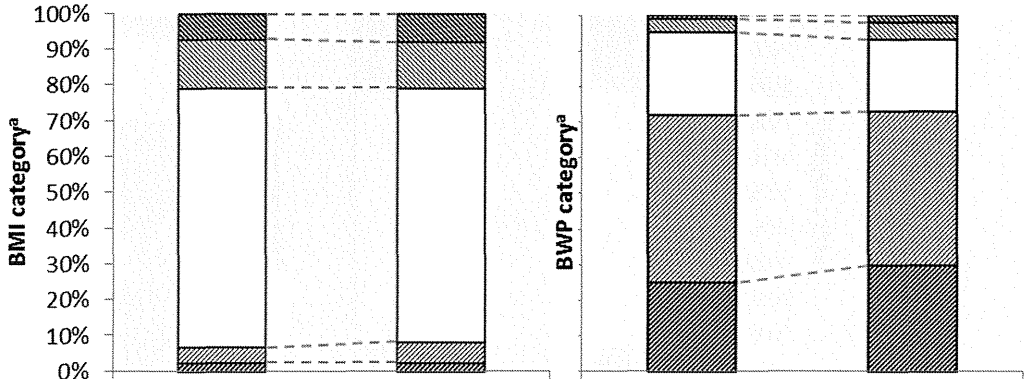

	Uninvolved (n = 5941)	Involved (n = 1440)	Uninvolved (n = 7054)	Involved (n = 1715)
Underweight	7.1	8	0.9	1.9
Slightly underweight	13.6	12.7	4	4.8
Normal weight	72.5	71	23.2	20.4
Slightly overweight	4.2	5.7	47.1	43.1
Overweight	2.6	2.6	24.9	29.7
	Interpersonal violence (within one year)		Interpersonal violence (within one year)	

[a]The number of the missing data were 1715 for BMI and 313 for BWP.

Abbreviations: BMI, body mass index; BWP, body weight perception.

Figure 1. Percentages for the BMI and BWP categories in adolescent females by interpersonal violence perpetration.
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Table 1 presents percentages for demographics and psychological and behavioral problems by violent behavior. Next, Figures 1 and 2 show percentages for the BMI and BWP categories by interpersonal violence perpetration and violence toward objects, respectively. The incidence rates of interpersonal violence perpetration and violence toward objects were 19.6% (1,776/9,065) and 34.9% (3,167/9,068), respectively. Meanwhile, the distribution of the number of diets was as follows: never = 60.2% (n = 5,481), 1 time = 7.4% (n = 670), 2 times = 10.9% (n = 995), 3 times = 8.3% (n = 759), 4 times = 1.5% (n = 134), 5 times = 3.9% (n = 354), 6 times = 0.5% (n = 48), 7 times = 0.2% (n = 20), 8 times = 0.1% (n = 12), 10 times = 1.6% (n = 146), 12 times = 0.0% (n = 2), more than 13 times = 0.8% (n = 74), missing values = 4.6% (n = 417).

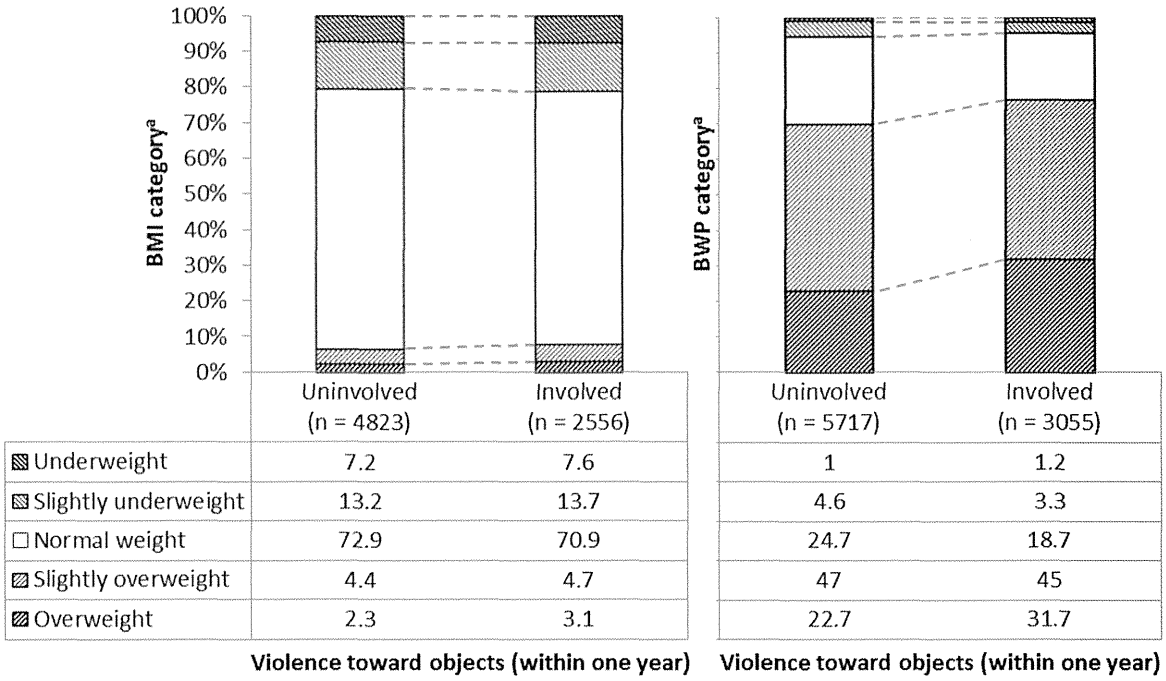
The increased number of diets was associated with the increased prevalence of both interpersonal violence perpetration (OR = 1.18, 95% CI 1.08–1.29, $p<0.001$) and violence toward objects (OR = 1.34, 95% CI 1.24–1.45, $p<0.001$), after adjusting for age, BMI, BWP, the GHQ-12 total score, victimization, and substance use (Table 2). In terms of the categories of BMI and BWP, the "overweight" BWP was associated with violence toward objects (OR = 1.29, 95% CI 1.07–1.54, $p<0.05$). On the other hand, the "Underweight" and "Slightly underweight" BMI were related to violence toward objects [(OR = 1.28, 95% CI 1.01–1.62, $p<0.05$) and (OR = 1.27, 95% CI 1.07–1.51, $p<0.05$), respectively]. The "Underweight" BWP was related to interpersonal violence perpetration (OR = 2.30, 95% CI 1.38–3.84, $p<0.05$). Except for recreational drug use, all other factors were independently associated with both interpersonal violence perpetration and violence toward objects. Recreational drug use was significantly related to interpersonal violence perpetration, but not to violence toward objects.

Discussion

To the best of our knowledge, this is the first study to examine whether repeated dieting is associated with violent behavior. We found a relationship between an increased number of diets and the incidence of interpersonal violence perpetration and violence toward objects in a local representative sample of female adolescents (n = 9,112). The incidence rate of interpersonal violence perpetration (19.6%) in this study was comparable to the rate of the national youth risk behavior survey conducted in the United States (24.4%) [3].

Maladaptive weight-loss behavior accompanied by frequent dieting could have an impact on the occurrence of violence. Maladaptive behavior classified as moderate includes skipping meals, eating a very little amount of food, and using food substitutes. Female dieters with moderate behavior are at risk of developing severe behavior such as self-induced vomiting and the use of laxatives, diuretics, and diet pills [41]. Chronic dieters tend to show severe behavior [42]. The maladaptive weight-loss behavior increase the risk of poor intake of grains, calcium, iron, vitamin B-6, folate, and zinc among female adolescents [43]. Among these nutritional insufficiencies, iron deficiency is the most common and can lead to irritability in young people [44,45]. Accordingly, a lack of basic nutrients resulting from chronic dieting can potentially cause violent behavior.

Apart from weight-control behavior, the perception of being overweight was associated with violent behavior. Dieting was related to not only an overweight condition but also body-image dissatisfaction [30]. Among female adolescents, the perception of



[a]The number of the missing data were 1715 for BMI and 313 for BWP.

Abbreviations: BMI, body mass index; BWP, body weight perception.

Figure 2. Percentages for the BMI and BWP categories in adolescent females by violence toward objects.
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Table 2. Associations between violent behavior and age, the number of diets, BMI, and BWP in adolescent females.[a]

	Interpersonal violence perpetration		*Violence toward objects*	
	Crude OR (95%CI)	**Adjusted OR [b] (95% CI)**	**Crude OR (95%CI)**	**Adjusted OR [b] (95% CI)**
Age	0.80 (0.77–0.82)**	0.76 (0.73–0.79)**	0.93 (0.91–0.96)**	0.85 (0.82–0.88)**
The number of diets (ever)	1.24 (1.16–1.32)**	1.18 (1.08–1.29)**	1.52 (1.43–1.61)**	1.34 (1.24–1.45)**
BMI category				
Underweight	1.13 (0.91–1.40)	1.02 (0.77–1.34)	1.07 (0.89–1.28)	1.28 (1.01–1.62)*
Slightly underweight	0.93 (0.78–1.10)	0.94 (0.76–1.15)	1.04 (0.90–1.20)	1.27 (1.07–1.51)*
Normal weight	1.00	1.00	1.00	1.00
Slightly overweight	1.38 (1.06–1.78)*	1.20 (0.90–1.62)	1.07 (0.85–1.35)	0.92 (0.70–1.19)
Overweight	0.98 (0.69–1.42)	0.93 (0.62–1.40)	1.36 (1.02–1.82)*	1.13 (0.80–1.58)
BWP category				
Underweight	2.14 (1.40–3.27)**	2.30 (1.38–3.84)*	1.21 (0.80–1.82)	1.11 (0.68–1.83)
Slightly underweight	1.24 (0.96–1.59)	1.26 (0.92–1.72)	0.72 (0.57–0.90)*	0.78 (0.58–1.04)
About right	1.00	1.00	1.00	1.00
Slightly overweight	0.85 (0.77–0.95)*	1.01 (0.85–1.19)	0.92 (0.85–1.01)	1.13 (0.98–1.31)
Overweight	1.28 (1.14–1.43)**	1.04 (0.84–1.29)	1.58 (1.43–1.74)**	1.29 (1.07–1.54)*

[a]*The sample size was 6908 for interpersonal violence perpetration and 6903 for violence toward objects depending on the missing date that have been excluded from the statistical analyses.*
[b]ORs adjusted for GHQ-12 total score, being bullied and violence from adults, tobacco and alcohol use, and the use of recreational drugs.
*$p<0.05$;
**$p<0.001$.
Abbreviations: BMI, body mass index; BWP, body weight perception; OR, odds ratio; CI, confidence interval.
doi:10.1371/journal.pone.0107744.t002

being overweight was more common than having a body weight that was considered overweight [14]. This gap can cause dissatisfaction in their body shape and as a result, they begin dieting [46]. The "overweight" BWP is considered to provoke frustration that may be related to violence toward objects. On the other hand, the both actually being underweight and perception of being underweight are associated with violent behavior. These associations suggests that the physical and mental state of low body-weight can relate to irritability [26], emotional dysregulation, poor impulse control [27,28] independently. However, these speculations are weakened by the fact that a large sample size could find statistically significant results, even with small differences. In contrast, the cumulative number of diets showed a consistent and strong relationship with violent behavior.

The present study has several limitations. First, our study design was cross-sectional, which made it impossible to prove a causal connection. It means that violent behavior occurred before the onset of a weight-loss diet among some participants. That is, our results indicate that violent behavior might predict underweight BMI, extreme BWP, and repeated dieting. Second, although the GHQ-12 is a valid measure for the severity of depression and anxiety and the total score was used in logistic regression analysis, the confounding effect of common adolescent psychiatric disorders (i.e. ADHD and conduct disorder [9,12,20,21]) was not taken into account. It is also possible that observed associations are attributed to childhood abuse as a confounding factor [17,18]. This is because victimization, particularly in childhood, is considered as a cause that predisposes female adolescents to both violence perpetration [7,10] and disordered eating [18,47]. In spite of our attempt to control for victimization, this control was not sufficient due to the short investigation period. In addition, we did not handle some violence-related social factors (i.e. low academic performance [6,7] and parent–child and peer relationship [8–10]) as potential confounding factors. Consequently, an over- or under-estimation of the association is possible. Third, because this survey was performed in schools, responses from absent students were unavailable. Young people who are engaged in violent behavior and/or repeated dieting may be more likely to be absent from school than those who are not. Finally, the term "weight-loss diet" was not precisely defined, and thus, it included various methods and periods of weight-loss behaviors that female adolescents subjectively interpreted.

In conclusion, the cumulative number of diets is associated with both interpersonal violence perpetration and violence toward objects in female adolescents. In addition, underweight BMI and extreme BWP are associated with violent behavior. Therefore, this study suggested that the subjective number of diets may be clinically useful as a screening marker for violent behavior in female adolescents. Further prospective studies are required to investigate the mechanism of repeated dieting that can lead to violent behavior in female adolescents.

Author Contributions

Conceived and designed the experiments: SS YO. Performed the experiments: AN SS TS NO. Analyzed the data: NS NW. Wrote the paper: NS TA TAF.

References

1. Krug EG, Mercy JA, Dahlberg LL, Zwi AB (2002) [World report on violence and health]. Biomedica 22 Suppl 2: 327–336.
2. WHO Regional Office for Europe. Social determinants of health and well-being among young people. Health Behaviour in School-aged Children (HBSC) study: international report from the 2009/2010 survey. Available: http://www.hbsc.org/publications/international/. Accessed 7 April 2014.
3. Eaton DK, Kann L, Kinchen S, Shanklin S, Flint KH, et al. (2012) Youth risk behavior surveillance - United States, 2011. MMWR Surveill Summ 61: 1–162.
4. Ministry of Education Culture, Sports, Sceience and Technology Research on issues over teacher guidance with respect to student misbehavior. Available: http://www.mext.go.jp/b_menu/toukei/chousa01/shidou/1267646.htm. Accessed 7 April 2014 (in Japanese).
5. Laufer A, Harel Y (2003) The role of family, peers and school perceptions in predicting involvement in youth violence. Int J Adolesc Med Health 15: 235–244.
6. Swahn MH, Donovan JE (2004) Correlates and predictors of violent behavior among adolescent drinkers. The Journal of adolescent health: official publication of the Society for Adolescent Medicine 34: 480–492.
7. Chang JJ, Chen JJ, Brownson RC (2003) The role of repeat victimization in adolescent delinquent behaviors and recidivism. The Journal of adolescent health: official publication of the Society for Adolescent Medicine 32: 272–280.
8. Blitstein JL, Murray DM, Lytle LA, Birnbaum AS, Perry CL (2005) Predictors of violent behavior in an early adolescent cohort: similarities and differences across genders. Health education & behavior: the official publication of the Society for Public Health Education 32: 175–194.
9. Herrenkohl TI, Maguin E, Hill KG, Hawkins JD, Abbott RD, et al. (2000) Developmental risk factors for youth violence. The Journal of adolescent health: official publication of the Society for Adolescent Medicine 26: 176–186.
10. Resnick MD, Ireland M, Borowsky I (2004) Youth violence perpetration: what protects? What predicts? Findings from the National Longitudinal Study of Adolescent Health. The Journal of adolescent health: official publication of the Society for Adolescent Medicine 35: 424 e421–410.
11. Ellickson PL, Tucker JS, Klein DJ (2001) High-risk behaviors associated with early smoking: results from a 5-year follow-up. The Journal of adolescent health: official publication of the Society for Adolescent Medicine 28: 465–473.
12. Fang X, Massetti GM, Ouyang L, Grosse SD, Mercy JA (2010) Attention-deficit/hyperactivity disorder, conduct disorder, and young adult intimate partner violence. Arch Gen Psychiatry 67: 1179–1186.
13. Neumark-Sztainer D, Hannan PJ (2000) Weight-related behaviors among adolescent girls and boys: results from a national survey. Arch Pediatr Adolesc Med 154: 569–577.
14. Kaneko K, Kiriike N, Ikenaga K, Miyawaki D, Yamagami S (1999) Weight and shape concerns and dieting behaviours among pre-adolescents and adolescents in Japan. Psychiatry Clin Neurosci 53: 365–371.
15. Ojala K, Vereecken C, Valimaa R, Currie C, Villberg J, et al. (2007) Attempts to lose weight among overweight and non-overweight adolescents: a cross-national survey. Int J Behav Nutr Phys Act 4: 50.
16. Neumark-Sztainer D, Paxton SJ, Hannan PJ, Haines J, Story M (2006) Does body satisfaction matter? Five-year longitudinal associations between body satisfaction and health behaviors in adolescent females and males. J Adolesc Health 39: 244–251.
17. Rayworth BB, Wise LA, Harlow BL (2004) Childhood abuse and risk of eating disorders in women. Epidemiology 15: 271–278.
18. Favaro A, Tenconi E, Santonastaso P (2010) The interaction between perinatal factors and childhood abuse in the risk of developing anorexia nervosa. Psychol Med 40: 657–665.
19. Blaine B (2008) Does depression cause obesity? A meta-analysis of longitudinal studies of depression and weight control. J Health Psychol 13: 1190–1197.
20. Yoshimasu K, Barbaresi WJ, Colligan RC, Voigt RG, Killian JM, et al. (2012) Childhood ADHD is strongly associated with a broad range of psychiatric disorders during adolescence: a population-based birth cohort study. J Child Psychol Psychiatry 53: 1036–1043.
21. Cortese S, Angriman M, Maffeis C, Isnard P, Konofal E, et al. (2008) Attention-deficit/hyperactivity disorder (ADHD) and obesity: a systematic review of the literature. Crit Rev Food Sci Nutr 48: 524–537.
22. French SA, Jeffery RW (1994) Consequences of dieting to lose weight: effects on physical and mental health. Health psychology: official journal of the Division of Health Psychology, American Psychological Association 13: 195–212.
23. Pugliese MT, Lifshitz F, Grad G, Fort P, Marks-Katz M (1983) Fear of obesity. A cause of short stature and delayed puberty. N Engl J Med 309: 513–518.
24. Daee A, Robinson P, Lawson M, Turpin JA, Gregory B, et al. (2002) Psychologic and physiologic effects of dieting in adolescents. South Med J 95: 1032–1041.
25. Maeda M, Yamamoto M, Yamauchi K (1999) Prevalence of anemia in Japanese adolescents: 30 years' experience in screening for anemia. Int J Hematol 69: 75–80.
26. French SA, Story M, Downes B, Resnick MD, Blum RW (1995) Frequent dieting among adolescents: psychosocial and health behavior correlates. American journal of public health 85: 695–701.
27. Polivy J (1996) Psychological consequences of food restriction. J Am Diet Assoc 96: 589–592; quiz 593–584.

28. Ackard DM, Croll JK, Kearney-Cooke A (2002) Dieting frequency among college females: association with disordered eating, body image, and related psychological problems. J Psychosom Res 52: 129–136.
29. Stice E, Hayward C, Cameron RP, Killen JD, Taylor CB (2000) Body-image and eating disturbances predict onset of depression among female adolescents: a longitudinal study. Journal of abnormal psychology 109: 438–444.
30. Crow S, Eisenberg ME, Story M, Neumark-Sztainer D (2006) Psychosocial and behavioral correlates of dieting among overweight and non-overweight adolescents. The Journal of adolescent health: official publication of the Society for Adolescent Medicine 38: 569–574.
31. Smith-Khuri E, Iachan R, Scheidt PC, Overpeck MD, Gabhainn SN, et al. (2004) A cross-national study of violence-related behaviors in adolescents. Arch Pediatr Adolesc Med 158: 539–544.
32. Devaud C, Jeannin A, Narring F, Ferron C, Michaud PA (1998) Eating disorders among female adolescents in Switzerland: prevalence and associations with mental and behavioral disorders. Int J Eat Disord 24: 207–216.
33. Nishida A, Tanii H, Nishimura Y, Kajiki N, Inoue K, et al. (2008) Associations between psychotic-like experiences and mental health status and other psychopathologies among Japanese early teens. Schizophr Res 99: 125–133.
34. Himes JH, Hannan P, Wall M, Neumark-Sztainer D (2005) Factors associated with errors in self-reports of stature, weight, and body mass index in Minnesota adolescents. Annals of epidemiology 15: 272–278.
35. Ministry of Education Culture, Sports, Science and Technology School Health Statistical Survey. Available: http://www.mext.go.jp/b_menu/toukei/chousa05/hoken/1268826.htm. Accessed 7 April 2014 (in Japanese).
36. Kato N, Sato K, Takimoto H, Sudo N (2009) Construction of BMI for age references for Japanese children from the 2000 national growth survey. J Jap Auxol 15: 37–44.
37. Goldberg DP, Rickels K, Downing R, Hesbacher P (1976) A comparison of two psychiatric screening tests. The British journal of psychiatry: the journal of mental science 129: 61–67.
38. Kaneita Y, Ohida T, Osaki Y, Tanihata T, Minowa M, et al. (2007) Association between mental health status and sleep status among adolescents in Japan: a nationwide cross-sectional survey. The Journal of clinical psychiatry 68: 1426–1435.
39. Baksheev GN, Robinson J, Cosgrave EM, Baker K, Yung AR (2011) Validity of the 12-item General Health Questionnaire (GHQ-12) in detecting depressive and anxiety disorders among high school students. Psychiatry research 187: 291–296.
40. Doi Y, Minowa M (2003) Factor structure of the 12-item General Health Questionnaire in the Japanese general adult population. Psychiatry and clinical neurosciences 57: 379–383.
41. Neumark-Sztainer D, Wall M, Guo J, Story M, Haines J, et al. (2006) Obesity, disordered eating, and eating disorders in a longitudinal study of adolescents: how do dieters fare 5 years later? J Am Diet Assoc 106: 559–568.
42. Story M, Rosenwinkel K, Himes JH, Resnick M, Harris LJ, et al. (1991) Demographic and risk factors associated with chronic dieting in adolescents. Am J Dis Child 145: 994–998.
43. Neumark-Sztainer D, Hannan PJ, Story M, Perry CL (2004) Weight-control behaviors among adolescent girls and boys: implications for dietary intake. J Am Diet Assoc 104: 913–920.
44. Mansson J, Johansson G, Wiklund M, Baigi A, Marklund B (2005) Symptom panorama in upper secondary school students and symptoms related to iron deficiency. Screening with laboratory tests, questionnaire and interventional treatment with iron. Scand J Prim Health Care 23: 28–33.
45. Ballin A, Berar M, Rubinstein U, Kleter Y, Hershkovitz A, et al. (1992) Iron state in female adolescents. Am J Dis Child 146: 803–805.
46. Suka M, Sugimori H, Yoshida K, Kanayama H, Sekine M, et al. (2005) Body image and body satisfaction play important roles in the path to dieting behavior in Japanese preadolescents: The Toyama birth cohort study. Environ Health Prev Med 10: 324–330.
47. Smolak L, Murnen SK (2002) A meta-analytic examination of the relationship between child sexual abuse and eating disorders. Int J Eat Disord 31: 136–150.

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Regular Article

Effects of risperidone and aripiprazole on neurocognitive rehabilitation for schizophrenia

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Aim: Methods to improve neurocognitive impairments are of important research interest. This study sought to examine the synergistic effects of neurocognitive rehabilitation and antipsychotics for schizophrenia.

Methods: Subjects were 43 patients diagnosed with schizophrenia or schizoaffective disorder in a randomized trial of the effects of neurocognitive rehabilitation or a quasi-randomized experimental trial of supported employment with neurocognitive rehabilitation. We compared the effects of risperidone and aripiprazole in neurocognitive rehabilitation for schizophrenia. Subjects were divided into the following groups: (i) the control-risperidone group (CR group) ($n = 13$); (ii) the rehabilitation-risperidone group (RR group) ($n = 9$); (iii) the control-aripiprazole group (CA group) ($n = 10$); and (iv) the rehabilitation-aripiprazole group (RA group) ($n = 11$). Subjects in the rehabilitation group were engaged in computer-based cognitive exercises (24 sessions) with bridging group (12 sessions) over 12 weeks. Psychiatric symptoms, neurocognitive functioning and social functioning assessments were evaluated at baseline and at 12 weeks.

Results: A two-way ANOVA with neurocognitive rehabilitation and antipsychotic medication as factors revealed a significant interaction effect on motor speed. Working memory and motor speed significantly improved in the RA group compared with the CA group. We found no significant improvements between the CR group and the RR group.

Conclusion: A synergistic effect of neurocognitive rehabilitation and aripiprazole was observed as improvement of motor speed. In patients treated with aripiprazole, neurocognitive rehabilitation appeared to improve working memory and motor speed. Further studies of synergistic effects of neurocognitive rehabilitation and antipsychotic medication are necessary to verify these findings.

Key word: antipsychotic medication, neurocognitive rehabilitation, schizophrenia, synergistic effect.

NEUROCOGNITIVE DEFICITS IN schizophrenia are among the strongest predictors of social outcomes as well as key functional outcome domains, such as the ability to develop social skills and function independently in the community.[1,2] Therefore, methods to improve neurocognitive impairments through pharmacological treatment and cognitive remediation are of important research interest.[3]

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It was generally thought that atypical antipsychotics would improve neurocognitive functioning. But some published reports suggest that the magnitude of neurocognitive functioning for antipsychotics is lower than previously expected. For example, in a double-blind study, antipsychotics, such as olanzapine, quetiapine, and risperidone, produced modest improvement in neurocognitive functioning.[4] In 20 clinical trials for cognitive enhancement, atypical antipsychotic medications moderately improved some aspects of cognitive functioning in patients with schizophrenia.[5]

Next, the influence of neurocognitive rehabilitation on neurocognitive functioning came to attract attention. A meta-analysis was conducted of 26 randomized, controlled trials of cognitive remediation in schizophrenia, including 1151 patients.[6] Cognitive remediation was associated with a medium effect size for cognitive performance.

Then, are there any synergistic effects of cognitive rehabilitation and antipsychotics? And when performing a cognitive rehabilitation, are there differences in the effect of cognitive rehabilitation depending on the type of antipsychotic drugs? A limited number of studies have examined the effects of antipsychotic medications in cognitive remediation. In one study, 36 subjects with treatment-refractory schizophrenia were exposed to a standardized token economy milieu, highly structured training of activities of daily living (ADL) and twice-daily training sessions in social and independent living skills.[7] Subjects taking risperidone and haloperidol showed significant improvements in ADL and neurocognitive performance, and no significant differences were found between groups. Twenty-two schizophrenia patients were randomly allocated to the cognitive remediation group or the intensive occupational therapy group.[8] In both groups, approximately half of the subjects were prescribed either typical antipsychotic or atypical antipsychotic drugs. Cognitive flexibility and memory were found to significantly improve in the cognitive remediation group compared to the intensive occupational therapy group. In the cognitive remediation group, atypical antipsychotics exhibited more improvement in cognitive flexibility than typical antipsychotics, but the difference was not significant.

As mentioned above, it is not yet possible to conclude on the effects of antipsychotics on neurocognitive rehabilitation or the synergistic effects of antipsychotics and neurocognitive rehabilitation. Although the effects of antipsychotics on neurocognitive functioning from the viewpoint of psychopharmacology might be guessed to some extent, this is difficult to demonstrate because of limited previous research findings. First, we carried out the exploratory research of how atypical antipsychotics influence neurocognitive functioning and the synergistic effects of antipsychotics and neurocognitive rehabilitation were observed.

METHODS

Participants

Forty-three outpatients were diagnosed with schizophrenia or schizoaffective disorder and were aged 20–45 years at registration in a randomized trial of the effects of neurocognitive rehabilitation (study 1, $n = 13$) or a quasi-randomized experimental trial of the supported employment with neurocognitive rehabilitation (study 2, $n = 30$). Subjects did not report any of the following: (i) evidence of an organic central nervous system disorder; (ii) a history of drug or alcohol abuse; or (iii) mental retardation. All patients gave written informed consent to participate in the study, according to the procedures, which were approved by the ethics committee at each site. Subjects were engaged in computer-based neurocognitive rehabilitation for 12 weeks. They were divided into the following groups: (i) the control-risperidone group (CR group) ($n = 13$; study 1 $n = 5$, study 2 $n = 8$); the rehabilitation-risperidone group (RR group) ($n = 9$; study 1 $n = 4$, study 2 $n = 5$); (iii) the control-aripiprazole group (CA group) ($n = 10$; study 1 $n = 4$, study 2 $n = 6$); and (iv) the rehabilitation-aripiprazole group (RA group) ($n = 11$; study 1 $n = 0$, study 2 $n = 11$).

Psychiatric symptoms and demographic assessments

All patients were evaluated with the Positive and Negative Syndrome Scale (PANSS). Premorbid intelligence was estimated using the National Adult Reading Test Japanese version (JART).[9,10]

Neurocognitive functioning assessment

The Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) requires less than 35 min to complete in patients with schizophre-

nia.[11,12] The BACS-J has been validated as a reliable and practical scale to evaluate neurocognitive functioning.[12] The verbal memory, working memory, motor speed, category instances, letter fluency, processing speed, and executive function domains were tested. All test measures were converted to standardized z-scores by setting the sample mean of each measure at baseline to zero and the standard deviation to 1.

Social functioning assessment

The Life Assessment Scale for the Mentally Ill (LASMI) was developed to assess disability in daily life or community functioning.[13,14] The LASMI is composed of the following five categories: (i) daily living; (ii) interpersonal relations; (iii) work skills; (iv) endurance and stability; and (v) self-recognition. Each category is composed of several items, with each item being rated on a 5-point scale (no problem = 0 to a serious problem = 4). Lower scores indicate higher degrees of independent living in the community. In our study, the 'Interpersonal Relations' category (LASMI-I) and 'Work' category (LASMI-W) were used.

The above assessment is evaluated by psychiatrists or clinical psychologists.

Study 1

Using a central registration system, participants in six sites were randomized to either a neurocognitive rehabilitation group ($n = 30$) that was immediately treated, or to a wait-list control group ($n = 31$) that waited for 12 weeks before being treated. Subjects were engaged in computer-based cognitive exercises (COGPACK version 6.0 Marker Software, Ladenburg, Germany), which provided practice across a broad range of neurocognitive functions, including attention and concentration, psychomotor speed, learning and memory, and executive functions. The trainers instructed participants about how to complete the cognitive exercises, provided encouragement, and suggested strategies for improving performance on challenging exercises. Sessions required approximately 60 min, with subjects typically completing two sessions per week for 12 weeks. In addition to computer exercises, subjects participated in one session of bridging group per week for 12 weeks. Topics in the bridging group included social skills training and preparation for community living, the role of cognition in job performance and problem-solving about compensatory strategies for dealing with common challenges on the job. Psychiatric symptoms, neurocognitive functioning and social functioning assessments were evaluated at baseline and at 12 weeks.

Study 2

The subjects took part in quasi-randomized experimental trials in 11 sites. Depending on recruitment periods, subjects were assigned to either a supported employment alone group ($n = 57$) or to a supported employment with neurocognitive rehabilitation group ($n = 52$). During the assessment phase, a thorough cognitive assessment of the participants was conducted, as well as recording a detailed employment history. During the cognitive training phase, subjects were engaged in two sessions of the same cognitive training per week for 12 weeks and took part in one session of bridging group per week for 12 weeks, as in study 1. During the job search planning phase, the supported employment specialist and participants met together to plan the job search, based on the participant's vocational preference. Following job attainment, the cognitive training specialist and subject discussed job support strategies to enhance the transfer of cognitive skills in the computer training exercises, and to minimize the effects of any persisting cognitive impairments. Psychiatric symptoms, neurocognitive functioning and social functioning assessments were evaluated at baseline and at 12 weeks.

Subjects extracted from study 1 or study 2 for this analysis

We defined antipsychotic medication as a participants' main drug treatment if it accounted for more than 70% of chlorpromazine mg equivalents (CPZeq) dose at baseline.[15] The four groups were made up of patients for whom 70% of CPZeq dose was risperidone or aripiprazole. Subjects were excluded if they exhibited any of the following: (i) the main drug was changed by more than 30% of CPZeq dose during cognitive training; or (ii) biperiden mg equivalents (BPDeq) dose was changed during cognitive training.

Statistical analyses

Group differences of demographic characteristics, psychiatric symptoms and neurocognitive function-

ing at baseline were examined with one-way ANOVA and Bonferroni tests. Two-way ANOVA with neurocognitive rehabilitation and antipsychotic medications as factors was used to compare changes in PANSS, BACS-J, and LASMI scores for 12 weeks. One-way ANOVA was used to compare changes in PANSS, BACS-J, and LASMI during 12 weeks between the CR group and the RR group or between the CA group and the RA group.

RESULTS

Demographic data (Table 1)

The results revealed no significant difference in demographic characteristics or psychiatric symptoms or neurocognitive functioning at baseline between the four groups. The mean duration of illness was 152.00 ± 71.51 months in the CR group, 126.00 ± 98.33 months in the RR group, 132.00 ± 81.58 months in the CA group, and 115.64 ± 89.20 months in the RA group.

Comparison of integrated effect of neurocognitive rehabilitation and antipsychotic medication (Table 2)

A two-way ANOVA with neurocognitive rehabilitation and antipsychotic medication as factors revealed a significant interaction effect on motor speed ($F = 4.38$, $P \leq 0.05$). However, there were no main effects on motor speed. We found no significant interaction effect on social function and psychiatric symptoms.

We examined the effects of aripiprazole or risperidone on neurocognitive rehabilitation. Working memory ($F = 12.5$, $P \leq 0.01$) and motor speed ($F = 5.81$, $P \leq 0.05$) were significantly improved in the RA group compared with the CA group. We

Table 1. Demographic data, psychiatric symptoms and neurocognitive functioning at baseline

	CR group $n = 13$		RR group $n = 9$		CA group $n = 10$		RA group $n = 11$		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F
Age (years)	33.85	7.28	36	6.52	38.5	4.4	35.09	7.82	0.95
Duration of illness (months)	152	71.51	126	98.33	132	81.58	115.64	89.2	0.38
CPZeq (mg per day)	474.23	297.33	461.11	479.44	395	230.58	363.71	215.56	0.32
BPDeq (mg per day)	1.31	1.84	0.67	1.12	0.1	0.32	0.45	0.82	2.01
JART (score)	102.27	10.91	99.44	12.22	101.2	9.21	101.18	10.85	0.06
PANSS score									
Positive symptoms	11.77	3.7	11.33	5.1	10.3	4	13.64	3.56	1.25
Negative symptoms	16.31	4.79	13.56	4.33	15.6	5.23	19.36	4.57	2.60
General psychology	26.92	10.36	25.22	6.69	28.8	8.48	34.09	8.34	2.04
Total	55	17.92	50.11	14.41	54.7	15.69	67.09	13.54	2.25
BACS (Z-score)									
Verbal memory	0.09	0.58	0.38	0.7	0.13	0.82	−0.01	0.86	0.48
Working memory	−0.09	0.89	0.63	1.33	0.52	1.25	0.05	0.94	1.10
Motor speed	−0.23	0.98	0.28	0.89	0.44	0.64	−0.43	0.71	2.63
Verbal fluency	0.03	1.3	0.5	0.87	−0.06	0.6	−0.33	1.35	0.95
Processing speed	0.33	1.15	0.09	0.97	−0.12	0.84	−0.27	0.91	0.81
Executive functions	−0.62	1.54	−0.43	1.45	0.28	0.73	0.41	0.68	2.09
Composite score	−0.06	0.82	0.29	0.65	0.14	0.47	−0.11	0.77	0.70

BACS, Brief Assessment of Cognition in Schizophrenia; BPDeq, biperiden mg equivalents; CA group, control-aripiprazole group; CPZeq, chlorpromazine mg equivalents; CR group, control-risperidone group; JART, National Adult Reading Test Japanese version; PANSS, Positive and Negative Syndrome Scale; RA group: rehabilitation-aripiprazole group; RR group, rehabilitation-risperidone group.

Table 2 Synergistic effect of neurocognitive rehabilitation and antipsychotic medication

	Drug	Control		Rehabilitation		F		
		Mean	SD	Mean	SD	Rehabilitation	Drug	Drug×rehabilitation
PANSS								
Positive symptoms	RIS	−0.92	1.38	−1.67	1.58	4.30*	2.68	1.31
	APZ	1.30	2.00	−1.27	4.29			
Negative symptoms	RIS	−1.15	2.38	−1.56	1.33	0.55	0.37	0.08
	APZ	−0.40	2.80	−1.27	3.88			
General psychology	RIS	−0.54	4.35	−2.56	2.01	3.23	0.03	0.32
	APZ	0.70	5.48	−3.18	7.61			
Total score	RIS	−2.62	6.33	−5.78	3.70	3.90	0.65	0.61
	APZ	1.60	8.98	−5.73	12.59			
LASMI								
Interpersonal relations	RIS	−1.92	3.04	−4.22	6.83	1.97	1.22	0.02
	APZ	−0.50	5.02	−2.36	4.43			
Work	RIS	−0.85	1.14	−2.33	4.09	4.56*	0.32	0.58
	APZ	0.60	4.01	−2.55	4.37			
BACS (Z-score)								
Verbal memory	RIS	0.18	1.10	0.43	0.45	0.87	0.39	0.01
	APZ	0.35	0.46	0.57	0.90			
Working memory	RIS	0.19	0.94	0.35	0.74	3.85	6.07*	1.50
	APZ	−0.60	0.60	0.08	0.23			
Motor speed	RIS	0.56	0.67	0.40	0.43	1.43	1.47	4.38*
	APZ	−0.01	0.42	0.55	0.62			
Verbal fluency	RIS	0.04	0.88	0.39	0.77	0.28	0.72	0.82
	APZ	0.47	0.65	0.38	0.86			
Processing speed	RIS	−0.10	0.38	0.36	0.69	3.47	1.16	1.64
	APZ	0.25	0.42	0.33	0.42			
Executive functions	RIS	0.28	1.45	0.74	0.35	0.13	0.95	1.64
	APZ	0.37	0.45	0.11	0.62			
Composite score	RIS	0.16	0.41	0.40	0.31	2.95	0.02	0.22
	APZ	0.20	0.32	0.33	0.33			

Two-way factorial ANOVA.
*$P < 0.05$.
APZ, aripiprazole; BACS, Brief Assessment of Cognition in Schizophrenia; LASMI, Life Assessment Scale for the Mentally Ill; PANSS, Positive and Negative Syndrome Scale; RIS, risperidone.

found no significant improvements between the CR group and the RR group.

DISCUSSION

Synergistic effect of neurocognitive rehabilitation and antipsychotic medication

The synergistic effect of neurocognitive rehabilitation and aripiprazole was observed as an improvement of motor speed. No previous studies have examined the synergistic effect of neurocognitive rehabilitation and antipsychotic medication, including aripiprazole, and little research has examined the different neurocognitive effects of aripiprazole and risperidone. In a 12-month, open-label study, 698 patients with early-stage schizophrenia who were prescribed antipsychotics were assessed at baseline and at 12 months.[16] Risperidone and aripiprazole demonstrated greater improvements on the composite score, processing speed, working memory, executive functioning and visual memory at 12 months. There was no significant difference in improvement across all neurocognitive domains between risperidone and

aripiprazole. In another previous study, a total of 129 patients with schizophrenia participating in two double-blind trials and one open-label trial comparing the effects of different atypical antipsychotics on cognition were assessed at admission and at 8 weeks.[17] Significant improvements in reaction time and cognition index were observed following risperidone treatment. Reaction time, reaction quality and cognition index significantly improved with aripiprazole treatment. In contrast, the study reported no significant differences in cognition index improvement between the risperidone and aripiprazole group. The details of the different neurocognitive effects of risperidone and aripiprazole are currently unclear. In one study, 85 inpatients with schizophrenia were randomly assigned to a cognitive remediation group or to a control condition.[18] Cognitive remediation was found to be associated with significant improvements on motor speed, verbal learning, and memory for 12 weeks. The integrated effect of neurocognitive rehabilitation and aripiprazole might be expected to improve motor speed. According to the findings of our present study, we plan to expand the scope of the present preliminary investigations by randomized controlled trial in future.

Effects of neurocognitive rehabilitation in aripiprazole

Working memory and motor speed significantly improved in the RA group compared with the CA group. Few previous studies have examined the neurocognitive effects of aripiprazole. Aripiprazole was reported to demonstrate greater improvement in composite scores, processing speed, working memory, executive functioning and visual memory at 12 months.[16] Aripiprazole is reported to exhibit a partial agonistic effect against the dopamine D_2 receptor, and has a lower risk of extrapyramidal syndromes than other antipsychotics.[19,20] In aripiprazole, the effect of neurocognitive rehabilitation might result in improvement of motor speed and working memory.

Effect of neurocognitive rehabilitation in risperidone

We found no significant improvements between the CR group and the RR group. A previous meta-analysis suggested that effect sizes for processing speed, working memory, learning, and delayed recall in risperidone were significant. In contrast, improvements in verbal fluency, vigilance and selective attention were found to be greater following quetiapine and olanzapine treatment, compared with risperidone.[21] In one study, patients with schizophrenia were randomly assigned to receive treatment with either quetiapine ($n = 73$) or risperidone ($n = 97$) for an 8-week period.[22] Scores on Part A of the Trail-making Test were significantly improved with risperidone compared with quetiapine. In one double-blind 14-week trial, schizophrenia patients were assigned to receive risperidone ($n = 26$), olanzapine ($n = 26$), clozapine ($n = 24$) or haloperidol ($n = 25$).[23] Risperidone yielded significant improvements in processing speed and attention ($P < 0.03$), but there were no significant differences between medication types. Among patients receiving risperidone, the effect of neurocognitive rehabilitation might result in improvement of processing speed. In future, we plan to examine the effects of neurocognitive rehabilitation in risperidone or aripiprazole to replicate the findings of this research, examining a greater number of subjects and using randomized trials of intervention and antipsychotic medication.

Limitations

The current study involves a number of potential limitations. First, the sample size was small. Second, the raters were not blind, meaning there is a possibility that some raters may have expected the neurocognitive rehabilitation group to exhibit more psychiatric symptoms, neurocognitive functioning and social functioning. Third, study 1 and 2 did not involve randomization of antipsychotic medication. Finally, all groups were prescribed an antipsychotic drug as their main treatment, but were not necessarily receiving only one drug. It will be important to further examine these findings, using randomized trials of intervention, with subjects prescribed a single antipsychotic medication.

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REFERENCES

1. Harvey PD, Howanitz E, Parrella M *et al.* Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: A comparison across treatment sites. *Am. J. Psychiatry* 1998; **155**: 1080–1086.
2. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am. J. Psychiatry* 1996; **153**: 321–330.
3. Milev P, Ho BC, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow-up. *Am. J. Psychiatry* 2005; **162**: 495–506.
4. Keefe RS, Sweeney JA, Gu H *et al.* Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: A randomized, double-blind 52-week comparison. *Am. J. Psychiatry* 2007; **164**: 1061–1071.
5. Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am. J. Psychiatry* 2001; **158**: 176–184.
6. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. *Am. J. Psychiatry* 2007; **164**: 1791–1802.
7. Liberman RP, Gutkind D, Mintz J *et al.* Impact of risperidone versus haloperidol on activities of daily living in the treatment of refractory schizophrenia. *Compr. Psychiatry* 2002; **43**: 469–473.
8. Wykes T, Reeder C, Corner J, Williams C, Everitt B. The effects of neurocognitive remediation on executive processing in patients with schizophrenia. *Schizophr. Bull.* 1999; **25**: 291–307.
9. Nelson HE, O'Connell A. Dementia: The estimation of premorbid intelligence levels using the new adult reading test. *Cortex* 1978; **14**: 234–244.
10. Matsuoka K, Uno M, Kasai K, Koyama K, Kim Y. Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: Japanese version of National Adult Reading Test. *Psychiatry Clin. Neurosci.* 2006; **60**: 332–339.
11. Keefe RS, 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.* 2004; **68**: 283–297.
12. Kaneda Y, Sumiyoshi T, Keefe R, Ishimoto Y, Numata S, Ohmori T. Brief assessment of cognition in schizophrenia: Validation of the Japanese version. *Psychiatry Clin. Neurosci.* 2007; **61**: 602–609.
13. Iwasaki S, Miyauchi M, Oshima I *et al.* The development of Life Assessment Scale for the Mentally Ill: An assessment of the reliability. *Seishin Igaku* 1994; **36**: 1139–1151 (in Japanese).
14. Nemoto T, Kashima H, Mizuno M. Contribution of divergent thinking to community functioning in schizophrenia. *Prog. Neuropsychopharmacol Biol. Psychiatry* 2007; **31**: 517–524.
15. Ikebuchi E, Suzuki H, Ando N *et al.* Effects of atypical antipsychotics in a program improving insight into schizophrenia. *Seishin Igaku* 2007; **49**: 607–617 (in Japanese).
16. Guo X, Zhai J, Wei Q *et al.* Neurocognitive effects of first- and second-generation antipsychotic drugs in early-stage schizophrenia: A naturalistic 12-month follow-up study. *Neurosci. Lett.* 2011; **503**: 141–146.
17. Riedel M, Schennach-Wolff R, Musil R *et al.* Neurocognition and its influencing factors in the treatment of schizophrenia-effects of aripiprazole, olanzapine, quetiapine and risperidone. *Hum. Psychopharmacol.* 2010; **25**: 116–125.
18. Lindenmayer JP, MuGurk SR, Mueser KT *et al.* A randomized controlled trial of cognitive remediation among inpatients with persistent mental illness. *Psychiatry Serv.* 2008; **59**: 241–247.
19. Lawler CP, Prioleau C, Lewis MM *et al.* Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. *Neuropsychopharmacology* 1999; **20**: 612 – 627.
20. Potkin SG, Saha AR, Kujawa MJ *et al.* Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch. Gen. Psychiatry* 2003; **60**: 681–690.
21. Woodward ND, Purdon SE, Meltzer HY, Zald DH. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *Int. J. Neuropsychopharmacol.* 2005; **8**: 457–472.
22. Harvey PD, Patterson TL, Potter LS, Zhong K, Brecher M. Improvement in social competence with short-term atypical antipsychotic treatment: A randomized, double-blind comparison of quetiapine versus risperidone for social competence, social cognition, and neuropsychological functioning. *Am. J. Psychiatry* 2006; **163**: 1918–1925.
23. Bilder RM, Goldman RS, Volavka J *et al.* Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. *Am. J. Psychiatry* 2002; **159**: 1018–1028.

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Efficacy and safety of aripiprazole once-monthly in Asian patients with schizophrenia: A multicenter, randomized, double-blind, non-inferiority study versus oral aripiprazole

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ABSTRACT

Objective: This study was designed to evaluate efficacy and safety of aripiprazole once-monthly (AOM) by verifying non-inferiority of AOM to oral aripiprazole in Asian patients with schizophrenia.
Method: The study consisted of a screening phase and three phases: an oral conversion phase (≤12 weeks), an oral stabilization phase (≤12 weeks) and a 52-week double-blind phase. Patients meeting stabilization criteria for 4 weeks during the oral stabilization phase were randomly assigned (1:1) to AOM (400 mg) or oral aripiprazole (6–24 mg/day). The primary endpoint was Kaplan–Meier estimated rate of non-exacerbation of psychotic symptoms/non-relapse at Week 26.
Results: A total of 724 patients were screened, and 502 patients entered the oral stabilization phase. Of 455 patients randomized in the double-blind phase, 228 received AOM and 227 received oral aripiprazole. The non-exacerbation of psychotic symptoms/non-relapse rates at Week 26 were 95.0% (AOM) and 94.7% (oral aripiprazole) and the difference was 0.3% (95% CI: −3.9,4.5), thus non-inferiority of AOM compared to oral aripiprazole with respect to non-exacerbation of psychotic symptoms/non-relapse rate was shown with a margin of −3.9% which is well above the pre-defined non-inferiority limit (−15%). The proportions of patients meeting exacerbation of psychotic symptoms/relapse criteria and stabilization of psychotic symptoms/maintenance criteria were 6.6% and 92.5% in both groups. Discontinuation rates due to all reasons were 25.9% (AOM) and 33.5% (oral aripiprazole). AOM was well tolerated as well as oral aripiprazole.
Conclusions: Non-inferiority of AOM to oral aripiprazole was established. AOM is efficacious in maintenance treatment of stabilized schizophrenia, with comparable efficacy and tolerability to oral aripiprazole.
Clinical Trials Registration: JapicCTI-101175

1. Introduction

Schizophrenia is a chronic disease, and maintenance treatment to keep stabilization of symptoms is important as well as acute treatment. In addition, continuation of the medication is essential for relapse prevention. However, adherence to medication is difficult in patients with schizophrenia because of lack of insight, cognitive impairment and drug-related side effects. There are some reports that discontinuation of medication and poor adherence increase risk of relapse or hospitalization (Robinson et al., 1999; Higashi et al., 2013). Long-acting injectable antipsychotics provide the potential for improvement in adherence to medication and reduction of relapse in schizophrenic patients.

Aripiprazole is a second generation antipsychotic with a partial agonism at dopamine D_2 receptors and serotonin 5-HT_{1A} receptors and an antagonism at 5-HT_{2A} receptors (Burris et al., 2002). Aripiprazole is approved for treatment of schizophrenia in more than 65 countries

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including the USA, the EU and Japan. Aripiprazole has demonstrated efficacy in acute and long-term treatment and low incidence of side effects, metabolic side effects, and changes in weight (Kasper et al., 2003; Marder et al., 2003; Potkin et al., 2003). Furthermore, oral aripiprazole has indicated to be effective for prevention of relapse in patients with chronic, stable schizophrenia (Pigott et al., 2003). Thus, aripiprazole is a suitable long-term treatment options for schizophrenia.

Aripiprazole long-acting injectable offers a continuous medication delivery with a favorable dosing interval to maintain symptom stability and prevent relapse as well as rehospitalization. Indeed, aripiprazole once-monthly is approved for maintenance treatment of schizophrenia in the USA, Canada, and the EU. In a phase III study, time to impending relapse was significantly delayed with 400 mg of aripiprazole once-monthly compared with placebo (Kane et al., 2012). In a second phase III study, non-inferiority of aripiprazole once-monthly to oral aripiprazole was demonstrated, and the proportion of patients meeting impending-relapse criteria was significantly higher in patients treated with a sub-therapeutic dose of 50 mg of aripiprazole once-monthly than in patients treated with either 400 mg of aripiprazole once-monthly or oral aripiprazole (Fleischhacker et al., 2014).

The Aripiprazole Long-acting Formulation Psychiatry Asian (ALPHA) study was designed to evaluate efficacy of aripiprazole once-monthly by verifying non-inferiority of aripiprazole once-monthly, the long-acting injectable, to oral aripiprazole as well as assess its safety profile in Asian stabilized patients with schizophrenia. The results of the trial were intended for the regulatory submission of aripiprazole once-monthly for treatment of schizophrenia in Japan.

2. Materials and methods

2.1. Study design

This multicenter, randomized, double-blind, non-inferiority study was conducted at 91 sites in Japan, Malaysia, Taiwan, and the Philippines between July 2010 and June 2013, in accordance with the Declaration of Helsinki. Prior to study entry, written informed consent was obtained from all patients, if required, from legally acceptable representatives.

The study consisted of a screening phase and three phases: an oral conversion phase (phase 1, up to 12 weeks), an oral stabilization phase (phase 2, up to 12 weeks) and a double-blind phase (phase 3, 52 weeks). Eligibility was determined during the screening phase. In the oral conversion phase, patients were switched from other antipsychotic(s) to oral aripiprazole monotherapy (6–24 mg/day, once or twice a day) within 12 weeks. In the oral stabilization phase, patients were stabilized on oral aripiprazole (6–24 mg/day once daily) and stabilization of psychotic symptoms/maintenance for 4 weeks was confirmed. The stabilization criteria were defined as meeting all of the following criteria for 4 consecutive weeks: 1) Outpatient status; 2) Positive and Negative Syndrome Scale (PANSS; 1–7 rating system, Kay et al., 1987) total score ≤80; 3) lack of specific psychotic symptoms on the PANSS, as measured by a score of <4 (moderate) on each of the following items: conceptual disorganization (P2), suspiciousness (P6), hallucinatory behavior (P3), and unusual thought content (G9); 4) Clinical Global Impressions-Severity (CGI-S; Guy, 1976a) score of <4 (moderately ill); and 5) Clinical Global Impressions-Severity of Suicidality (CGI-SS) score of <2 (mildly suicidal) on part 1 and <5 (minimally worsened) on part 2.

Patients meeting stabilization criteria for 4 weeks during the oral stabilization phase were randomized 1:1 to either aripiprazole once-monthly group or oral aripiprazole group using permuted block method according to the instruction of the Interactive Voice Response System or the Interactive Web Response System. In the aripiprazole once-monthly group, aripiprazole once-monthly was administered into the gluteal muscle once every 4 weeks, over 52 weeks (13 times in total) using a double-dummy design. The starting dose of aripiprazole once-monthly was 400 mg in all patients. However, patients could have a single decrease to aripiprazole once-monthly 300 mg and could have their dose increased back to 400 mg, if needed. Placebo tablets were administered once daily, however, for only 2 weeks after the start of the double-blind phase, aripiprazole tablets were concomitantly administered at dose of either 6 or 12 mg/day that corresponded with the dose of oral aripiprazole used at the end of the oral stabilization phase, to maintain the plasma concentration of aripiprazole. That is, 6 mg/day was administered in patients receiving either 6 or 12 mg/day at the end of the oral stabilization phase, and 12 mg/day was used in patients receiving either 18 or 24 mg/day at the end of the oral stabilization phase. The dose range for the oral aripiprazole (6–24 mg/day) is in accordance with the aripiprazole label in Japan.

In the oral aripiprazole group, aripiprazole tablets were orally administered once daily for 52 weeks at the dose administered at the end of the oral stabilization phase. The dose could be reduced once by 6 mg/day from Week 4 and the dose could be increased back to the original dose if needed. Placebo injectable was administered once every 4 weeks.

In the double-blind phase, the treatment allocation code for the administration of the investigational product was double-blind, meaning that the investigators and the subjects did not know whether the treatment group was the aripiprazole once-monthly group or the oral aripiprazole group. The sponsor's trial personnel, such as those involved in monitoring (blinded), data management, or data analysis, did not access to the treatment allocation code during the conduct of the trial. Only the subject enrollment center had access to the treatment allocation code for this trial, only if it is needed in an emergency.

2.2. Patients

2.2.1. Inclusion criteria

Patients eligible for enrollment in the screening phase were required to be 18 years of age or over and met the Diagnostic and Statistical Manual of Mental health Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for schizophrenia as a diagnosis. Patients were also required to have had a Body Mass Index (BMI) of 18.5–35.0.

Patients in the oral stabilization phase (phase 2) were required to meet any of the following: 1) patients who were able to complete conversion to aripiprazole tablet monotherapy within 12 weeks after the start of phase 1, 2) patients receiving aripiprazole monotherapy at time of informed consent, 3) patients considered to be capable of receiving aripiprazole tablet monotherapy and who had not received any antipsychotics for at least 12 weeks, at time of informed consent. In addition, patients were adjusted appropriately to"prohibited concomitant medications" and "restricted concomitant medications" requirements stipulated in this protocol.

Patients in the double-blind phase (phase 3) were required to meet the stabilization criteria as stated above.

2.2.2. Exclusion criteria

Patients were excluded if they: had a DSM-IV-TR diagnosis other than schizophrenia; had a complication or a history of diabetes, diabetic ketoacidosis, or diabetic coma; had liver, kidney, heart or hematopoietic organ dysfunction; or were lactating or pregnant. In addition, patients were excluded if they had a complication or a history of polydipsia, Parkinson's disease, tardive dyskinesia, neuroleptic malignant syndrome, rhabdomyolysis, paralytic ileus, alcohol dependence or drug abuse, suicide attempt or self-injury, cerebral vascular disorder, convulsive disorders including epilepsy, organic brain disorder, agranulocytosis or granulocytopenia, or other complications. Patients who had received electroconvulsive therapy within 12 weeks prior to informed consent, who had participated in any other clinical trials within 24 weeks prior to informed consent, for whom clozapine had been ineffective or had responded only to clozapine, and who had been

judged by the investigator or subinvestigator to be inappropriate for inclusion in this trial for any other reasons were excluded.

2.3. Assessments

The primary efficacy endpoint was the non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 in the double-blind phase calculated by Kaplan–Meier method. Exacerbation of psychotic symptoms/relapse was defined as meeting any of the following 4 criteria:

1) CGI-I score of ≥5 (minimally worse) and A {an increase on any of 4 individual PANSS items [conceptual disorganization (P2), hallucinatory behavior (P3), suspiciousness (P6), unusual thought content (G9)] to a score of ≥5 (moderate severe) with an absolute increase of ≥2 on that specific item since randomization} or B [an increase on any of those PANSS items to a score of ≥5 (moderate severe) and an absolute increase of ≥4 on the combined score of those items since randomization].
2) Hospitalization due to exacerbation of psychotic symptoms.
3) CGI-SS score of 4 (severely suicidal) or 5 (attempted suicide) on part 1 and/ or 6 (much worse) or 7 (very much worse) on part 2.
4) Violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

It is reasonable to support that non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 is an endpoint because it was verified that the time to relapse was significantly longer for aripiprazole compared with placebo for 26 weeks (Pigott et al., 2003). When exacerbation of psychotic symptoms/relapse criteria was met during the double-blind phase (52 weeks), the trial was discontinued at that point.

The secondary endpoints were the following items in the double-blind phase: time to exacerbation of psychotic symptoms/relapse, non-exacerbation/non-relapse rate at each time point other than Week 26, mean change in PANSS total score and each subscale total score, proportion of patients meeting exacerbation of psychotic symptoms/relapse criteria, proportion of patients meeting stabilization of psychotic symptoms/maintenance criteria, proportion of patients achieving remission [a score of ≤3 on each of the following specific PANSS items, maintained for a period of 6 months: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), blunted affect (N1), passive/apathetic social withdrawal (N4), lack of spontaneity and flow of conversation (N6), mannerisms and posturing (G5), unusual thought content (G9)], mean change in CGI-S score, mean CGI-I score, and time to discontinuation due to any reason.

In addition, mean change in MOS 36-Item Short-Form Health Survey (SF-36) was used to assess quality of life (Fukuhara et al. 1998a, b).

Safety was evaluated by adverse events (AEs), clinical laboratory tests (including prolactin levels), vital signs, body weight, 12-lead electrocardiography, Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS; Inada, 2009), Abnormal Involuntary Movement Scale (AIMS; Guy, 1976b), Barnes Akathisia Rating Scale (BARS; Barnes, 1989), CGI-SS, Columbia Suicidal Severity Rating Scale (C-SSRS), injection site reaction, and self-assessment of injection site pain [visual analog scale (VAS)].

2.4. Statistical analyses

The primary efficacy sample included all patients who had received at least one dose of double-blind study medication and for whom the post-dosing efficacy parameter data had been obtained. The safety sample included randomized patients who had received at least one dose of double-blind study medication and for whom the post-dosing

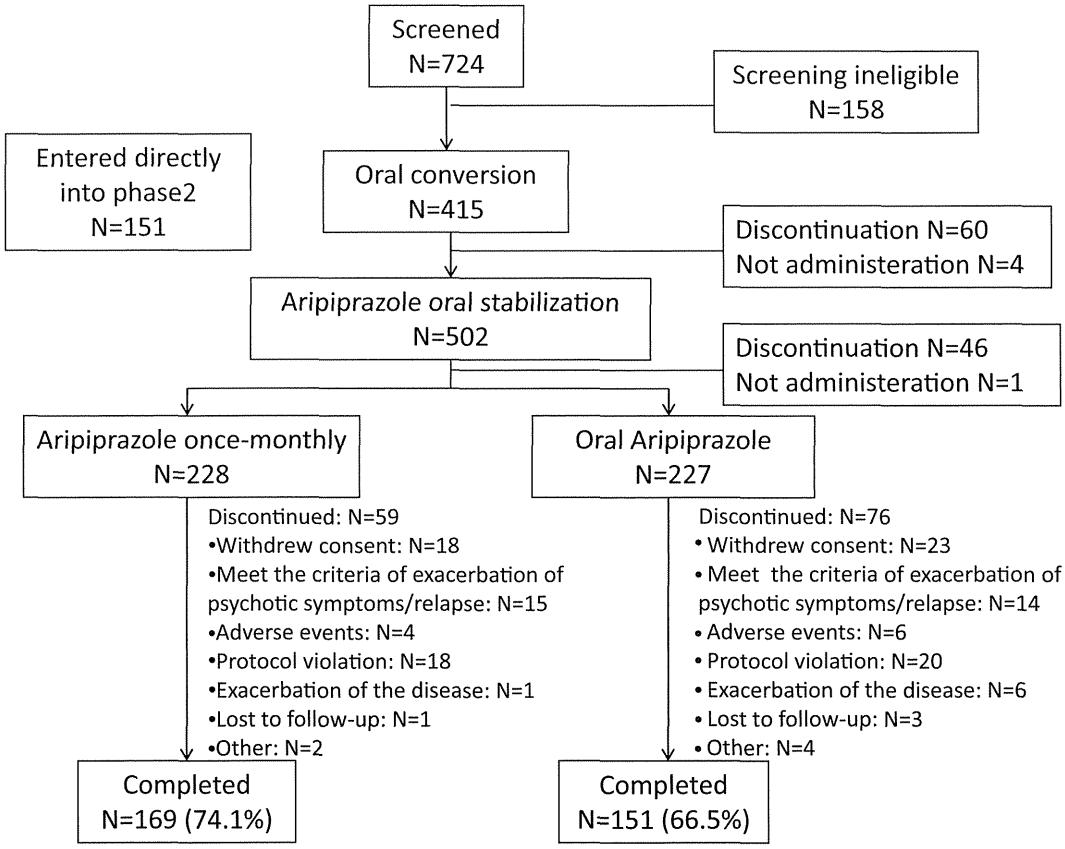

Fig. 1. Patient disposition.

safety parameter had been obtained. Analyses were conducted using LOCF data.

The primary efficacy endpoint in this trial was the non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 in the double-blind phase calculated by the Kaplan–Meier method. The objective of the primary efficacy analysis was to show the non-inferiority of 400 mg of aripiprazole once monthly to oral aripiprazole (6–24 mg), over a 52-week administration period from the start of administration in the double-blind phase, using the non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 calculated by the Kaplan–Meier method as a marker.

In the efficacy sample, the non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 was calculated for each group using the Kaplan–Meier method. The difference (400 mg of aripiprazole once-monthly to 6–24 mg of oral aripiprazole) and the two-sided 95% confidence-interval (CI) of that difference were calculated. When the lower limit of the two-sided 95% CI of that difference was greater than or equal to −15%, 400 mg of aripiprazole once-monthly was judged to be non-inferior to 6–24 mg aripiprazole tablets. The non-inferiority margin was set at 15%, based on the exacerbation rate and non-exacerbation rate in placebo groups and active drug group in the previous studies (Pigott et al., 2003, European Medicines Agency, 2008; Hough et al., 2010).

Regarding the time to exacerbation of psychotic symptoms/relapse, the hazard ratio and the two-sided 95% CI of that ratio were calculated using the Cox proportional hazards model. Changes in PANSS total score, each positive, negative, and general psychopathology subscale scores, and CGI-S were analyzed using analysis of covariance (ANCOVA) model using LOCF dataset, with the treatment group as main effect, and with the baseline of the double-blind phase as a covariate. Mean CGI-I scores at each time point were assessed by the Cochran–Mantel–Haenszel test, based on row mean score statistics.

The 95% CIs of the differences in percentages were calculated for the proportions of patients meeting exacerbation of psychotic symptoms/relapse criteria, patients meeting stabilization of psychotic symptoms/maintenance criteria, and patients achieving remission.

The results of all statistical tests were interpreted at the 5% significance level.

The sample size was calculated as follows: It is assumed that the hazard ratio of aripiprazole once-monthly and oral aripiprazole was the same and remained constant regardless of the time point. The expected dropout rate was 20% at Week 26 due to reasons other than dropout under the definition of exacerbation of psychotic symptoms/relapse, such as withdrawal of consent and discontinuation due to AEs, and the non-exacerbation/non-relapse rate at Week 26 was set at 75% according to the Kaplan–Meier method. A 10,000-time simulation in which there was a ≥90% probability that the lower limit of the two-sided 95% CI for the difference in non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 was equal or exceeded −15% found 410 patients in a randomized population.

3. Results

3.1. Patient disposition

In total, 724 patients were screened, of whom 566 were eligible to enter this study; 415 patients entered the oral conversion phase (phase 1) and 151 patients entered the oral stabilization phase (phase 2) directly. Of 455 patients randomized in the double-blind phase (phase 3), 228 received aripiprazole once monthly and 227 received oral aripiprazole (Fig. 1). Of the randomized patients, 169 (74.1%) in the aripiprazole once-monthly and 151 (66.5%) in oral aripiprazole completed the study. Reasons for treatment discontinuation are provided in Fig. 1.

Baseline demographics and patient characteristics are shown in Table 1 and were similar between groups. All patients were Asian. The majority of patients were from Japan (52.1%), followed by the Philippines (18.9%), Malaysia (18.5%) and Taiwan (10.5%).

Table 1
Baseline demographic and clinical characteristics of randomized patients.

Characteristic		Aripiprazole once-monthly (n = 228)	Oral aripiprazole (n = 227)
		n (%)	n (%)
Gender, male		136 (59.6)	141 (62.1)
Age (years), mean ± SD		40.2 ± 12.6	38.2 ± 10.3
Baseline weight (kg), mean ± SD		65.2 ± 13.1	64.9 ± 12.8
Baseline BMI (kg/m^2), mean ± SD		24.4 ± 4.0	24.1 ± 3.9
Country	Japan	118 (51.8)	119 (52.4)
	Malaysia	43 (18.9)	41 (18.1)
	Philippines	42 (18.4)	44 (19.4)
	Taiwan	25 (11.0)	23 (10.1)
Type DSM-IV-TR	Paranoid type	143 (62.7)	142 (62.6)
	Disorganized type	10 (4.4)	10 (4.4)
	Catatonic type	4 (1.8)	10 (4.4)
	Undifferentiated type	53 (23.2)	45 (19.8)
	Residual type	18 (7.9)	20 (8.8)
Age of first episode (years), mean ± SD		26.5 ± 9.6	26.5 ± 8.6
Time since first episode (mon), mean ± SD		163.3 ± 130.5	139.9 ± 113.2
Baseline severity at the oral stabilization phase, mean ± SD			
PANSS total score		57.6 ± 13.3	56.0 ± 13.3
CGI-S		3.0 ± 0.8	2.8 ± 0.8
Baseline severity at the double-blind phase, mean ± SD			
PANSS total score		54.4 ± 12.4	53.3 ± 12.7
CGI-S		2.8 ± 0.8	2.7 ± 0.8
Final dose of aripiprazole at the oral stabilization phase			
6 mg/day		32 (14.0)	27 (11.9)
12 mg/day		57 (25.0)	87 (38.3)
18 mg/day		66 (28.9)	46 (20.3)
24 mg/day		73 (32.0)	67 (29.5)

3.2. Treatment exposure

At the end of oral stabilization phase, the overall distribution of the final dose of aripiprazole was as follows: 6 mg/day 13.0%, 12 mg/day 31.6%, 18 mg/day 24.6%, and 24 mg/day 30.8%.

Of the patients who received aripiprazole once-monthly (n = 228), 186 patients (81.6%) received at least 7 injections and 168 patients (73.7%) received at least 13 injections. Of the patients who received aripiprazole once-monthly (n = 228), 207 patients (90.8%) started on and continued to receive 400 mg with no change in dose and 19 patients (8.3%) reduced to 300 mg and continued on the lower dose. Mean dose of aripiprazole once-monthly during the double-blind phase was 393.79 ± 21.02 mg (mean ± SD).

Of the patients who received oral aripiprazole (n = 227), 173 patients (76.2%) received oral aripiprazole for more than 26 weeks and 149 patients (65.6%) received oral aripiprazole for 52 weeks. Of the patients who received oral aripiprazole, 210 patients (92.5%) kept the dose of placebo injectable with no change in dose and 16 patients (7.0%) reduced the dose and continued with the lowered dose. The mean dose of oral aripiprazole was 15.69 ± 6.16 mg/day and the mean duration of administration was 279.9 ± 129.4 days.

3.3. Efficacy

The non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 in the double-blind phase calculated by the Kaplan–Meier method was 95.0 ± 1.5% for aripiprazole once-monthly and 94.7 ± 1.6% for oral aripiprazole and the difference was 0.3% (95% CI: −3.9,4.5) (Table 2). Thus, the non-inferiority of aripiprazole once-monthly compared to oral aripiprazole with respect to non-exacerbation of psychotic symptoms/non-relapse rate was shown with a margin of −3.9% which is well above the non-inferiority limit

Table 2
Non-exacerbation of psychotic symptoms/non-relapse rate at Week 26 by the Kaplan–Meier method.

	Non-exacerbation of psychotic symptoms/non-relapse rate, % (SE)	Difference	95% confidence-interval of that difference	Non-inferiority margin
Aripiprazole once-monthly	95.0 (1.5)	0.3	−3.9, 4.5	−15%
Oral aripiprazole	94.7 (1.6)			

of −15% that was pre-defined in the study protocol. The non-exacerbation of psychotic symptoms/non-relapse rate after 26 weeks up to 52 weeks was 92.9–94.5% in aripiprazole once-monthly and 92.3–94.1% in oral aripiprazole and was similar between both groups.

Regarding time to exacerbation of psychotic symptoms/relapse, the hazard ratio between aripiprazole once-monthly and oral aripiprazole using the Cox proportional hazards model was 0.94 (95% CI: 0.46, 1.92) (Fig. 2).

The proportion of patients meeting exacerbation of psychotic symptoms/relapse criteria at the endpoint was 6.6% in both groups, and the proportion of patients meeting stabilization of psychotic symptoms/maintenance criteria at the endpoint was 92.5% and high in both groups. The proportion of patients achieving remission criteria in patients maintained for a period of 6 months was 69.4% (129/186) for aripiprazole once-monthly and 71.1% (123/173) for oral aripiprazole (Table 3).

PANSS total scores (±SE) at baseline during the double-blind phase were 54.4 ± 0.8 in aripiprazole once-monthly and 53.3 ± 0.8 in oral aripiprazole. At Week 52, the mean changes from baseline in PANSS total scores, positive scores, negative scores, and general psychopathology scores were similar between both groups. In addition, the mean changes in CGI-S scores during the double-blind phase were comparable between both groups (0.0 ± 0.1 in aripiprazole once-monthly and −0.1 ± 0.1 in oral aripiprazole) and were stable. The mean CGI-I score at Week 52 was 3.5 ± 0.1 in both groups (Table 4).

Discontinuation rates due to all reasons was 25.9% for aripiprazole once-monthly and 33.5% for oral aripiprazole, and the hazard ratio of aripiprazole once-monthly to oral aripiprazole for time to discontinuation due to all reasons was 0.74 (95% CI: 0.52, 1.03) (Cox proportional hazards model) (Fig. 3).

SF-36 mental component summary and physical component summary (±SE) at baseline were 47.3 ± 0.8 and 49.4 ± 0.6 for aripiprazole once-monthly, respectively, and 47.5 ± 0.8 and 49.9 ± 0.7 for oral aripiprazole, respectively. Mean changes in metal component summary in SF-36 at Week 52 were 0.82 ± 0.60 for aripiprazole once-monthly and 0.38 ± 0.61 for oral aripiprazole (the difference: 0.44, 95% CI: −1.24, 2.12, ANCOVA). Mean changes in physical component summary at Week 52 were 0.23 ± 0.58 for aripiprazole once-monthly and −0.27 ± 0.58 for oral aripiprazole (the difference: 0.50, 95% CI: −1.11, 2.11, ANCOVA).

3.4. Safety and tolerability

3.4.1. Adverse events

During the double-blind phase, 176 (77.2%) patients in the aripiprazole once-monthly group and 180 (79.3%) patients in the oral aripiprazole group experienced at least 1 treatment-emergent adverse event (TEAE). TEAEs with an incidence of at least 5% in either group in the double-blind phase are shown in Table 5. The common AEs in either

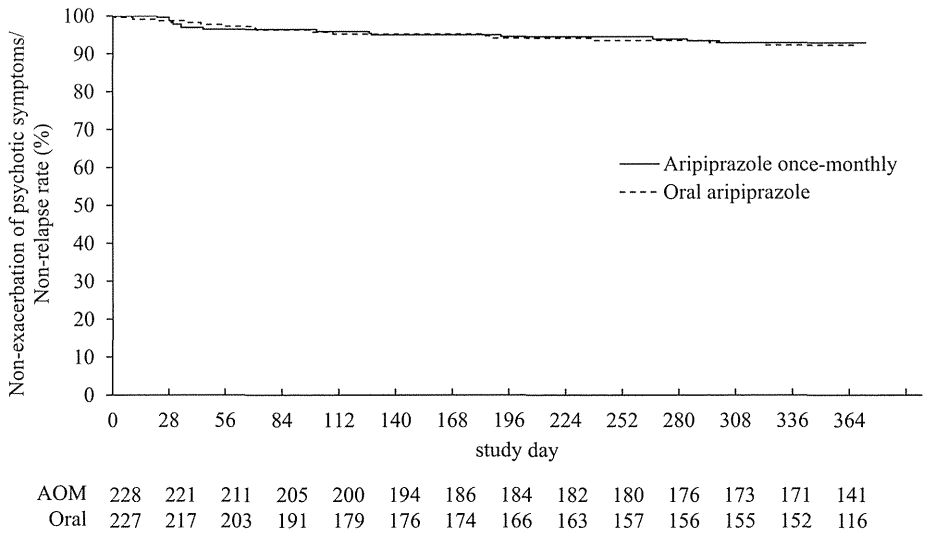

Fig. 2. Time to exacerbation of psychotic symptoms/relapse in double-blind phase calculated by the Kaplan–Meier method. Hazard ratio was 0.94 (95% CI: 0.46, 1.92) (Cox proportional hazard model).

Table 3
Proportion of patients meeting exacerbation of psychotic symptoms/relapse criteria, meeting stabilization of psychotic symptoms/maintenance criteria, and achieving remission criteria.

Proportion of patients	Aripiprazole once-monthly (n = 228)	Oral aripiprazole (n = 227)	95% confidence-interval of the difference
Exacerbation of psychotic symptoms/ relapse	6.6% (n = 15)	6.6% (n = 15)	−4.6, 4.5
Stabilization of psychotic symptoms/maintenance	92.5% (n = 211)	92.5% (n = 210)	−4.8, 4.9
Remission[a]	69.4% (n = 129)	71.1% (n = 123)	−11.2, 7.7

[a] Remission rate in patients who continued treatment for a period of 6 months (Aripiprazole once-monthly; n = 186, oral aripiprazole: n = 173).

Table 4
Mean change in secondary efficacy outcomes in the double-blind phase (LOCF).

Rating scale[a]	Aripiprazole once-monthly (n = 228)	Oral aripiprazole (n = 227)	Difference	(95% CI)
PANSS total score, mean (SE)				
Double-blind baseline	54.4 (0.8)	53.3 (0.8)		
Change to Week 52	−2.3 (0.8)	−2.7 (0.8)	0.4	(−1.8, 2.5)[b]
PANSS positive score, mean (SE)				
Double-blind baseline	11.5 (0.2)	11.4 (0.2)		
Change to Week 52	−0.3 (0.2)	−0.3 (0.2)	0.0	(−0.7, 0.7)[b]
PANSS negative score, mean (SE)				
Double-blind baseline	15.9 (0.3)	15.2 (0.3)		
Change to Week 52	−1.1 (0.2)	−1.0 (0.2)	−0.1	(−0.7, 0.6)[b]
PANSS general score, mean (SE)				
Double-blind baseline	27.0 (0.4)	26.8 (0.4)		
Change to Week 52	−0.9 (0.4)	−1.3 (0.4)	0.4	(−0.7, 1.6)[b]
CGI-S score, mean (SE)				
Double-blind baseline	2.8 (0.1)	2.7 (0.1)		
Change to Week 52	0.0 (0.1)	−0.1 (0.1)	0.0	(−0.1, 0.2)[b]
CGI-I score, mean (SE)				
Change to Week 52	3.5 (0.1)	3.5 (0.1)	0.0	(−0.2, 0.2)[c]

[a] PANSS = Positive and Negative Syndrome Scale; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity of illness.
[b] ANCOVA with the score at the baseline of the double blind phase as a covariate and treatment as a factor.
[c] Cochran–Mantel–Haenszel test, based on row mean score statistics.

group were injection-site pain, nasopharyngitis, injection-site erythema, injection-site induration, weight gain, insomnia, akathisia, injection-site dilation, schizophrenia, and diarrhea. The majority of AEs were mild (aripiprazole once-monthly 57.9%, oral aripiprazole 56.4%) or moderate (aripiprazole once-monthly 15.8%, oral aripiprazole 18.1%) in severity. The incidences of side effects by aripiprazole once-monthly and oral aripiprazole were 57% (130/228 patients) and 49.3% (112/227 patients), respectively (Supplementary Table 2). Serious AEs occurred in 13 patients (5.7%) in aripiprazole once-monthly and in 20 patients (8.8%) in oral aripiprazole. The serious AEs reported by ≥2% of patients in either groups were schizophrenia (n = 7, 3.1%) in aripiprazole once-monthly and schizophrenia (n = 8, 3.5%) in oral aripiprazole. Two deaths were reported during the study: 1 patient (cardiac sudden death) receiving aripiprazole once-monthly and 1 patient (head injury) receiving oral aripiprazole.

Table 5
Adverse events occurring during the double-blind phase.

Adverse event	Aripiprazole once-monthly (n = 228)		Oral aripiprazole (n = 227)	
	n	(%)	n	(%)
Injection-site pain	64	(28.1)	43	(18.9)
Nasopharyngitis	55	(24.1)	54	(23.8)
Injection-site erythma	34	(14.9)	22	(9.7)
Injection-site induration	26	(11.4)	11	(4.8)
Weight gain	18	(7.9)	12	(5.3)
Insomnia	17	(7.5)	20	(8.8)
Akathisia	15	(6.6)	14	(6.2)
Injection-site dilation	15	(6.6)	11	(4.8)
Schizophrenia	12	(5.3)	17	(7.5)
Diarrhea	10	(4.4)	15	(6.6)

Occurring at an incidence of ≥5% in either group.

Discontinuation due to AEs in the double-blind treatment phase occurred in 17 patients (7.5%) in aripiprazole once-monthly and 26 patients (11.5%) in oral aripiprazole. AEs resulting in discontinuation that occurred in ≥1% of patients in any group were schizophrenia (n = 11, 4.8%) and unwanted pregnancy (n = 1, 1.1%) in aripiprazole once-monthly and schizophrenia (n = 14, 6.2%), hallucinations (n = 3, 1.3%), and unwanted pregnancy (n = 1, 1.2%) in oral aripiprazole. Patients who experienced AEs leading to dose reduction totaled 16 (7.0%) in aripiprazole once-monthly and 13 (5.7%) in oral aripiprazole, and all did not discontinue after dose reduction.

The numbers of patients with suicidal ideation in aripiprazole once-monthly and oral aripiprazole were 2 (0.9%) and 2 (0.9%) during the double blind phase. There is no significant difference in the proportion of patients with suicidal ideation between aripiprazole once-monthly and oral aripiprazole during the double-blind phase using C-SSRS (0.0–3.1% and 0.0–2.2%). CGI-SS (part 1) and CGI-SS (part 2) were unchanged at 1.0–1.1 and 3.9–4.0, respectively, over 52 weeks in both aripiprazole once-monthly and oral aripiprazole.

3.4.2. Extrapyramidal symptoms

During the double-blind phase, 16.2% of aripiprazole once-monthly and 14.1% of oral aripiprazole patients experienced AEs related to extrapyramidal symptoms. Incidence of akathisia, the most common extrapyramidal symptom, was 5.7% in aripiprazole once-monthly and 6.2% in oral aripiprazole. There was 1 report of tardive dyskinesia in oral aripiprazole. Mean changes in DIEPSS total scores ± SD at Week 52

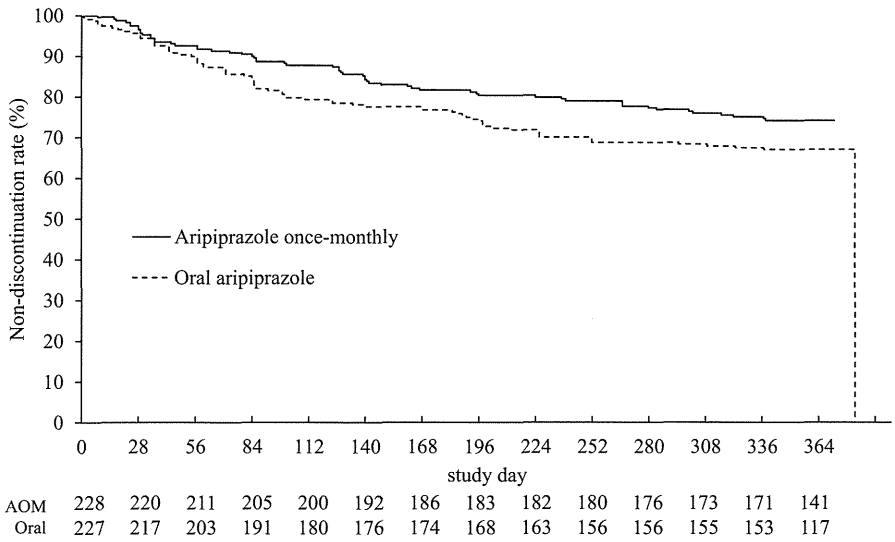

Fig. 3. Time to discontinuation due to all reasons. Hazard ratio of aripiprazole once-monthly to oral aripiprazole was 0.74 (95% CI: 0.52, 1.03) (Cox proportional hazards model).

were −0.2 ± 0.9 (n = 168) in aripiprazole once-monthly and −0.2 ± 0.8 (n = 149) in oral aripiprazole. Mean changes in AIMS total scores at Week 52 were −0.1 ± 0.4 (n = 168) in aripiprazole once-monthly and 0.0 ± 0.5 (n = 149) in oral aripiprazole groups. Regarding akathisia, BARS Global Clinical Assessment of Akathisia scores were 0.1 ± 0.4 (n = 228) at baseline and remained at 0.1 ± 0.3 (n = 168) at Week 52 in aripiprazole once-monthly, and 0.1 ± 0.5 (n = 227) at baseline and remained at 0.1 ± 0.3 (n = 149) at Week 52 in oral aripiprazole. 25% and 23.8% of patients used an anti-parkinsonian drug in aripiprazole once-monthly and oral aripiprazole during the double-blind phase.

3.4.3. Injection-site reaction related adverse events

Of the AEs, the AEs occurring with a greater than 5% difference between aripiprazole once-monthly and oral aripiprazole were injection-site pain, injection-site erythema, and injection-site induration.

Injections of aripiprazole once-monthly were generally well tolerated. There was no discontinuation due to AEs related to injection site reaction in both groups. In self-assessment of injection site pain using the VAS (0–100), mean VAS score after the first injection was 3.5 in aripiprazole once-monthly and 2.5 in oral aripiprazole. Mean VAS scores at the second injection and later were similar in both groups. At the final injection, mean VAS score was 0.8 in aripiprazole once-monthly and 1.6 in oral aripiprazole.

3.4.4. Weight gain and laboratory results

The mean weight changes ± SD during the double-blind phase were 0.87 ± 4.45 kg (n = 168) in aripiprazole once-monthly and 1.44 ± 5.23 kg (n = 149) in oral aripiprazole. The mean and median levels of blood chemistry test items, such as total cholesterol, LDL, HDL, and glucose, were within the normal range in both groups during the double-blind phase (Supplementary Table 3). Mean serum prolactin levels ± SD for aripiprazole once-monthly and oral aripiprazole were 6.8 ± 11.8 ng/mL (n = 228) and 6.8 ± 9.1 ng/mL (n = 227), within the normal range, at baseline and stable within the levels of 5.2–6.0 ng/mL and 5.9–6.3 ng/mL, respectively. Mean changes in prolactin level at Week 52 were −1.6 ± 9.3 ng/mL (n = 167) and −0.5 ± 3.0 ng/mL (n = 149) in aripiprazole once-monthly and oral aripiprazole, respectively.

4. Discussion

This multicenter, randomized, double-blind study proved non-inferiority of aripiprazole once-monthly at 400 mg to oral aripiprazole in Asian patients with schizophrenia, suggesting that aripiprazole once-monthly is effective and exhibit a similar safety/tolerability profile compared to oral aripiprazole. The results of PANSS and CGI evaluation showed that aripiprazole once-monthly as well as oral aripiprazole maintained symptom control in stabilized patients with schizophrenia for 52 weeks. Previous studies reported that oral aripiprazole demonstrated sustained long-term efficacy with favorable safety and tolerability for 52 weeks (Kasper et al., 2003), and relapse prevention in patients with chronic and stable schizophrenia for 26 weeks (Pigott et al., 2003). Aripiprazole once-monthly is non-inferior to oral aripiprazole formulation, which is approved for maintenance treatment of schizophrenia. Therefore, aripiprazole is suitable for long-term treatment in schizophrenia.

In the aripiprazole once-monthly group, relapse rate was 6.6%, and rates of stabilization/maintenance and remission rates in patients who continued for 6 months were high at 92.5% and 69.4%, respectively. Additionally, the rate of discontinuation due to all reasons was lower in the aripiprazole once-monthly group (25.9%) than in oral aripiprazole group (33.5%). These results were similar to the findings of the two previous pivotal studies (Kane et al., 2012, Fleischhacker et al., 2014). The reproducibility of these results may provide support for wider use of aripiprazole once-monthly in clinical practice in Asia and confer a reliable treatment for patients with schizophrenia.

In long-term treatment of antipsychotics, consideration should be given to AEs, such as weight gain, metabolic side effects, and tardive dyskinesia. The incidence of AEs in aripiprazole once-monthly was consistent with that in oral aripiprazole in this study and the previous studies (Kasper et al., 2003; Pigott et al., 2003) and there were no additional unexpected AEs in this study. The incidence of weight gain in aripiprazole once-monthly was low and mean weight change for 52 weeks was less than 1 kg. Akathisia was the most common reported extra pyramidal symptoms-related AEs in the both groups, however, the severity was mainly mild and akathisia was managed successfully by dose reduction and with the addition of an anticholinergic parkinsonian drug.

The incidences of AEs related to injection reaction and pain were higher in aripiprazole once-monthly than in oral aripiprazole. However, the majority was mild in severity, and there was no discontinuation due to AEs related to injection site. Additionally, assessment of injection site pain by patients was similar between both groups from the second injection to the final injection.

The recent meta-analysis of randomized controlled trials of relapse prevention comparing long-acting injectable antipsychotics to oral antipsychotics demonstrated that long-acting injectable antipsychotics were not superior to oral antipsychotics (Kishimoto et al., 2014). On the other hand, a meta-analysis of mirror-image studies, which might reflect real-life clinical practice, showed that long-acting injectable antipsychotics were superior to oral antipsychotics for relapse prevention (Kishimoto et al., 2013). Furthermore, Kirson et al. (2013) reported that long-acting injectable antipsychotics showed advantages in observational studies but no advantages in randomized controlled studies. Thus, study design is an important factor. Our study was designed to verify non-inferiority of aripiprazole once-monthly to oral aripiprazole, and patients received more frequent monitoring and assessments than usual care. Therefore, the patients that participated in this controlled study might show better adherence in oral aripiprazole group.

Some methodological limitations of our study need to be considered. The inclusion of stabilized patients with aripiprazole for 4 weeks and the exclusion of patients with medical comorbidities do not accurately reflect real-world setting. The previous studies included aripiprazole once-monthly 50 mg (a sub-threshold therapeutic dose for assay sensitivity) or placebo (Fleischhacker et al., 2014, Kane et al., 2012), however, the current study does not include either aripiprazole once-monthly at 50 mg or placebo arm.

We demonstrated that non-inferiority of aripiprazole once-monthly compared to oral aripiprazole in this study with a margin of −3.9% which is well above the pre-specified non-inferiority limit of −15%. The results are similar to the finding another study (Fleischhacker et al. 2014). In conclusion, our findings demonstrate that aripiprazole once-monthly at 400 mg is efficacious in maintenance treatment of stabilized patients with schizophrenia, with comparable efficacy and favorable tolerability to oral aripiprazole.

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Contributors

Dr. Ishigooka, Dr. Nakamura, and Mr. Shimizu contributed to interpretation of the data and writing and revision of the manuscript. Dr. Ishigooka, Dr. Nakamura, Dr. Fujii, Dr. Iwata, Dr. Kishimoto, Dr. Iyo, Dr. Uchimura, Dr. Nishimura, and Mr. Shimizu contributed to and have approved the final manuscript.

Conflict of interest

The findings of this study were presented at the 9th Annual Meeting of the Japanese Society of Schizophrenia Research, held in Kyoto, Japan on March 14th, 2014 and at the 29th CINP World Congress, held in Vancouver, Canada on June 23rd, 2014.

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References

Barnes, T.R.E., 1989. A rating scale for drug-induced akathisia. Br. J. Psychiatry 154, 672–676.

Burris, K.D., Molski, T.F., Xu, C., Ryan, E., Tottori, K., Kikuchi, T., Yocca, F.D., Molinoff, P.B., 2002. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J. Pharmacol. Exp. Ther. 302, 381–389.

European Medicines Agency, 2008. Assessment Report for Zypadhera. Doc. Ref.: EMEA/608654/2008.

Fleischhacker, W.W., Sanchez, R., Perry, P.P., Jin, N., Peters-Strickland, T., Johnson, B.R., Baker, R.A., Eramo, A., McQuade, R.D., Carson, W.H., Walling, D., Kane, J.M., 2014. Aripiprazole once-monthly for treatment of schizophrenia: a double-blind, randomized, non-inferiority study. Br. J. Psychiatry 205, 135–144.

Fukuhara, S., Bito, S., Green, J., Hsiao, A., Kurosawa, K., 1998a. Translation, Adaptation, and validation for the SF-36 health survey for use in Japan. J. Clin. Epidemiol. 51, 1037–1044.

Fukahara, S., Ware, J.E., Kosinski, M., Wade, S., 1998b. Psychometric and clinical test of validity of the Japanese SF-36 Health Survey. J. Clin. Epidemiol. 51, 1045–1053.

Guy, W. (Ed.), 1976a. ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. US Department of Health, Education, and Welfare, Washington, DC, pp. 218–222.

Guy, W. (Ed.), 1976b. ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. US Department of Health, Education, and Welfare, Washington, DC, pp. 534–537.

Higashi, K., Medic, G., Littlewood, K.J., Diez, T., Granström, O., De Hert, M., 2013. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther. Adv. Psychopharmacol. 3, 200–218.

Hough, D., Gopal, S., Vijapurkar, U., Lim, P., Morozova, M., Eerdekens, M., 2010. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr. Res. 116, 107–117.

Inada, T., 2009. DIEPSS: A Second-generation Rating Scale for Antipsychotic-induced Extrapyramidal Symptoms: Drug-induced Extrapyramidal Symptoms Scale. Seiwa Shoten Publishers, Inc., Tokyo.

Kane, J.M., Sanchez, R., Perry, P.P., Jin, N., Johnson, B.R., Forbs, R.A., McQuade, R.D., Carson, W.H., Fleischhacker, W.W., 2012. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. J. Clin. Psychiatry 73, 617–624.

Kasper, S., Lerman, M.N., McQuade, R.D., Saha, A., Carson, W.H., Ali, M., Archibald, D., Ingenito, G., Marcus, R., Pigott, T., 2003. Efficacy and safety of aripiprazole vs. haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. Int. J. Neuropsychopharmacol. 6, 325–337.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kirson, N.Y., Weiden, P.J., Yermakov, S., Huang, W., Samuelson, T., Offord, S.J., Greenberg, P.E., Wong, B.J., 2013. Efficacy and effectiveness of depot versus oral antipsychotics in schizophrenia: synthesizing results across different research designs. J. Clin. Psychiatry 74, 568–575.

Kishimoto, T., Nitta, M., Borenstein, M., Kane, J.M., Correll, C.U., 2013. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J. Clin. Psychiatry 74, 957–965.

Kishimoto, T., Robenzadeh, A., Leucht, C., Leucht, S., Watanabe, K., Mimura, M., Borenstein, M., Kane, J.M., Correll, C.U., 2014. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophr. Bull. 40, 192–213.

Marder, S.R., McQuade, R.D., Stock, E., Kaplita, S., Marcus, R., Safferman, A.Z., Saha, A., Ali, M., Iwamoto, T., 2003. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr. Res. 61, 123–136.

Pigott, T.A., Carson, W.H., Saha, A.R., Torbeyns, A.F., Stock, E.G., Ingenito, G.G., Aripiprazole Study Group, 2003. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. J. Clin. Psychiatry 64, 1048–1056.

Potkin, S.G., Saha, A.R., Kujawa, M.J., Carson, W.H., Ali, M., Stock, E., Stringfellow, J., Ingenito, G., Marder, S.R., 2003. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. Arch. Gen. Psychiatry 60, 681–690.

Robinson, D., Woerner, M.G., Alvir, J.M., Bilder, R., Goldman, R., Geisler, S., Koreen, A., Sheitman, B., Chakos, M., Mayerhoff, D., Lieberman, J.A., 1999. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch. Gen. Psychiatry 56, 241–247.

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Regular Article

Increased prefrontal hemodynamic change after atomoxetine administration in pediatric attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy

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Aim: Atomoxetine, approved in Japan for the treatment of pediatric attention-deficit/hyperactivity disorder (ADHD) in April 2009, is a nonstimulant that is thought to act presynaptically via the inhibition of norepinephrine reuptake. Near-infrared spectroscopy is a non-invasive optical tool that can be used to study oxygenation and hemodynamic changes in the cerebral cortex. The present study examined the effects of a clinical dose of atomoxetine on changes in prefrontal hemodynamic activity in children with ADHD, as measured by near-infrared spectroscopy using the Stroop Color–Word Task.

Methods: Ten children with ADHD participated in the present study. We used 24-channel near-infrared spectroscopy to measure the relative concentrations of oxyhemoglobin in the frontal lobes of participants in the drug-naïve condition and those who had received atomoxetine for 8 weeks. Measurements were conducted every 0.1 s during the Stroop Color–Word Task. We used the ADHD Rating Scale-IV-Japanese version (Home Version) to evaluate ADHD symptoms.

Results: We found a significant decrease in ADHD Rating Scale-IV-Japanese version scores, from 30.7 to 22.6 ($P = 0.003$). During the Stroop Color–Word Task, we found significantly higher levels of oxyhemoglobin changes in the prefrontal cortex of participants in the atomoxetine condition compared with those in the drug-naïve condition.

Conclusions: This increase in oxyhemoglobin changes might indicate an intensified prefrontal hemodynamic response induced by atomoxetine. Near-infrared spectroscopy is a sensitive tool for measuring the pharmacological effects of atomoxetine in children with ADHD.

Key words: atomoxetine, functional neuroimaging study, near-infrared spectroscopy, pediatric attention-deficit/hyperactivity disorder, prefrontal hemodynamic response.

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