Psychology
2012. Vol.3, Special Issue, 758-761
Published Online September 2012 in SciRes (http://www.SciRP.org/journal/psych)
http://dx.doi.org/10.4236/psych.2012.329115

Working Memory in Patients with Major Depressive Disorder

Yasuhiro Kaneda
Department of Psychiatry, Iwaki Clinic, Tokushima, Japan
Email: kaneday-tsh@umin.ac.jp

Received May 2nd, 2012; revised June 4th, 2012; accepted July 7th, 2012

Objective: Patients with major depressive disorder (MDD) have been reported to perform less well in neurocognitive tests than normal control subjects. The author tested the hypotheses that verbal working memory (WM) is predictive of the functional outcome in patients with MDD. **Methods:** In this naturalistic longitudinal study, the subjects consisted of 22 adult outpatients receiving paroxetine as antidepressant therapy. Functional outcome was rated on a scale of 0 (non-impaired) to 3 (severely impaired). **Results:** 1) At 12 weeks, nine of the 22 patients currently experiencing MDD exhibited full remission; 2) significantly decreased 7-item Hamilton Rating Scale for Depression (HAM-D7) scores were observed during the 12-week study period, while Digit Sequencing Task (DST) scores increased significantly; 3) at baseline, functional outcomes correlated significantly with HAM-D7 scores, but, at 12 weeks, correlated significantly with both HAM-D7 and DST scores. Furthermore, when looking at only patients in full or partial remission (mild depression), functional outcome correlated more strongly with DST than with HAM-D7 scores. **Conclusions:** A deficit of verbal WM correlated with the functional outcome after treatment in patients with MDD. Antidepressant therapy with paroxetine might contribute to improvement of verbal WM.

Keywords: Depression; Functional Outcome; Paroxetine; Symptomatlogy; Working Memory

Introduction

Major depressive disorder (MDD) is a significant health problem, with major economic implications, and estimates of the economic burden of depression range from $52 billion in 1990 to $83 billion in 2000 (Malone, 2007). Among others, the effect on employment is considered to have a great impact on the societal costs of depression, due to lost income, lost productivity, and disability income payments.

In previous studies (Kaneda et al., 2009, 2010), the author demonstrated that neurocognitive performance was more important than the clinical symptoms in predicting the future employment status in patients with schizophrenia, and among the neurocognitive functions, verbal working memory (WM) was found to be the most important for determining the employment outcome. Patients with MDD also have been reported to perform less well in neurocognitive tests than normal control subjects, even after their depression is successfully treated with newer-generation antidepressants (Gualtieri et al., 2006, Reppermund et al., 2009, Porter et al., 2003). Recently, Gualtieri & Morgan (2008) reported that substantial numbers of patients with depression exhibit cognitive impairment. However, until date, little attention has been paid to the relation between neurocognitive performance and the psychosocial or functional outcomes in studies of depression compared to those of bipolar disorder (Kennedy et al., 2007). Kitagawa & Koyama (2009) have suggested a relationship between functional outcomes and neurocognitive functions in depression, but their result has not been duplicated.

Thus, the author first tested the hypothesis that the deficit of neurocognitive performance, namely verbal WM, existed even after remission (Kaneda, 2009b). In this naturalistic cross-sectional study, the subjects consisted of 54 clinic adult out-patients and 54 age- and sex-equated healthy comparison subjects. The assessments were performed using the 7-item Hamilton Rating Scale for Depression (HAM-D7) for the severity of depression, and the Digit Sequencing Task (DST) for evaluation of verbal WM (methodological details are described below). The DST scores were significantly less in both patients with current episode of MDD and in full remitted or partial remitted (mildly depressed) patients than in controls. Also there were no signifycant correlations between DST scores and the dose of antidepressants or benzodiazepines in full remitted or partial remitted (mildly depressed) patients.

Since verbal WM was demonstrated to be poorly performed in patients with MDD, another study was conducted to verify the suggestion that verbal WM is predictive of the functional outcome in patients with MDD after remission.

Methods

Subjects

Twenty-two consecutive adult outpatients (21 - 64 years of age) were enrolled in this prospective, open-label study. All subjects satisfied the DSM-IV (American Psychiatric Association, 1994) criteria for a current episode of unipolar MDD (non-psychotic) and were receiving paroxetine with or without sulpiride or benzodiazepines. Patients had no co-morbid psychiatric disorders, nor any medical, neurological, or developmental conditions that could affect cognition (e.g., attention deficit hyperactivity disorder, brain injury, mild cognitive impairment, chronic pain). The investigation was carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from all subjects.

Assessments

The assessments were performed using the following instruments: 1) the 7-item Hamilton Rating Scale for Depression

(HAM-D7; McIntyre et al., 2005) to determine the severity of depression and remission status; full remission was defined as a score of 3 or less, partial remission (mild depression) as a score of 10 or less on the HAM-D7, and 2) the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) Digit Sequencing Task (DST) to assess verbal WM (the patients were presented with clusters of numbers in random order of increasing length, and asked to recount these numbers in the right order, from lowest to highest, to the investigator). The BACS DST has been validated in normal control subjects (Keefe et al., 2004). The DST scores in each depression group were normalized for the respective age- and sex-matched control groups (data available on request). Functional outcome (productivity), including the ability to go to work, do household chores, go to school and so on, was assessed by the author based on interviews with patients and their partners/parents/children, and was graded on a 0 - 3 scale: 0 = non-impaired, 1 = mildly impaired, 2 = moderately impaired, 3 = severely impaired. The clinical assessments were performed on two occasions: 1) on the day of entry and 2) after approximately 12 weeks (a mean period of 90.6 days, SD = 14.2).

Analyses

The JMI software (Version 8.0.1) for Macintosh was used to perform the analyses. For numerical variables, the *t*-test for independent group comparisons was used to compare differences in variables between the two groups. The clinical assessment scores were compared between the two assessments by repeated-measure analysis of variance (ANOVA). Pearson's correlation was used to examine the relationships between two numerical variables. A logistic regression model with forward selection criteria was used to predict functional outcomes using functional outcome as a dependent variable and depressive and verbal WM scores as independent variables. The level of significance was set at $p < .05$.

Results

The demographic characteristics at baseline are presented in **Table 1**. At baseline, eight of the 22 patients (36%) were taking paroxetine, and two were taking sulpiride. In addition, 12 of the 22 patients (55%) were taking benzodiazepines. At the time of the second assessment, all patients were receiving treatment with paroxetine (mean dose, 28.8 mg), and one patient was taking sulpiride in addition to paroxetine. Fourteen of the 22 patients (64%) were being treated with benzodiazepines (mean dose, 4.7 mg).

At the second assessment conducted after 12 weeks, according to symptom severity scores, nine of the 22 patients (41%) with a current episode of MDD were in full remission. In addition, normalization of work function was seen in eight patients of these nine patients (89%).

A significant decrease in HAM-D7 scores from 11.0 ± 3.8 to 5.5 ± 4.9 ($p < .0001$) was observed during the 12-week study period. In addition, DST scores (z-score) increased significantly during the same period (from –1.1 ± 1.1 to –.7 ± 1.4, $p < .05$).

At baseline, functional outcomes were correlated significantly with HAM-D7 scores (r = .56, $p < .01$), but not DST scores, whereas at 12 weeks, functional outcomes correlated significantly with both DST (r = –.46, $p < .05$) and HAM-D7 (r = .72, $p < .001$) scores. When looking only at patients in full or partial remission (mild depression), functional outcome correlated more strongly with DST (r = –.74, $p < .001$) than with HAM-D7 (r = .51, $p < .05$) scores.

There was no significant relation between DST and HAM-D7 scoresat either baseline or at 12 weeks.

According to multiple regression analysis with a forward stepwise procedure, the DST scores at baseline contributed more strongly to the prediction of functional outcome at 12 weeks (F = 1.9, df = 1, $p = .19$) than did HAM-D7 scores (F = .1, df = 1, $p = .74$). On the other hand, HAM-D7 scores at baseline contributed more strongly to the prediction of HAM-D7 scores at 12 weeks (F = 4.8, df = 1, $p < .05$) than did DST scores (F = 1.2, df = 1, $p = .29$).

Discussion

The findings of this study suggest a correlation between a verbal WM deficit associated with MDD and post-treatment functional outcome. When looking at only patients in full or partial remission (mild depression), the correlation was more apparent. These findings are consistent with those of a previous cross-sectional study carried out by the author (Kaneda, 2009a). Kitagawa & Koyama (2009) have also suggested a relationship between functional outcomes and neurocognitive functions in depression. In their review, Kennedy et al. (2007) suggested that residual symptoms after remission of depression may lead to enduring psychosocial impairment, as many subtle neurocognitive deficits. While the findings of this study do not underscore the importance of clinical remission from depression, a defined objective outcome indicated by a quantifiable score with a depressive symptom measurement tool, symptomatic full remission should always be the primary goal of treatment, since it is the optimal outcome for patients with depression (McIntyre et al., 2005). However, the present findings do suggest that enhancement of verbal WM function, e.g., via cognitive rehabilitation, may facilitate normalization of functioning which is an important component of remission (Zimmerman et al., 2006).

In terms of predictive factors, previous studies have described the value of neurocognitive functions for predicting symptomatic improvement, mainly in geriatric patients with depression (Marcos et al., 2005). However, in this study, HAM-D7 scores were found to be more important for predicting symptomatic improvement than DST scores used to assess verbal WM, a finding well in line with that reported by Biringer et al. (2007), who showed that neurocognitive function at baseline did not predict amelioration of depressive symptoms over time in young adults. The present results, however, suggest verbal WM to be more important for predicting functional out-

Table 1.
Demographic Data.

N (F/M)	Age (yr.)	Education (yr.)	Age at onset (yr.)	Antidepressant dose (mg/d)[a]	Benzodiazepines dose (mg/d)[b]
22 (9/13)	37.9 (13.3)	12.5 (2.9)	36.8 (13.0)	7.7 (13.3)	2.0 (3.2)

Note: Data are expressed as means (SD); [a]Paroxetine equivalent; [b]Diazepam equivalent.

comes than depressive symptoms. Therefore, in order to obtain a better functional outcome, it may be important to place more emphasis on pretreatment verbal WM than depressive symptoms.

The findings of this study also suggest again that MDD-associated deficits in verbal WM exist both in acute depression and after the treatment of depression. These findings are consistent with those of previous studies conducted by the author (Kaneda, 2009b) and by Nebes et al. (2003), who found that verbal WM dysfunction persisted in older depressed patients even after their mood disorder had responded to antidepressant medications. The observations made herein may be explained by an impairment of WM/central executive functions in MDD, as suggested by Rose & Ebmeier (2006), since executive function impairment is considered to be, at least to some degree, trait-related (Porter et al., 2003).

Regarding the effects of antidepressant medications on cognitive function, a significant increase in DST scores was observed during 12-week treatment with paroxetine in the present study. Although a potential effect which would be maximized by testing twice within 5 days (Keefe et al., 2004), cannot be completely ruled out, paroxetine is suggested to possibly improve cognitive function in depressed subjects. Antidepressant medications may also have some negative effects on cognitive function (Gorenstein et al., 2006, Hindmarch, 2009). Cassano et al. (2002), in their double-blind, randomized, parallel-group, multicenter study comparing paroxetine and fluoxetine treatment for 1 year, found that improvement, rather than deterioration, was observed in most of the tested cognitive functions. It has been speculated that paroxetine may have indirect effects which improve cognitive function via amelioration of depression, and that this could outweigh the mildly toxic effects of paroxetine (Hindmarch, 2009).

A limitation of this study is that the possible influence of benzodiazepines (Stewart, 2005) on verbal WM function could not be completely ruled out. Another limitation of this study is that patients with full and partial remission (mild depression) were analyzed together, mainly because there were few patients with full remission. Also, a longer observation may be needed to allow sufficient recovery of verbal WM function. Therefore, a further long-term study of patients showing remission of depression, who are no longer taking medication, might be necessary to confirm the present results.

Acknowledgements

This work was supported in part by grants from Daido Life Welfare Foundation (2009), the Japanese Association of Neuro-Psychiatric Clinics (Ken TANAKA Memorial Grant, 2008), and the Charitable Trust Kimi IMAI Memorial Stress Associated Diseases Research Aid Fund (2009, 2010). This study was presented in part at the 20th Annual Meeting of the Japanese Society of Clinical Neuropsychopharmacology, held jointly with the 40th Annual Meeting of the Japanese Society of Neuropsychopharmacology, in Sendai, Japan, and 164th Annual Meeting of the American Psychiatric Association in Honolulu, USA.

REFERENCES

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders, Fourth Edition (DSM-IV).* Washington DC: American Psychiatric Association.

Biringer, E., Mykletun, A., Sundet, K., Kroken, R., Stordal, K. I., & Lund, A. (2007). A longitudinal analysis of neurocognitive function in unipolar depression. *Journal of Clinical and Experimental Neuropsychology, 29,* 879-891. doi:10.1080/13803390601147686

Cassano, G. B., Puca, F., Scapicchio, P. L., & Trabucchi, M. (2002). Paroxetine and fluoxetine effects on mood and cognitive functions in depressed nondemented elderly patients. *The Journal of Clinical Psychiatry, 63,* 396-402. doi:10.4088/JCP.v63n0504

Gorenstein, C., de Carvalho, S. C., Artes, R., Moreno, R. A., & Marcourakis, T. (2006). Cognitive performance in depressed patients after chronic use of antidepressants. *Psychopharmacology, 185,* 84-92. doi:10.1007/s00213-005-0274-2

Gualtieri, C. T., Johnson, L. G., & Benedict, K. B. (2006). Neurocognition in depression: Patients on and off medication versus healthy comparison subjects. *The Journal of neuropsychiatry and clinical neurosciences, 18,* 217-225. doi:10.1176/appi.neuropsych.18.2.217

Gualtieri, C. T., & Morgan, D. W. (2008). The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: An unaccounted source of variance in clinical trials. *The Journal of Clinical Psychiatry, 69,* 1122-1130. doi:10.4088/JCP.v69n0712

Hindmarch, I. (2009). Cognitive toxicity of pharmacotherapeutic agents used in social anxiety disorder. *International Journal of Clinical Practice, 63,* 1085-1094. doi:10.1111/j.1742-1241.2009.02085.x

Kaneda, Y. (2009a). Verbal working memory and functional outcome in patients with unipolar major depressive disorder. *World Journal of Biological Psychiatry, 10,* 591-594. doi:10.1080/15622970903183705

Kaneda, Y. (2009b). Verbal working memory impairment in patients with current episode of unipolar major depressive disorder and in remission. *Clinical Neuropharmacology, 32,* 346-347. doi:10.1080/15622970903183705

Kaneda, Y., Jayathilak, K., & Meltzer, H. (2010). Determinants of work outcome in neuroleptic-resistant schizophrenia and schizoaffective disorder: Cognitive impairment and clozapine treatment. *Psychiatry Research, 178,* 57-62. doi:10.1016/j.psychres.2009.04.001

Kaneda, Y., Jayathilak, K., & Meltzer, H. Y. (2009). Determinants of work outcome in schizophrenia and schizoaffective disorder: Role of cognitive function. *Psychiatry Research, 169,* 178-179. doi:10.1016/j.psychres.2008.08.003

Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The brief assessment of cognition in schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia Research, 68,* 283-297. doi:10.1016/j.schres.2003.09.011

Kennedy, N., Foy, K., Sherazi, R., McDonough, M., & McKeon, P. (2007). Long-term social functioning after depression treated by psychiatrists: A review. *Bipolar Disorders, 9,* 25-37. doi:10.1111/j.1399-5618.2007.00326.x

Kitagawa, N., & Koyama, T. (2009). Assessment of neurocognitive function in mood disorders and its utilization to clinical practice. *Rinsho Seishin Igaku (Japanese Journal of Clinical Psychiatry), 38,* 437-445.

Malone, D. C. (2007). A budget-impact and cost-effectiveness model for second-line treatment of major depression. *Journal of Managed Care Pharmacy, 13,* S8-18.

Marcos, T., Portella, M. J., Navarro, V., Gasto, C., Rami, L., Lazaro, L., & Salamero, M. (2005). Neuropsychological prediction of recovery in late-onset major depression. *International Journal of Geriatric Psychiatry, 20,* 790-795. doi:10.1002/gps.1363

McIntyre, R. S., Konarski, J. Z., Mancini, D. A., Fulton, K. A., Parikh, S. V., Grigoriadis, S., Grupp, L. A., Bakish, D., Filteau, M. J., Gorman, C., Nemeroff, C. B., & Kennedy, S. H. (2005). Measuring the severity of depression and remission in primary care: Validation of the HAMD-7 scale. *Canadian Medical Association Journal, 173,* 1327-1334. doi:10.1503/cmaj.050786

Nebes, R. D., Pollock, B. G., Houck, P. R., Butters, M. A., Mulsant, B. H., Zmuda, M. D., & Reynolds III, C. F., (2003). Persistence of cognitive impairment in geriatric patients following antidepressant treatment: A randomized, double-blind clinical trial with nortriptyline and paroxetine. *Journal of Psychiatric Research, 37,* 99-108. doi:10.1016/S0022-3956(02)00085-7

Porter, R. J., Gallagher, P., Thompson, J. M., & Young, A. H. (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *The British Journal of Psychiatry, 182,* 214-220. doi:10.1192/bjp.182.3.214

Reppermund, S., Ising, M., Lucae, S., & Zihl, J. (2009). Cognitive impairment in unipolar depression is persistent and non-specific: Further evidence for the final common pathway disorder hypothesis. *Psychological Medicine, 39,* 603-614. doi:10.1017/S003329170800411X

Rose, E. J., & Ebmeier, K. P. (2006). Pattern of impaired working memory during major depression. *Journal of Affective Disorders, 90,* 149-161. doi:10.1016/j.jad.2005.11.003

Stewart, S. A. (2005). The effects of benzodiazepines on cognition. *The Journal of Clinical Psychiatry, 66,* 9-13.

Zimmerman, M., McGlinchey, J. B., Posternak, M. A., Friedman, M., Attiullah, N., & Boerescu, D. (2006). How should remission from depression be defined? The depressed patient's perspective. *The American Journal of Psychiatry, 163,* 148-150. doi:10.1176/appi.ajp.163.1.148

