RESEARCH ARTICLE

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# Efficacy of rivastigmine transdermal patch on activities of daily living: item responder analyses

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**Objective:** In Alzheimer's disease (AD), rivastigmine has demonstrated statistically significant efficacy *versus* placebo on cognition and activities of daily living (ADL). The aim of this retrospective analysis was to further evaluate the treatment effects of rivastigmine on individual ADL items.

**Methods:** This exploratory analysis focused on the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) outcome from a large, international, 24-week, controlled trial of rivastigmine once-daily transdermal patch and twice-daily capsules in AD (CENA713D2320, NCT00099242). Percentages of patients ''improving'' or ''not worsening'' on individual ADL items were calculated and changes from baseline with rivastigmine *versus* placebo were evaluated.

**Results:** Patients received rivastigmine patch (9.5 mg/24 h; $n = 247$), capsule (12 mg/day; $n = 254$), and placebo ($n = 281$). Statistically significant changes from baseline in composite ADCS-ADL scores in both rivastigmine treatment groups *versus* placebo ($p < 0.05$) had previously been reported. In this responder analysis of the subset of patients who showed baseline functional impairments on each item, statistically significant differences favoring rivastigmine were seen on the following functions: bathing, clearing dishes, obtaining a beverage, garbage disposal, traveling, shopping, writing, using household appliances, and talking about current events. A responder analysis of emergence of ADL impairment was not as sensitive to treatment effects.

**Conclusions:** These findings suggest that rivastigmine may benefit specific ADL, particularly in patients who are already exhibiting functional impairment. Further research is required to improve understanding of how drugs such as rivastigmine exert their clinical effects. Copyright © 2010 John Wiley & Sons, Ltd.

**Key words:** Alzheimer's disease; rivastigmine; patch; transdermal; activities of daily living
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## Introduction

Alzheimer's disease (AD) is characterized by a deterioration in the ability to conduct activities of daily living (ADL). As such, impaired ADL due to cognitive impairment are considered an essential part of the criteria for dementia and should be routinely assessed (Waldemar *et al*., 2007).

Basic ADL include self-maintenance skills such as washing, dressing, grooming, toileting, eating, and general mobility. Instrumental ADL are activities such as planning a meal, making a telephone call, and managing medications or finances, which require more complex, higher-level thinking (Lawton and Brody, 1969). Early AD is typically associated with loss of more complex instrumental ADL, while basic ADL become impaired in later disease stages (Gauthier *et al*., 1997). As well as having a direct negative impact on the individual with dementia (Broe *et al*., 1998), a decline in the ability to perform day-to-day activities inevitably places growing pressure on the caregiver (Razani *et al*., 2007). It is a major contributing factor

for the eventual need for alternative care or nursing home placement (Severson *et al*., 1994).

Reviews of the available literature have demonstrated that a cause–effect relationship exists between cognitive impairment and the ability to perform ADL (i.e., subjects with low cognitive performance being at greater risk of functional impairment), which is independent of demographic, medical, and lifestyle factors (Barberger-Gateau and Fabrigoule, 1997). As well as the global association between cognitive impairment and functional disability, certain individual ADL have been more closely associated with cognitive impairment than others (Dodge *et al*., 2005). Monitoring of ADL can aid accurate, early diagnosis (Desai *et al*., 2004). Studies that underpin the relationship between cognitive impairment and ADL have tended to focus on global cognitive or neuropsychiatric dysfunction. More recently, researchers have begun investigating specific elements of cognitive impairment responsible for diminished ADL, to better understand the symptoms associated with functional impairments in AD, e.g., Boyle *et al*. (2003; Boyle, 2004).

Rivastigmine is a cholinesterase inhibitor indicated for the symptomatic treatment of mild to moderate AD and Parkinson's disease dementia (PDD). It has demonstrated significant efficacy *versus* placebo on the ''ABCs'' of dementia—ADL, behavior, and cognitive performance—in AD and PDD trial populations (Corey-Bloom *et al*., 1998; Rösler *et al*., 1999; Emre *et al*., 2004). It has also shown efficacy in the amelioration of attentional and/or executive function deficits in patients with AD, PDD, dementia with Lewy bodies (DLB), and subcortical vascular dementia (VaD) (Bullock and Lane, 2007).

In a recent large international trial, rivastigmine transdermal patches and capsules provided statistically significant efficacy *versus* placebo on ADL as assessed by total scores on the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) scale (Winblad *et al*., 2007a,b). *Post-hoc* analyses of individual items of the ADCS-ADL scale to investigate treatment effects have been conducted previously (Feldman *et al*., 2006). We provide here an analysis of the individual ADCS-ADL items from the rivastigmine patch trial. This is a retrospective analysis, for exploratory purposes only, intended to be hypothesis forming and to provide a basis for future research.

## Methods

The development program for the transdermal rivastigmine patch included a 24-week double blind randomized clinical trial in patients with mild to moderate AD. The full methodology has been published previously (Winblad *et al*., 2007a). In summary, patients (50–85 years; Mini-Mental State Examination [MMSE] scores of 10–20) with probable AD were randomized to four treatment groups: rivastigmine 9.5 mg/24 h patch, rivastigmine 17.4 mg/24 h patch, rivastigmine capsules 12 mg/day, or placebo. This paper focuses on the 9.5 mg/24 h patch, which is the approved target dose. The study was conducted in 21 countries.

Patients were titrated, tolerability permitting, to their target dose in 4-week intervals and then maintained at their highest well-tolerated dose (target patch size or capsule). Patients in the target 9.5 mg/24 h rivastigmine patch group received a 4.6 mg/24 h rivastigmine patch for Weeks 1–4 and then the target 9.5 mg/24 h rivastigmine patch for the remainder of the study. Patients in the rivastigmine capsule group started on 3 mg/day (1.5 mg BID) and were titrated every 4 weeks in steps of 3 mg/day to a maximum of 12 mg/day.

Primary efficacy parameters were the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog) and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). ADL were assessed as a secondary measure using the 23-item ADCS-ADL inventory (Galasko *et al*., 1997). The ADCS-ADL is an informant-rated questionnaire with possible scores of 0–78, where 78 represents full independent functioning with no impairment. Other secondary efficacy measures assessed in the trial included the Ten Point Clock-Drawing Test and Trail-Making Test Part A, as measures of executive function and attention, respectively. Patients were evaluated at baseline and at Weeks 16 and 24.

On an item-by-item basis, whether or not an ADL improved, remained stable or declined over 6 months during the trial was tabulated. The frequencies of these ADL categories were then evaluated for treatment effects. Analyses were based on an observed case (OC) population and included only patients who were assessed on individual ADCS-ADL items. Of particular interest were those ADL potentially related to executive function/attention: instrumental tasks (e.g., using the phone or managing finances) that require a higher degree of executive function/attention than basic ADL. The study was not powered to determine statistical significance on individual items, nevertheless non-adjusted *p*-values for the two treatment groups *versus* placebo were calculated based on the Cochran-Mantel-Haenzel test blocking for country.

Relationships among cognitive impairment, functional abilities, and global dementia severity were

examined in the trial population. Change scores were calculated for the ADCS-ADL, ADCS-CGIC, Trail-Making Test Part A and Ten Point Clock-Drawing Test at 24 weeks. Correlations between scores on the different instruments were assessed by examining scatter plots and calculating Spearman correlation coefficients.

## Results

Patients with mild to moderate AD were randomized to active treatment or placebo (Winblad *et al*., 2007a). Demographic and baseline characteristic data for the overall study population have been published (mean age 73.6 years, 66.6% women, mean MMSE score 16.5); no significant differences were observed between treatment arms at baseline (Winblad *et al*., 2007a). A total of 247, 254, and 281 patients in the rivastigmine 9.5 mg/24 h patch, capsule 12 mg/day, and placebo groups, respectively, provided Week 24 ADL data. Statistically significant effects were also observed in both treatment groups on composite ADCS-ADL scores ($p < 0.05$; Figure 1), a secondary outcome of the trial (Winblad *et al*., 2007a). Rivastigmine 9.5 mg/24 h patch and 12 mg/day capsules provided statistically significant effects over placebo on both primary outcome measures (ADAS-cog and ADCS-CGIC).

The frequencies with which functional impairments were observed in patients across the individual ADCS-ADL items at baseline are summarized in Figure 2. Functional impairment was most frequently seen (occurring in > 75% of patients) in items that assessed instrumental ADL: using the telephone (89.0%); being able to talk about a TV program 24 h after watching it (85.5%); going shopping (78.0%); keeping appointments (80.6%); reading (76.7%); being able to talk about something >1 h after reading it (90.8%); and writing (95.4%). In contrast, ADL that appeared to be most preserved in the study population (impairment occurring in <25% of patients) were the basic abilities, such as to eat (22.4%), walk (17.2%), and toilet (16.1%).

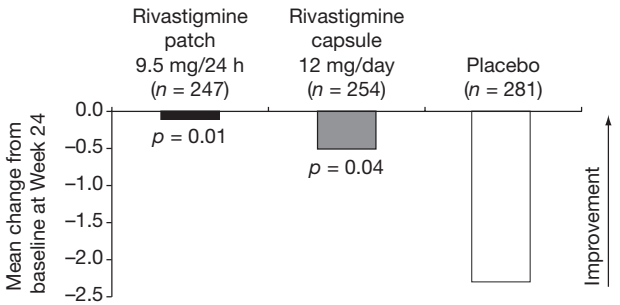



Figure 1 Changes from baseline at 24 weeks in composite ADCS-ADL scores (Winblad *et al*., 2007a). ITT (LOCF) analysis; *$p < 0.05$ *versus* placebo. Reproduced from *Expert Rev Neurotherapeutics* (Cummings and Winblad, 2007) with permission of Expert Reviews Ltd.

Results of the full-itemized ADCS-ADL "improvement" responder analysis—patients who had less than maximal functionality at baseline, but who improved during the course of the study—are provided in Figure 3. Statistically significant treatment effects were observed on the following functional activities: (1) basic: bathing ($p = 0.04$, both rivastigmine groups); clearing dishes ($p = 0.01$, capsule group); (2) higher level: obtaining a beverage ($p = 0.03$, patch group); (3) simple motor: garbage disposal ($p = 0.005$, capsule group); (4) connectedness/autonomy: traveling ($p = 0.02$, capsule group); selecting items when out shopping ($p = 0.03$, patch group); talking about current events outside of home ($p = 0.04$, patch group); writing ($p = 0.03$ and 0.02, patch and capsule, respectively); and using household appliances ($p = 0.047$, patch group). A summary of these statistically significant improvements associated with rivastigmine treatment is provided in Table 1. The responder analysis that focused on all patients "not worsening" on individual items of the ADCS-ADL scale was less sensitive to treatment effects. A statistically significant advantage in terms of functional stability was observed on the higher level "obtaining a beverage" item only (data not shown; $p = 0.009$).

Non-significant, yet marked numerical differences (>25% change *versus* placebo) were seen between the percentages of patients improving in rivastigmine treatment groups (patch and/or capsule) *versus* placebo on items that evaluated: toileting, dressing (selecting clothes and getting dressed), using the telephone, watching TV (selecting program), making conversation (patch), preparing a meal or snack, being left alone at home, and talking about current affairs (including events on TV and at home) (Figure 3). Similar non-significant, numerical treatment differences (>5% change *versus* placebo) were seen on many of the same items on which improvements were noted in terms of functional stabilization (data not shown). In both responder analyses [improving (Figure 3) and not worsening] there appeared to be a numerical trend for statistical significance provided by rivastigmine patch *versus* capsules.

Associations between the ADCS-ADL items and cognition and clinicians' impression of change were evaluated with Spearman correlations. At baseline, total scores on the ADCS-ADL reflected associations with the ADAS-cog ($r = -0.55$), Trail-Making Test Part A ($r = -0.34$), and Ten Point Clock-Drawing Test ($r = 0.31$); in each case, $p < 0.0001$. At Week 24,

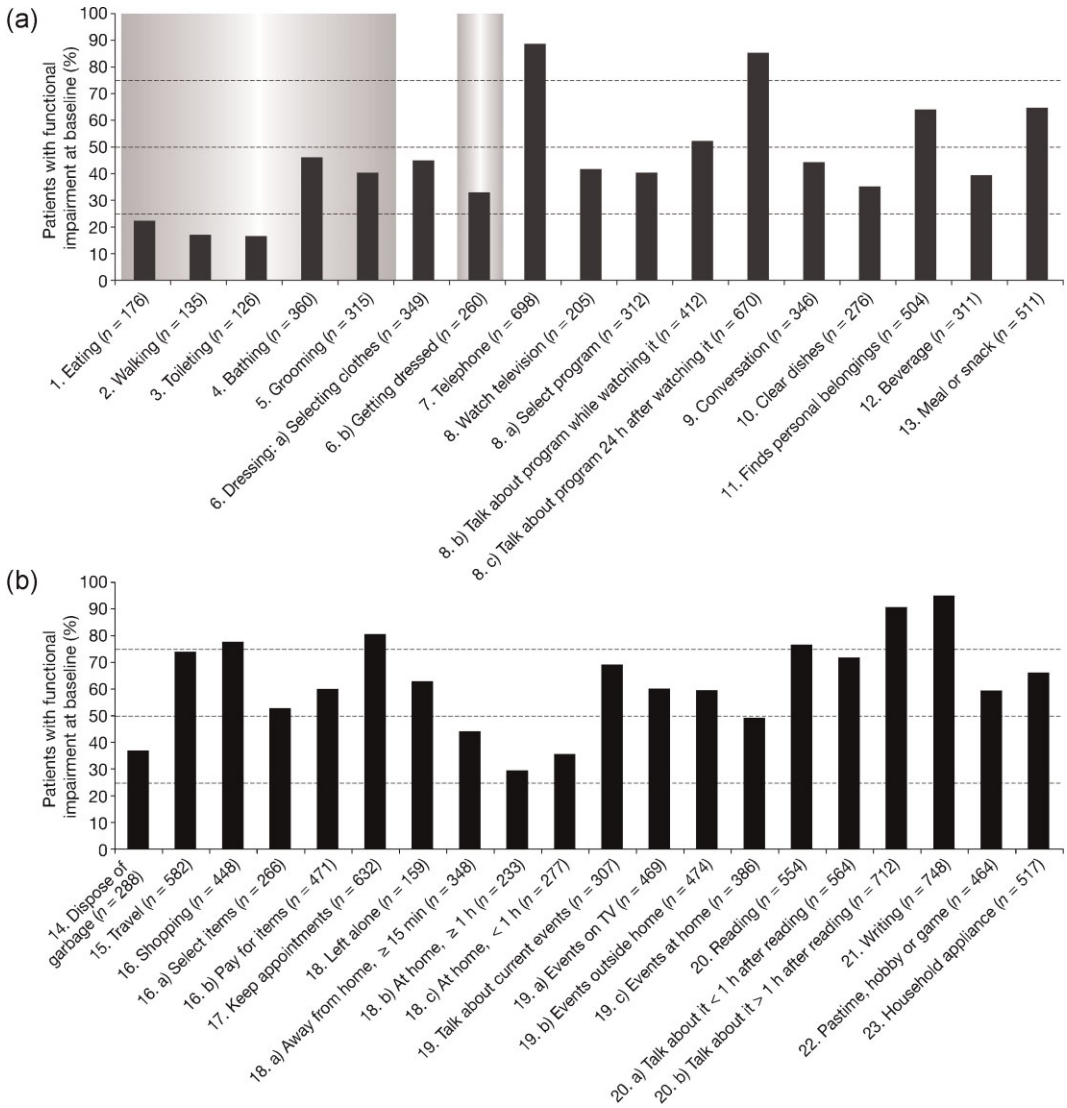



Figure 2 Frequency of functional impairment across individual ADCS-ADL items at baseline (OC population): (a) ADL items 1–13; and (b) ADL items 14–23. The six basic ADL are shaded to differentiate them from instrumental ADL.

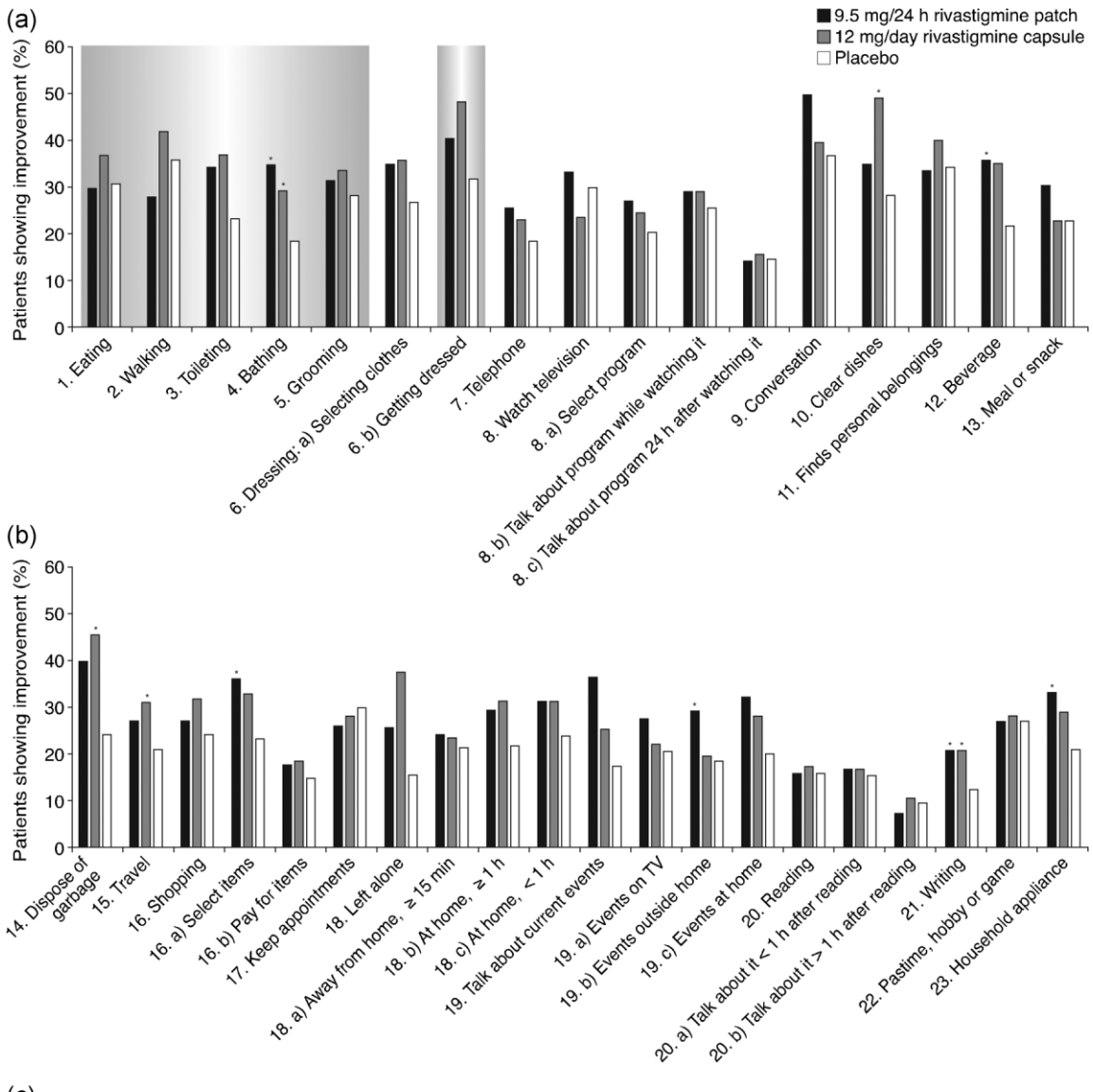
these associations remained statistically significant for the respective measures ($r = -0.60$, $-0.44$, and 0.43; each $p < 0.0001$) (Figure 4). Further, 24-week change on the ADCS-CGIC was found to be associated with 24-week change in the total ADL score ($r = -0.37$; $p < 0.0001$), as were 24-week changes in ADAS-cog ($r = -0.33$; $p < 0.0001$), Trail-Making Test Part A ($r = -0.12$; $p < 0.0001$) and the Ten Point Clock-Drawing Test ($r = 0.08$; $p = 0.0081$).

## Discussion

ADL dependency in AD impacts both patient and caregiver quality of life (Kurz *et al*., 2003; Andersen *et al*., 2004). Further, the loss of ADL is associated with increased healthcare costs and institutionalization (Hill *et al*., 2006), while antidementia treatment can reduce the costs associated with care provision (Weycker *et al*., 2007; Hatoum *et al*., 2009). Therefore, improvement, stabilization, or slowing the rate of decline of daily living skills are key components of effective therapy for AD. Studies published to date (utilizing numerous validated scales) have shown that cholinesterase inhibitors provide modest but clinically meaningful positive effects on ADL in patients with mild to moderate AD (Schneider *et al*., 1998; Burns *et al*., 1999; Tariot *et al*., 2000; Wilcock *et al*., 2000; Winblad *et al*., 2001).

Statistically significant improvements from baseline with rivastigmine (transdermal patch and capsule)




(c)

| | 1 | 2 | 3 | 4 | 5 | 6A | 6B | 7 | 8 | 8A | 8B | 8C | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 16A | 16B | 17 | 18 | 18A | 18B | 18C | 19 | 19A | 19B | 19C | 20 | 20A | 20B | 21 | 22 | 23 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 9.5 mg/24 h patch (n) | 14 | 9 | 12 | 30 | 22 | 29 | 26 | 47 | 16 | 20 | 30 | 25 | 43 | 24 | 44 | 31 | 41 | 28 | 41 | 31 | 22 | 21 | 42 | 9 | 22 | 16 | 20 | 31 | 36 | 37 | 32 | 22 | 24 | 13 | 41 | 34 | 44 |
| 12 mg/day capsule (n) | 20 | 16 | 13 | 31 | 30 | 36 | 33 | 45 | 14 | 22 | 33 | 29 | 41 | 37 | 58 | 29 | 32 | 37 | 52 | 40 | 20 | 24 | 51 | 18 | 22 | 21 | 26 | 22 | 28 | 26 | 30 | 27 | 26 | 21 | 43 | 36 | 41 |
| Placebo (n) | 15 | 15 | 8 | 21 | 31 | 31 | 26 | 40 | 22 | 22 | 35 | 30 | 38 | 23 | 53 | 20 | 35 | 22 | 37 | 34 | 14 | 22 | 59 | 8 | 22 | 17 | 21 | 17 | 30 | 27 | 26 | 29 | 28 | 21 | 29 | 39 | 34 |

Figure 3 Percentages of patients with less than maximal functionality at baseline "improving" on individual ADCS-ADL item scores in AD patients receiving rivastigmine patch (9.5 mg/24 h), capsules (12 mg/day), or placebo for 24 weeks (OC population): (a) ADL items 1–13, (b) ADL items 14–23, and (c) numbers of patients assessed in each study arm per ADL item. The six basic ADL are shaded to differentiate them from instrumental ADL. $^*p < 0.05$ *versus* placebo.

*versus* placebo have been demonstrated on total ADCS-ADL scores (Winblad *et al*., 2007a,b). This retrospective analysis of individual ADL from the same previously reported clinical trial of rivastigmine (patch and capsule) (Winblad *et al*., 2007a), shows that both instrumental and basic ADL activities can be maintained or improved with treatment when compared to placebo.

Rivastigmine treatment was superior to placebo on the overall ADCS-ADL score, as well as on most of the individual ADL items in the functional improvement responder analysis. A pooled analysis of three phase III studies of rivastigmine capsule was conducted in which the progressive deterioration scale (PDS) was the ADL secondary assessment tool (Schneider *et al*., 1998). Although different ADL scales cannot be directly compared, this revealed a similar trend with statistically significant improvements observed on 22 of 29 ADL items *versus* placebo. The majority of ADL items

Table 1 Summary of ADCS-ADL items for which a statistically significant percentage of patients with improvement was observed with rivastigmine patch (9.5 mg/24 h) or capsule (12 mg/day) treatment at 24 weeks (OC population)

| ADCS-ADL item | Patch | % | Capsule | % |
|---|---|---|---|---|
| 4. Bathing | ✓ | 34.9 | ✓ | 29.2 |
| 10. Clear dishes | | | ✓ | 49.3 |
| 12. Obtain beverage | ✓ | 36.0 | | |
| 14. Dispose of garbage | | | ✓ | 45.7 |
| 15. Travel | | | ✓ | 31.1 |
| 16. Shopping (a) select items | ✓ | 36.1 | | |
| 19. Talk about current events (b) events outside home | ✓ | 29.1 | | |
| 21. Writing | ✓ | 20.5 | ✓ | 20.7 |
| 23. Household appliance | ✓ | 33.1 | | |
| ADL count | 6/23 | | 5/23 | |

✓ Indicates $p < 0.05$ *versus* placebo.

that showed a treatment response were instrumental skills (eight out of the nine items; Table 1). This probably reflects the baseline proportions of impairment that were seen among the 23 ADL, as higher order skills were more impaired in the study population. This profile is typical of patients with mild to moderate AD, the most prominent baseline functional impairments being seen in instrumental ADL, which tend to decline earlier in the course of AD, while basic ADL are relatively preserved (Figure 2) (Gauthier *et al*., 1997). In addition, even though the patch and capsule groups were both associated with improvements in individual ADL functions, treatment resulted in somewhat different patterns of response, with only two items (bathing and writing) showing improvement in both treatment groups. The nature of this ''selective'' response on individual activities may reflect variability in caregiver awareness of impairment (Dassel and Schmitt, 2008), or patient opportunities that are provided by the carer for the patient to complete specific activities.

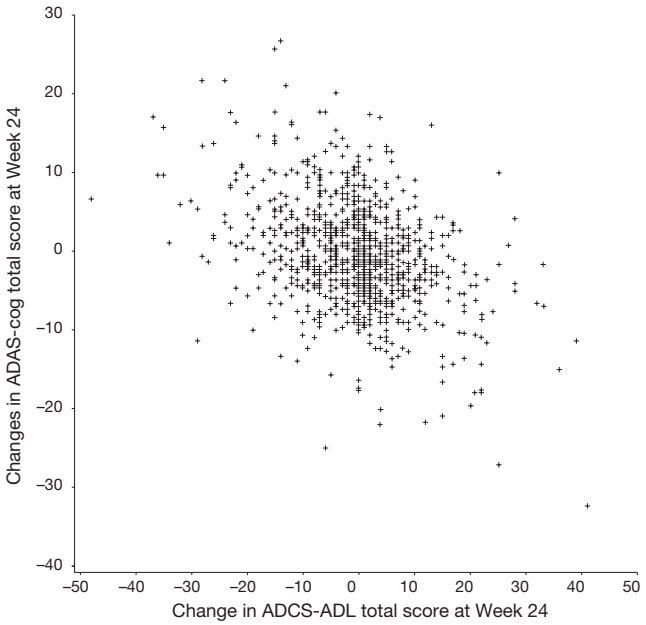



Figure 4 Spearman correlation scatter plot demonstrating association between ADCS-ADL total scores *versus* ADAS-cog at Week 24. ITT (LOCF) analysis ($r = -0.60$; $p < 0.0001$).

Functional stabilization (or ''not worsening'') was less sensitive to rivastigmine treatment effects than the improvement responder analysis. A statistically significant stabilization advantage was seen only on the ''obtaining a beverage'' item in the rivastigmine patch group. Given that only one item showed functional stabilization, it is possible that this finding is not reliable.

Both cognition and clinician ratings were associated with changes in ADL functions. These associations are not surprising as many ADL activities require cognition to underpin a given activity. At the same time, clinician ratings of patients' improvement with treatment also incorporate both cognition and ADL functioning.

Frontal system dysfunction is emerging as an important contributing factor to impairments in ADL among patients with AD (Boyle, 2004). Frontal system pathology results in executive dysfunction, a common feature of AD, which manifests as an inability to coordinate and perform everyday functions and processes (Swanberg *et al*., 2004; Bullock and Lane, 2007). Numerous studies have suggested a close correlation between executive function and attention (functions controlled by frontal lobe circuits) and ADL (Boyle *et al*., 2003; Boyle, 2004). Consistent with these findings, significant associations were noted between total ADCS-ADL scores and measures of executive

function and attention (Ten Point Clock-Drawing Test and Trail-Making Test Part A, respectively) in this trial, at baseline and at Week 24.

It seems feasible that some individual ADCS-ADL items may be more associated with executive function and/or attention than others. For example, an ability to select items when shopping is probably more likely than eating to reflect executive function. Executive dysfunction has been associated with disabilities in instrumental ADL even prior to dementia diagnosis (Royall, 2000). Rivastigmine has demonstrated efficacy in the amelioration of attentional and/or executive function deficits in patients with dementia (Bullock and Lane, 2007; Schmitt *et al*., 2009). Therefore, differing extents to which individual ADCS-ADL items are associated with executive function might also have contributed to the ''selective'' treatment responses observed on individual items. The observation that all but one of the ADL items for which a statistically significant percentage of patients improved was instrumental may be further supportive of this hypothesis.

This analysis is limited by its retrospective, *ad-hoc*, OC nature and on this basis is only exploratory. Subsequently, some of the individual item responder analyses are based on small patient populations and reported *p*-values are not adjusted for multiple comparisons. A new trial [study CENA713D US44 (ACTION)] to evaluate a higher dose rivastigmine patch (13.3 mg/24 h) in severe AD includes a measure of ADL as a coprimary measure. Nonetheless, the analyses presented provide helpful information.

## Conclusion

Rivastigmine may benefit specific ADL, particularly in patients who are already exhibiting functional impairment. Further research to fully elucidate how drugs such as rivastigmine exert their clinical effects, and the underlying basis for their selectivity, is warranted.

## Disclosures

In the past year, GA and GG have received personal compensation from Novartis for serving as consultants and speakers. GG was an investigator in the Novartis-sponsored study for which the current data were collected. FS has no potential conflict of interest to declare. JO and XM are full-time employees of Novartis Pharmaceutics, Inc., New Jersey, USA.

Keypoint

- Impaired ADL in Alzheimer's disease impacts both patient and caregiver quality of life; rivastigmine may benefit specific ADL.

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