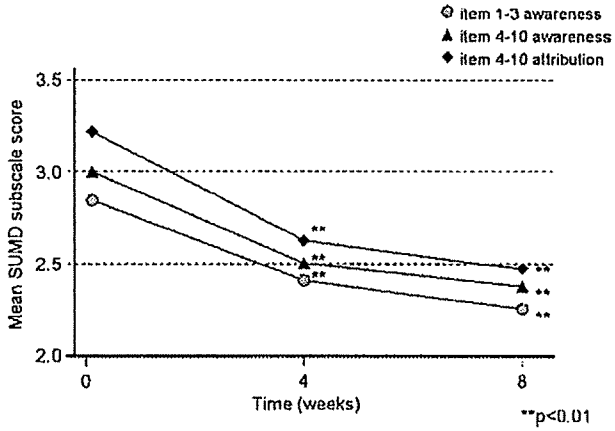

FIGURE 2. Mean changes in the SUMD global insight item scores and symptom item scores from baseline.

DISCUSSION

Patient adherence is of great importance for the treatment of psychosis, even during the prodromal phase; this is especially true among patients at imminent risk for psychosis. In the present study, we examined changes in insight and subjective experience after medication with aripiprazole because these factors are thought to contribute to patient adherence. Lappin et al[10] reported that individuals with an at-risk mental state often have unstable insight, with an acceleration in loss of insight occurring with disease progression. Therefore, to prevent or delay the onset of psychosis, improving patient insight and maintaining adherence to treatment are important.

In addition, subjective well-being is regarded as an indicator of the efficacy of a medication. Some first episode studies have demonstrated that poor treatment adherence was related to subjective wellness during the early disease stage.[22,23] Lambert et al[22] emphasized the importance of an early response to antipsychotic treatment for the long-term outcome of psychosis, particularly, the need to achieve a rapid improvement in subjective well-being.

This study showed a strong adherence to medication, with immediate improvements in insight and subjective well-being within 4 weeks. These results support our hypothesis that patient

adherence to medication may be associated with insight and self-experience. The immediate improvements in insight might be due to the drug profile of aripiprazole. Aripiprazole produces a clinical benefit in cognitive enhancement as a result of its role as a dopamine system stabilizer[24]; therefore, this dopamine partial agonist might modify impaired insight relevant to higher cognitive function.[25,26]

Although the SWNS total scores improved significantly at 4 weeks, however, they did not change significantly from baseline at 8 weeks. Given that the SOPS total scores and the GAF scales improved significantly from baseline at both 4 and 8 weeks, these improvements would lead to better subjective well-being, theoretically. However, the improvement on insight might cause awakening. Some recovered patients faced the difficulties in the real world, and consequently, they might often experience depression or anxiety. As an example, Kim et al[27] reported that greater insight and hopelessness were associated with attempted suicide and suicidal ideation. Karow et al[28] mentioned that patients with greater insight realize their restrictions more clearly, which contribute to poor quality of life. For such unstable subjective well-being, psychological interventions and medication should be needed.

This study has some limitations. The nonblinded, uncontrolled study design was one methodological weakness. The short-term effects of the medication, including the improvement in subjective well-being, could have been a placebo effect. However, a more strict study design might have caused poor adherence and is not suitable for the actual clinical treatment of prodromal patients. The prodromal population sometimes includes subjects with false-positive test results; therefore, medication should not be unconditionally administered to this population. Actually, psychological intervention alone has been effective for relieving prodromal symptoms and delaying the onset of psychosis,[4] and a naturalistic study showed that the use of antidepressants for at-risk individuals yielded better adherence and outcome than the use of antipsychotics.[7] On the other hand, a recent study demonstrated that dopamine function during the prodromal phase might be unstable,[29] suggesting that antipsychotics should be administered to individuals at imminent risk for psychosis. However, the use of antipsychotics during the prodromal phase remains controversial; consequently, antidepressant-controlled studies or further neurochemical remarks on the dopamine system are needed.

CONCLUSIONS

This trial suggests that aripiprazole not only produces a clinical benefit in prodromal subjects but also results in a high adherence to medication, with improvements in insight and subjective well-being. These results also support our hypothesis that adherence to medication might be associated with patient insight and self-experience. Although further placebo-controlled studies are needed, aripiprazole might be a first-line treatment for individuals at imminent risk for psychosis.

AUTHOR DISCLOSURE INFORMATION

The authors declare no funding or conflicts of interest.

REFERENCES

1. Kane JM, Krystal J, Correll CU. Treatment models and designs for intervention research during the psychotic prodrome. *Schizophr Bull.* 2003;29:747–756.
2. Simon AE, Ferrero FP, Merlo MC. Prodromes of first-episode psychosis: how can we challenge nonspecificity? *Compr Psychiatry.* 2001;42:382–392.
3. McGorry PD, Yung AR, Phillips LJ, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry.* 2002;59:921–928.
4. Morrison AP, French P, Walford L, et al. Cognitive therapy for the prevention of psychosis in people at ultra-high risk. Randomized controlled trial. *Br J Psychiatry.* 2004;185:291–297.
5. McGlashan TH, Zipursky RB, Perkins D, et al. Randomized double-blind clinical trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry.* 2006;163:790–799.
6. Woods SW, Martin A, Spector SG, et al. Effects of development on olanzapine adverse events. *J Am Acad Child Adolesc Psychiatry.* 2002;41:1435–1446.
7. Cornblatt BA, Lencz T, Smith CW, et al. Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. *J Clin Psychiatry.* 2007;68:546–557.
8. Ruhrmann S, Bechdolf A, Kuhn KU, et al. Acute effects of treatment for prodromal symptoms for people putatively in a late initial prodromal state of psychosis. *Br J Psychiatry.* 2007;191(suppl 51): 88–95.
9. Woods SW, Tully EM, Walsh BC, et al. Aripiprazole in the treatment of the psychosis prodrome. An open-label pilot study. *Br J Psychiatry.* 2007;191(suppl 51):96–101.
10. Lappin JM, Morgan KD, Valmaggia LR, et al. Insight in individuals with an at risk mental state. *Schizophr Res.* 2007;90:238–244.
11. David A, van Os J, Jones P, et al. Insight and psychotic illness: cross-sectional and longitudinal associations. *Br J Psychiatry.* 1995;167:621–628.
12. Smith TE, Hull JW, Goodman M, et al. The relative influences of symptoms, insight and neurocognition on social adjustment in schizophrenia and schizoaffective disorder. *J Nerv Ment Dis.* 1999;187:102–108.
13. Karow A, Czekalla J, Dittmann RW, et al. Association of subjective well-being, symptoms, and side effects with compliance after 12 months of treatment in schizophrenia. *J Clin Psychiatry.* 2007;68:75–80.
14. Naber D, Karow A, Lambert M. Subjective well-being under the neuroleptic treatment and its relevance for compliance. *Acta Pschiatr Scand Suppl.* 2005;427:29–34.
15. Garavan J, Browne S, Grevin M, et al. Compliance with neuroleptic medication in outpatients with schizophrenia; relationship to subjective response to neuroleptics; attitudes to medication and insight. *Compr Psychiatry.* 1998;39:215–219.
16. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull.* 2003;29: 703–715.
17. Kobayashi H, Nozaki S, Mizuno M. Reliability of the Structured Interview for Prodromal Syndromes Japanese version (SIPS-J). *Jpn Soc Psychiat.* 2005;15:168–174. Japanese.
18. Barnes TRE. A rating scale for drug-induced akathisia. *Br J Psychiatry.* 1989;154:672–676.
19. Naber D, Moritz S, Lambert M, et al. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. *Schizophr Res.* 2001;50:79–88.
20. Watanabe M, Matsumura H. Reliability and validity of Subjective Well-being under Neuroleptic drug treatment Short form, Japanese

version (SWNS-J). *Jpn J Clin Psychopharmacology.* 2003;6:905–912. [in Japanese].

21. Amador XF, Strauss DH, Yale SA, et al. Assessment of insight in psychosis. *Am J Psychiatry.* 1993;150:873–879.
22. Lambert M, Schimmelmann BG, Naber D, et al. Prediction of remission as a combination of symptomatic and functional remission and adequate subjective well-being in 2960 patients with schizophrenia. *J Clin Psychiatry.* 2006;67:1690–1697.
23. Lecomte T, Spidel A, Leclerc C, et al. Predictors and profiles of treatment non-adherence and engagement in services problems in early psychosis. *Schizophr Res.* 2008;102:295–302.
24. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry.* 2002;63:763–771.
25. Keshavan MS, Rabinowitz J, DeSmedt G, et al. Correlates of insight in first episode psychosis. *Schizophr Res.* 2004;70:187–194.
26. Saeedi H, Addington J, Addington D. The association of insight with psychotic symptoms, depression, and cognition in early psychosis: a 3-year follow-up. *Schizophr Res.* 2007;89:123–128.
27. Kim CH, Jayathilake K, Meltzer HY. Hopelessness, neurocognitive function, and insight in schizophrenia: relationship to suicidal behavior. *Schizophr Res.* 2003;60:71–80.
28. Karow A, Pajonk FG, Reimer J, et al. The dilemma of insight into illness in schizophrenia: self- and expert-rated insight and quality of life. *Eur Arch Psychiatry Clin Neurosci.* 2008;258: 152–159.
29. Howes OD, Montgomery AJ, Asselin MC, et al. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry.* 2009;66:13–20.

Progress in Neuro-Psychopharmacology & Biological Psychiatry 33 (2009) 1533–1536

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Cognitive training for divergent thinking in schizophrenia: A pilot study

Takahiro Nemoto [a,b,c,*], Ryoko Yamazawa [a], Hiroyuki Kobayashi [a], Nobuharu Fujita [a], Bun Chino [a], Chiyo Fujii [d], Haruo Kashima [a], Yuri Rassovsky [e], Michael F. Green [c,e], Masafumi Mizuno [f]

[a] Department of Neuropsychiatry, School of Medicine, Keio University, Tokyo, Japan
[b] Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, California, USA
[c] VA Greater Los Angeles Healthcare System, California, USA
[d] Department of Social Work, Saitama Prefectural University, Saitama, Japan
[e] Department of Psychiatry and Biobehavioral Sciences, UCLA Semel Institute for Neuroscience and Human Behavior, California, USA
[f] Department of Neuropsychiatry, School of Medicine, Toho University, Tokyo, Japan

ARTICLE INFO

Article history:
Received 28 July 2009
Received in revised form 26 August 2009
Accepted 26 August 2009
Available online 4 September 2009

Keywords:
Cognitive training
Divergent thinking
Negative symptoms
Schizophrenia
Social functioning

ABSTRACT

Individuals with schizophrenia demonstrate deficits in divergent thinking. This ability is indispensable for generating creative solutions and navigating the complexities of social interactions. In a pilot study, seventeen stable schizophrenia outpatients were randomly assigned to a training program for divergent thinking or a control program on convergent thinking. After eight weeks of training, participants in the divergent thinking program had significantly greater improvements on measures of idea fluency, negative symptoms, and interpersonal relations than did participants receiving the control program. These preliminary results suggest that interventions for divergent thinking in schizophrenia may lead to improvements in patients' social functioning.

1. Introduction

Over the last decade, the connection between cognitive deficits and functional outcome in schizophrenia has been consistently demonstrated (Green, 1996, 2006; Green et al., 2000). These findings have added emphasis to the development of cognitive rehabilitation approaches and their applications to schizophrenia (Bell et al., 2008; Kurtz et al., 2007; McGurk et al., 2007; Twamley et al., 2003; Velligan et al., 2006). We recently suggested that divergent thinking is one neurocognitive skill that deserves consideration as a potential target for intervention (Nemoto et al., 2007). Divergent thinking is typically applied when someone is confronted with questions that do not have a fixed single answer (Guilford, 1967). It is distinguished from convergent thinking, for which a single correct answer can be identified. More than other cognitive domains, divergent thinking is related to negative symptoms (Jaeger et al., 2006). Because most real life situations are unstructured and have no single correct answer for a given problem, intact divergent thinking would appear to be critical for successful social and interpersonal interactions. Consistent with this view, we recently found divergent thinking deficits in patients with schizophrenia using qualitative measures (Mizuno and Kashima, 2002; Nemoto et al., 2005; Yamashita et al., 2005). Also, in a separate study, we found that the impairment in generating high-quality responses on divergent thinking tasks was an important determinant of poor community functioning for patients (Nemoto et al., 2007).

Based on our recent findings of a relationship between divergent thinking and community functioning (Nemoto et al., 2007), we developed a training program specifically for divergent thinking deficits in schizophrenia and evaluated its effects on measures of divergent thinking (e.g. fluency measures), negative symptoms, and social functioning in a pilot study.

2. Methods

2.1. Participants

Seventeen Japanese stable outpatients with schizophrenia (9 men, 8 women) were recruited at 2 psychiatric hospitals (Oizumi Hospital and Jiundo Hospital) in Tokyo, Japan. Two trained psychiatrists diagnosed participants using the ICD-10 criteria (World Health Organization, 1993). The mean age of the patients was 30.3 (SD = 5.6) years, mean number of years of education was 13.0 (SD = 1.9), and mean illness chronicity was 5.4 (SD = 4.7) years from first psychotic symptoms. All patients were taking antipsychotic

Abbreviations: ANOVA, analysis of variance; GAF, Global Assessment of Functioning; ICD-10, International Classification of Diseases, Tenth Revision; PANSS, Positive and Negative Syndrome Scale; SFS, Social Functioning Scale; WAIS-R, Wechsler Adult Intelligence Scale—Revised.

* Corresponding author. Department of Neuropsychiatry, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Tel.: +81 3 3353 1211; fax: +81 3 5379 0187.
E-mail address: nemotaka@aol.com (T. Nemoto).

0278-5846/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2009.08.015

medications. Subjects were excluded if they had a history of alcohol dependence, substance abuse, or a neurological illness. Subjects were selected for right-handedness, as classified by the Edinburgh Inventory (Oldfield, 1971).

2.2. Materials

2.2.1. Cognitive training programs

Tasks that assess divergent thinking abilities present problems that have multiple solutions. Conversely, standard cognitive tasks typically assess convergent thinking, as they commonly have a single correct solution. Using teaching materials designed to improve thinking flexibility (Ito, 2002), we have developed a number of exercises to improve divergent thinking. For example, in the "rock–paper–scissors task" (Fig. 1) participants are asked to extend a single stroke with a pencil connecting icons, "rock," "paper," and "scissors," in that order, for as long as possible. Subjects can find several starting points (i.e. any rock), and there are many ways to extend strokes for each starting point. In addition to the rock–paper–scissors task, we also developed other tasks, including one called the "calculation tiles task." In this task subjects are provided with a grid (8 by 12) in which each cell contained a number ranging from 1 to 9. Subjects were also given several odd-shaped pieces created out of tiles. When placed on the grid, the shapes covered 6 of the numbers. The goal was to place the shapes in a way so that the 6 covered numbers yielded the highest sum. Several alternate versions of each task were constructed.

The control program consisted of making calculations and transcribing kana words into kanji (words were at elementary school level in Japan). Each of these tasks has only one correct answer, and thus involves convergent thinking. We compiled eight workbooks, each of which was to be completed in one week, for each of the two programs.

2.2.2. Outcome measures

The primary outcome measures evaluating divergent thinking included the Idea Fluency Test and the Design Fluency Test (Nemoto et al., 2005). These tests yield two types of indices: a lower level "stereotyped" response, and a "high-quality" response. We were interested in high-quality responses that require a change in viewpoint and flexibility of thinking. An example of a high-quality

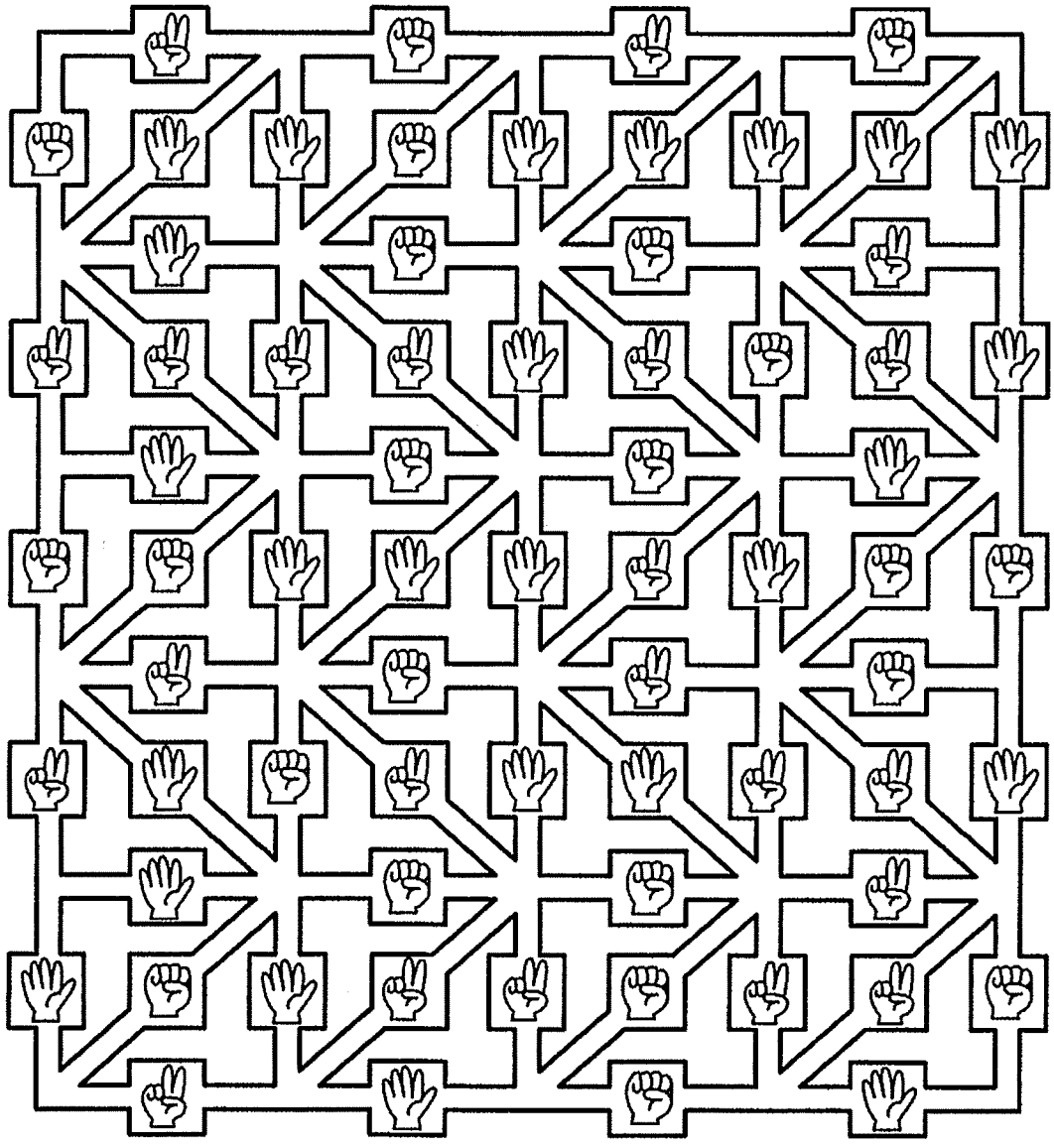

Fig. 1. The "rock–paper–scissors task" is one representative exercise designed to improve divergent thinking.
Reprinted from The Paper Challeran, Ito, R., Rock–paper–scissors task, page 10, 2002, with permission from PHP Institute.

response on the Idea Fluency Test would be if a subject suggests alternative uses of an empty can such as a roller or an ornament. Other fluency measures included the Letter and Category Fluency Tests (Benton, 1968; Kashima et al., 1986), but these tests had no qualitative indices. For each of these we used the total scores (sum of 3 letters at 60 sec each, and 3 categories at 60 sec each) as the dependent measure. Other measures of cognition included the Digit Span Backward of the WAIS-R (Wechsler, 1981), and Trail Making Test Part B (Reitan, 1958).

The Positive and Negative Syndrome Scale (PANSS; positive symptoms, negative symptoms, and general psychopathology subscales; Kay et al., 1987) was used to assess clinical symptoms, and the Social Functioning Scale (SFS; total score, and 7 subscale scores; Birchwood et al., 1990; Nemoto et al., 2008) was used to assess social functioning. In addition, the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) was used to measure global functioning (clinical and social combined). Clinical assessments and neurocognitive tests were administered at baseline and at the end of the eight-week training by raters who were blind to treatment conditions.

2.3. Procedures

Participants were randomly assigned to either the training program for divergent thinking or a control program for convergent thinking. Both training programs were administered as homework for 8 weeks, because the goal was to validate a training program that could be conducted by individuals at a location of their choosing. Each participant received a new workbook weekly and was instructed to practice the tasks for 15 min every day (6 days per week). Research staff interviewed participants each week to assess their compliance with the practice sessions and review their completed homework. Patients were asked how often they practiced, how long per session, and the staff compared the verbal reports to the completed homework to ensure accuracy. All participants demonstrated full compliance with the training. The protocol of the study was approved by the institutional review board of both Oizumi Hospital and Jiundo Hospital and was carried out in accordance with the latest version of the Declaration of Helsinki. After providing a complete description of the study, written informed consent was obtained from every subject.

2.4. Data analyses

The two groups were compared on demographics and baseline cognitive performance using *t*-tests for independent samples when data were normally distributed, and Mann–Whitney *U*-tests when they were not. A 2 by 2 (intervention group by time) repeated measures analysis of variance (ANOVA) was used to evaluate the effectiveness of the training program. The key dependent measures included: 1) high-quality responses on the Idea Fluency Test, 2) high-quality responses on the Design Fluency Test, 3) negative symptoms on the PANSS, 4) total score on the SFS, and 5) GAF. We also considered secondary cognitive and clinical variables, including subscales from the PANSS and SFS. A group by time interaction provided evidence of a treatment effect.

3. Results

3.1. Demographic and cognitive group differences at baseline

No significant differences in gender, age, education, duration of illness, antipsychotic medication dose, and scores on the Mini-Mental State Examination (Folstein et al., 1975) were observed between the two groups (Table 1). Similarly, the groups did not differ significantly at baseline on any of the key dependent measures (see Table 2). Antipsychotic medication was held constant throughout the duration of training.

Table 1
Demographic and clinical characteristics.

	DT training		Controls	
	Mean	SD	Mean	SD
N (male/female)	5/4		4/4	
Age (years)	28.4	5.7	32.4	5.0
Education (years)	12.6	1.9	13.5	1.9
Illness duration (years)	4.6	3.7	6.2	5.8
Medication dose (CPZ equiv)	325.9	302.1	324.1	230.3
MMSE	28.6	1.2	29.6	0.5

CPZ: chlorpromazine, DT: divergent thinking, and MMSE: Mini-Mental State Examination.

3.2. Efficacy of training for divergent thinking

A two-way repeated measures ANOVA showed a significant group by time interaction for the following key dependent variables: high-quality responses on the Idea Fluency Test, negative symptoms, and the GAF score. The results for both groups are summarized in Table 2 and data from the significant measures are graphically presented in Fig. 2. In addition, we found significant treatment effects on some secondary measures, including: the general psychopathology subscale of the PANSS and one component (interpersonal subscale) on the SFS. We found a trend for a treatment effect for category fluency.

4. Discussion

This pilot study evaluated a cognitive training program targeting divergent thinking deficits in schizophrenia. Participants who received the training program for divergent thinking had significantly greater improvements on three of the primary outcome measures (one index of idea fluency, negative symptoms, and the GAF), as well as two secondary measures (general psychopathology, and interpersonal relations) compared with participants in the control program.

To our knowledge, this program is the first intervention that is specifically developed to improve divergent thinking deficits in schizophrenia. An association was previously found between divergent thinking and negative symptoms (Jaeger et al., 2006) and

Table 2
Changes with treatment in cognitive function, psychopathology, and social functioning.

		DT training		Controls		ANOVA	*p*
		Mean	SD	Mean	SD	$F(1,15)$	
Idea Fluency Test	Baseline	4.2	2.3	4.6	4.2		
	Post	7.8	5.9	3.9	3.0	5.670	0.031
Design Fluency Test	Baseline	8.1	7.0	8.8	4.9		
	Post	8.3	7.1	7.3	4.9	0.303	0.590
Letter Fluency Test	Baseline	22.3	9.1	18.3	6.2		
	Post	24.8	11.3	22.4	6.5	0.376	0.549
Category Fluency Test	Baseline	33.2	11.0	33.3	9.6		
	Post	37.6	10.1	31.4	9.3	4.478	0.051
Digit Span	Baseline	7.4	2.8	6.6	1.6		
	Post	6.7	2.7	6.5	2.1	0.420	0.527
Trail Making Test	Baseline	155.2	68.2	155.0	30.0		
	Post	134.8	45.1	152.0	49.0	0.762	0.396
PANSS Positive	Baseline	10.1	4.3	13.0	4.8		
	Post	9.3	3.2	12.8	4.7	0.393	0.540
Negative	Baseline	17.3	4.2	20.6	5.2		
	Post	14.7	6.2	21.1	5.4	9.954	0.007
General	Baseline	30.0	7.5	32.9	7.4		
	Post	25.9	8.7	33.0	8.5	10.021	0.006
SFS Total	Baseline	108.3	20.3	124.8	32.3		
	Post	113.7	24.5	122.8	31.0	1.358	0.262
Interpersonal	Baseline	7.0	3.5	5.9	2.2		
	Post	8.3	4.0	5.9	2.0	8.067	0.012
GAF	Baseline	61.2	10.5	62.1	10.5		
	Post	71.3	17.3	62.3	11.5	11.781	0.004

DT: divergent thinking, PANSS: Positive and Negative Syndrome Scale, SFS: Social Functioning Scale, GAF: Global Assessment of Functioning, and Post: post-training.

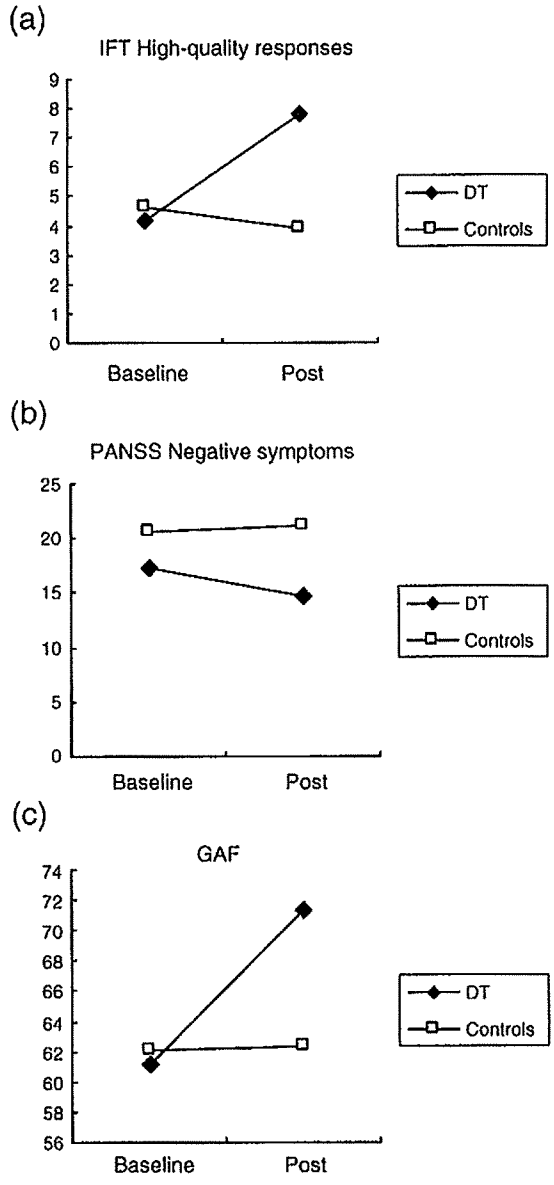

Fig. 2. Changes with treatment in: (a) the number of high-quality responses on the IFT, (b) the PANSS negative symptoms subscale, and (c) the GAF. IFT: Idea Fluency Test, PANSS: Positive and Negative Syndrome Scale, GAF: Global Assessment of Functioning, DT: divergent thinking training, and Post: post-training.

negative symptoms showed improvement in the current study. Given that divergent thinking involves spontaneity and a willingness to energetically engage in a task, it is not unreasonable that it might be linked to negative symptoms. One may speculate that training programs on divergent thinking may encourage a more active cognitive and behavioral style, and this could be reflected in improved negative symptoms.

This small and underpowered pilot study needs to be replicated to determine if the results are reliable. Also, it would be informative to examine this training program in additional clinical populations that have deficits in divergent thinking (e.g., patients with traumatic brain injury). Despite these limitations, the present study offers initial encouragement for improving divergent thinking skills in schizophrenia. Divergent thinking ability is needed for generating creative solutions in the social setting and navigating the complexities of social interactions. Therefore, efforts to improve divergent thinking skills in schizophrenia may be helpful for improving patients' social functioning.

5. Conclusion

This small pilot randomized clinical trial evaluated a cognitive training program targeting divergent thinking deficits in schizophrenia patients. The preliminary results suggest that interventions for divergent thinking in schizophrenia may lead to improvements in negative symptoms and patients' social functioning.

Acknowledgements

We thank Mr. Ryosuke Ito, who kindly consulted on the development of the tasks in the study, and Dr. Jin Hwan Choi for help in interpretation of the data. Funding for this study was provided by a grant to Takahiro Nemoto from the Research Group for Schizophrenia, Japan.

References

American Psychiatric Association. Diagnosis and statistical manual of mental disorders, fourth ed. Washington, DC: American Psychiatric Association; 1994.
Bell MD, Zito W, Greig T, Wexler BE. Neurocognitive enhancement therapy with vocational services: work outcomes at two-year follow-up. Schizophr Res 2008;105:18–29.
Benton AL. Differential behavioral effects in frontal lobe disease. Neuropsychologia 1968;6:53–60.
Birchwood M, Smith J, Cochrane R, Wetton S, Copestake S. The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programs with schizophrenic patients. Br J Psychiatry 1990;157:853–9.
Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state for the clinician. J Psychiatr Res 1975;12:189–98.
Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;153:321–30.
Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry 2006;67(suppl 9):3–8.
Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 2000;26:119–36.
Guilford JP. The nature of human intelligence. New York: McGraw-Hill; 1967.
Ito R. The Paper Challeran. Tokyo: PHP Institute; 2002 [in Japanese].
Jaeger J, Tatsuoka C, Berns SM, Varadi F. Distinguishing neurocognitive functions in schizophrenia using partially ordered classification models. Schizophr Bull 2006;32:679–91.
Kashima H, Handa T, Katoh M, Sakuma K, Muramatsu T, Yoshino A, et al. Disorders of attention due to frontal lobe lesion. Shinkei Kenkyu No Shimpo 1986;30:847–58 [in Japanese].
Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–76.
Kurtz MM, Seltzer JC, Shagan DS, Thime WR, Wexler BE. Computer-assisted cognitive remediation in schizophrenia: what is the active ingredient? Schizophr Res 2007;89:251–60.
McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. Am J Psychiatry 2007;164:1791–802.
Mizuno M, Kashima H. Neuropsychological investigation of the effects of psychiatric rehabilitation strategies for schizophrenia. In: Kashima H, Falloon IRH, Mizuno M, Asai M, editors. Comprehensive treatment of schizophrenia. Tokyo: Springer-Verlag; 2002. p. 20–7.
Nemoto T, Fujii C, Miura Y, Chino B, Kobayshi H, Yamazawa R, et al. Reliability and validity of the Social Functioning Scale Japanese version (SFS-J). Jpn Bull Soc Psychiatry 2008;17:188–95 [in Japanese].
Nemoto T, Kashima H, Mizuno M. Contribution of divergent thinking to community functioning in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:517–24.
Nemoto T, Mizuno M, Kashima H. Qualitative evaluation of divergent thinking in patients with schizophrenia. Behav Neurol 2005;16:217–24.
Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.
Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills 1958;8:271–6.
Twamley EW, Jeste DV, Bellack AS. A review of cognitive training in schizophrenia. Schizophr Bull 2003;29:359–82.
Velligan DI, Kern RS, Gold JM. Cognitive rehabilitation for schizophrenia and the putative role of motivation and expectancies. Schizophr Bull 2006;32:474–85.
Wechsler D. WAIS-R manual. New York: The Psychological Corporation; 1981.
World Health Organization. The ICD-10 classification of mental and behavioural disorders, diagnostic criteria for research. Geneva: World Health Organization; 1993.
Yamashita C, Mizuno M, Nemoto T, Kashima H. Social cognitive problem-solving in schizophrenia: associations with fluency and verbal memory. Psychiatry Res 2005;134:123–9.