

## **Cognitive and affective benefits of combination therapy with galantamine plus cognitive rehabilitation for Alzheimer's disease**

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Running head: Combination therapy for AD patients

## Abstract

**Aim:** The aim of present study was to compare the effects of a galantamine only therapy and a combination therapy with galantamine plus ambulatory cognitive rehabilitation for AD patients.

**Methods:** For this retrospective cohort study, we enrolled 86 patients with AD, dividing into 2 groups such as a galantamine only (group G, n=45) and a combination with galantamine plus ambulatory rehabilitation (group G+R, n=41). The present cognitive rehabilitation included a set of physical therapy, occupational therapy, and speech therapy for 1-2 hr once or twice a week. We compared mini mental state examination (MMSE) and frontal assessment battery (FAB) for cognitive assessment, and geriatric depression scale (GDS), apathy scale (AS) and Abe's BPSD score (ABS) for affective assessment in 2 groups with 6 months.

**Results:** Baseline MMSE was 20.2 and 18.7 in groups G and G+R, respectively. Other baseline data (FAB, GDS, AS, and ABS) were not also different between the 2 groups. Although group G kept all the scores stable until 6 months of the treatment, AS score showed a significant improvement in the group G+R as early as 3 months, followed by the MMSE and FAB improvements at 6 months (\*p=0.04 and \*p=0.02, respectively). GDS and ABS did not show any changes.

**Conclusion:** The combination therapy of galantamine plus ambulatory cognitive rehabilitation showed a superior benefit both on cognitive and affective functions than galantamine only therapy in AD patients.

**Key words:** Alzheimer's disease, Combination therapy, Galantamine, Cognitive function, Affective function

**Abbreviation:** ABS, Abe's BPSD score; AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; AS, apathy scale; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition; FAB, frontal assessment battery; GDS, geriatric depression scale; ICD-10, international classification of diseases, tenth revision; MMSE, mini-mental state examination; fMRI, functional magnetic resonance imaging.

## **Introduction**

Alzheimer's disease (AD) is the most common form of dementia characterized by progressive cognitive impairment, functional decline and neuropsychiatric symptoms (Di Iulio et al., 2010). Demographic factors (aging, female, and low education) and clinical factors (presence of medial temporal atrophy, white matter lesions, and vascular

risk factors) are related to developing AD (Launer et al., 1999; Kawas et al., 2000; Li et al., 2011; Tokuchi et al., 2014), where both pharmacological and non-pharmacological treatments are expected to prevent the progression of AD. For pharmacological treatments, acetylcholinesterase inhibitor (AChEI; donepezil, galanthamine, and rivastigmine) and N-methyl-D-aspartate receptor uncompetitive antagonist (memantine) are commonly used in the world.

On the other hand, non-pharmacological treatments includes several therapies such as physical exercise (Van de Winckel et al., 2004), reality orientation therapy (Onder et al., 2005), occupational therapy (Dooley et al., 2004) and a combination therapy of pharmacological and non-pharmacological treatments (Olazaran et al., 2004; Onder et al., 2005; Requena et al., 2006; Matsuzono et al., 2014). The combination therapies were effective for dementia, but most previous studies were with donepezil and only on cognitive functions (Onder et al., 2005; Requena et al., 2006; Matsuzono et al., 2014). However, there was few report on a combination therapy with galantamine and also on affective functions. In the present study, therefore, we retrospectively analyzed an effect of combination therapy with galantamine plus ambulatory cognitive rehabilitation both on cognitive and affective functions for AD patients.

## Methods

For this retrospective cohort study, we enrolled 86 patients with Alzheimer's disease (AD) who took galantamine. AD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or the International Classification of Diseases, Tenth Revision (ICD-10).

The 86 AD patients were divided into 2 groups depending on undertaking ambulatory rehabilitation or not; 45 patients (14 male and 31 female; age  $78.8 \pm 7.3$  years, mean  $\pm$  SD) were treated with only galantamine (group G), and 41 patients (16 male and 25 female; age  $79.0 \pm 7.8$  years) were with galantamine plus ambulatory rehabilitation (group G+R) over 6 months. Ambulatory rehabilitation therapies for the dementia patients include ① physical therapy (massed calisthenics), ② occupational therapy (group task for whickerwork or leatherwork, creative activity (drawing, cut out picture, knitting, and flower arrangement)), and ③ speech therapy (chorus music and watching theatrical performances). The group G+R patients took rehabilitation programs once or twice a week with 1-2 hr duration for each rehabilitation menu. On the other hand, group G patients took only a drug therapy without these ambulatory rehabilitation therapies (Table 1).

All patients received both neurological examination and cognitive tests, such as

mini-mental state examination (MMSE) (Folstein et al., 1975) and frontal assessment battery (FAB) (Dubois et al., 2000). Behavioral and psychological symptoms of dementia (BPSD) was evaluated using the geriatric depression scale (GDS) (Yesavage JA, 1988), apathy scale (AS) (Starkstein et al., 1993) and Abe's BPSD score (ABS) (Abe et al., 2013). Medical records were reviewed to assess each group of cognitive and affective states. At follow-up of 3 month (M) and 6 M later, cognitive and affective functions were reassessed in each group. Cognitive and affective assessments were performed using the same tests applied at the initial assessment, and possible differences were examined between the results of baseline and the follow-up timings for each group.

The criteria for exclusion were memantine use, previous psychosis, multiple sclerosis, motor neuron disease, Parkinson's disease, other major neurological diseases, or if they had medical or psychological conditions that prevented their assessment tasks.

Comparisons between demographic and clinical characteristics of the 2 groups (group G and group G+R) at baseline were performed with Mann-Whitney test for continuous variables, and with chi-square statistics for comparison of proportions. Changes in cognitive and affective assessment scores between baseline and each follow-up point were analyzed using the Wilcoxon signed-rank test. The scores of the 2

groups were compared using the Mann-Whitney among the timings of baseline, 3 M and 6 M. In addition, subscores of MMSE and FAB were assessed using the Mann-Whitney test. All statistical analyses were performed with the SPSS-J for Windows version 21.0 (IBM Corporation, Armonk, NY, USA). We selected  $p < 0.05$  as the threshold of significance.

This study was approved by the Ethics Committee on Epidemiological Studies of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (No. 694). Written informed consent was obtained from all participants.

## Results

The baseline demographic and clinical characteristics of the each group were shown in Table 2. Although all 5 clinical scores (MMSE, FAB, GDS, AS, and ABS) tended to be worse in group G+R than group G, no significant differences were found between the 2 groups in the 5 clinical scores as well as in age, gender, vascular risk factors (hypertension, hyperlipidemia, diabetes mellitus) and galantamine dose.

As compared to group G ( $-0.5 \pm 3.6$ ), the MMSE score showed a significant improvement at 6 M in the group G+R ( $1.2 \pm 3.3$ ,  $*p = 0.04$  vs group G) (Fig. 1). The FAB score also showed a significant improvement in the group G+R at 6 M ( $0.9 \pm 2.9$ ,

\* $p = 0.02$ ) than group G ( $-0.6 \pm 2.3$ ) (Fig. 1). As for affective functions, GDS and ABS showed improving tendency up to 6 M of the treatment, but not significant (Fig. 1). In contrast, the AS score showed significant improvements in the group G+R ( $-2.7 \pm 5.6$ , \* $p = 0.04$ ) than group G ( $5.4 \pm 10.7$ ) at 3M, and group G+R ( $-2.9 \pm 5.9$ , \* $p = 0.03$ ) than group G ( $1.9 \pm 6.2$ ) at 6 M, respectively (Fig. 1).

Regarding the subscores of the MMSE, copying figure was significantly preserved at 6 M in the group G+R ( $0.0 \pm 0.3$ , \* $p = 0.03$ ) compared to the decrease of the group G ( $-0.3 \pm 0.4$ ) (Fig. 2). In analysis of the FAB subscores, conflicting instructions showed a significant improvement at 6 M of the group G+R ( $0.7 \pm 1.0$ , \* $p = 0.03$ ) compared to the decline in the group G ( $-0.1 \pm 0.7$ ) (Fig. 2).

## Discussion

Our present study showed that the combination therapy of galantamine plus ambulatory rehabilitation significantly improved cognitive and affective functions of AD patients for 6 M (Fig. 1). AS showed a significant improvement as early as 3 M with the combination therapy, followed by the improvement of MMSE and FAB scores (Fig.1). On the other hand, there was no significant difference between the 2 groups (group G and group G+R) in GDS and ABS at 3 and 6 M, but these scores also tended



to be improved in the combination therapy group (Fig. 1).

Apathy is defined as a quantitative reduction of voluntary and goal-directed behaviors, which is related to prefrontal and basal ganglia lesions (Levy and Dubois, 2006). Among MMSE subscores, copying figure was significantly preserved in the group G+R (Fig. 2). Copying figure assesses constructional performance, which is closely related to global cognitive and constructional functions (Cormack et al., 2004) with temporal and parietal association (Ogawa and Inui, 2009; Melrose et al., 2013). Conflicting instruction which was improved in group G+R (Fig. 2) assesses behavioral self-regulation relating to the extensive network of subcortical and cortico-cortical connections of the frontal lobe (Pardo et al., 1990). The present study, therefore, suggests an early activation of prefrontal and basal ganglia against apathy, followed by cognitive activations including subcortical and cortico-cortical connections (Fig.1-2). Similar to our present cognitive rehabilitation (Table. 1), the mixture of physical, occupational, and speech therapies showed a brain activation in the left middle and inferior frontal gyri, the left insula, and the right medial parietal cortex by functional magnetic resonance imaging (fMRI) (van Paasschen et al., 2013).

Although cognitive rehabilitation improved both cognitive and affective functions in dementia patients (Aguirre et al., 2013; Toba et al., 2014; Matsuzono et al.,

2014), contrasting findings have also been reported (Davis et al., 2001; Cahn-Weiner et al., 2003; Aguirre et al., 2013). A randomized placebo-controlled study for 34 mild AD patients with training showed no significant improvement in 8 weeks compared to the group without training (Cahn-Weiner et al., 2003). In the present study, the combination therapy of galantamine plus ambulatory cognitive rehabilitation improved both cognitive and affective functions in late elder mild AD patients (Table 2, Fig. 1), consistent with the results of recent studies (Olazaran et al., 2004; Viola et al., 2011).

Social isolation is associated with increased risk of mental decline (Bassuk et al., 1999). On the other hand, ambulatory rehabilitation provides enriched social network and interaction, which could protect against mental decline (Fratiglioni et al., 2000; Wang et al., 2002). Our present study suggested that a set of mixed rehabilitation of physical, occupational, and speech therapies showed a beneficial effect on cognitive and affective functions in group G+R. The main limitation of the present study is the retrospective and non-random assignment of the patients between treatment groups, although we adjusted the data for age, gender, galantamine dose, cognitive and affective functions at baseline.

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### **Disclosure statement**

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## Figure legends

**Figure 1** Changes of cognitive and affective scores in galantamine only group

(group G, dotted line) and galantamine plus ambulatory cognitive rehabilitation

(group G+R, solid line). Note a significant improvement of AS as early as 3 M in

group G+R ( $*p<0.05$ ), followed by the improvement of MMSE and FAB at 6 M

( $*p=0.04$  and  $*p=0.02$ , respectively). AS, apathy scale; FAB, frontal assessment battery;

MMSE, mini-mental state examination.

**Figure 2** Subscores of MMSE and FAB between galantamine only (group G,

white bars) and galantamine plus ambulatory cognitive rehabilitation (group G+R,

black bars). Note the significant preservation of copying figure in MMSE at 6 M in

group G+R compared to the decrease of group G ( $*p=0.03$ ), and the significant

improvement of conflicting instructions in FAB at 6 M of the group G+R compared to

the decline in the group G ( $*p=0.03$ ). FAB, frontal assessment battery; MMSE,

mini-mental state examination.