American Journal of Alzheimer's Disease & Other Dementias®
25(8) 627-633

DOI: 10.1177/1533317510385808
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Effects of Transdermal Rivastigmine on ADAS-Cog Items in Mild-to-Moderate Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) patients treated with rivastigmine transdermal patch have shown statistically significant differences versus placebo on the AD Assessment scale—cognitive subscale (ADAS-cog). In this retrospective analysis of a double-blind, placebo- and active-controlled, 24-week clinical trial, the specific effects of rivastigmine patch on individual ADAS-cog items and cognitive domains (memory, language, and praxis) were explored. The mean baseline to week 24 changes were calculated for each ADAS-cog item and domain in this exploratory, hypothesis-generating analysis. Patients on 9.5 mg/24 h rivastigmine patch, 17.4 mg/24 h rivastigmine patch, and 3 to 12 mg/d rivastigmine capsules showed improvements over placebo on the memory and praxis ADAS-cog subscales. The rivastigmine patch groups also showed improvements on the language subscale. Significant differences versus placebo were seen on several individual item scores in the rivastigmine-treated groups. Rivastigmine patch was associated with improvements on the memory, praxis, and language domains of cognition in patients with mild-to-moderate AD.

Keywords

Alzheimer's disease, cognition, rivastigmine, transdermal patch

Introduction

The Alzheimer's Disease Assessment scale (ADAS) was developed in the early 1980s to rate the severity of the deficits commonly associated with Alzheimer's disease (AD).[1] Accordingly, the full scale assesses cognitive functions and noncognitive functions such as emotional and behavioral changes. The cognitive subscale of the ADAS (ADAS-cog) is regarded the "gold standard" cognitive measure for mild-to-moderate AD clinical trials.[2] It comprises 11 items that have been allocated (by previous factor analysis[3]) to represent 3 key cognitive domains: language, memory, and praxis. The ADAS-cog has high inter-rater and test–retest reliability, and it has been shown to reliably assess the stage of AD.[1,4] The overall ADAS-cog score ranges from 0 to 70, with a higher score indicating more severe cognitive impairment.[1]

The cholinesterase inhibitor rivastigmine is approved for the treatment of mild-to-moderate AD in the United States, Europe, and many other countries. It has been widely available for about a decade in oral formulations (capsules and oral solution). In 2007, the US Food and Drug Administration (FDA) approved the rivastigmine transdermal patch, which is associated with improved gastrointestinal tolerability compared with oral rivastigmine.[5] In clinical trials, patients treated with oral or transdermal rivastigmine have shown statistically significant differences versus placebo on the ADAS-cog.[5-8]

Although clinical trial data have demonstrated effects of rivastigmine on the cognitive symptoms of AD, there appears to be limited information pertaining to the characterization of these effects. Neuroimaging data suggest that rivastigmine might activate areas of the cortex that are involved in attentional processes.[9] For example, some exploratory electroencephalography (EEG), positron emission tomography (PET), and single photon emission computer tomography (SPECT) studies have pointed toward pharmacological activity in the frontal, temporal, and parietal cortices of patients with AD taking rivastigmine, particularly the anterior cingulate cortex.[10-12] These brain areas are associated with learning, working memory, and attention, and it has been hypothesized that rivastigmine might have particular efficacy in these cognitive domains.[9,13]

The objective of this retrospective analysis was to explore the specific effects of rivastigmine in patients with AD, using individual ADAS-cog item scores from a previous trial of the

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rivastigmine transdermal patch. As well as gaining clinical insights into the effects of this drug, the findings may contribute to existing hypotheses—or lead to further new ones—on drug effects in specific brain areas.

Methods

This was a retrospective analysis of an international, double-blind, placebo- and active-controlled, 24-week clinical trial designed to compare the efficacy and safety of rivastigmine patch versus rivastigmine capsules and placebo (Investigation of transDermal Exelon in ALzheimer's disease [IDEAL], Study CENA713D2320).[5] The full design of this study has been published previously.[5] In summary, patients had a diagnosis of Alzheimer's type dementia[14] and probable AD,[15] and a Mini Mental State Examination (MMSE) score[16] between 10 and 20. Eligible patients were randomly assigned to groups with a target dose of 9.5 mg/24 h rivastigmine patch, 17.4 mg/24 h rivastigmine patch, 12 mg/d rivastigmine capsules, or placebo.[5] Mean change in the total ADAS-cog score from baseline to week 24 was a primary outcome measure in this trial. Study procedures were reviewed by the Independent Ethics Committee or Institutional Review Board for each center, and the study was conducted according to the ethical principles of the Declaration of Helsinki (2000).

In the current analysis, the mean changes between baseline and week 24 were calculated for each ADAS-cog item score and cognitive domain score using an intent-to-treat (ITT) population, with a last observation carried forward (LOCF) imputation. This had been the primary efficacy analysis population in the original placebo-controlled trial, and it included all randomized patients with a pre- and post-baseline assessment of a primary variable. An analysis using the ITT observed case population gave similar results to the ITT-LOCF population analysis (data not shown). Although the study was not powered to detect statistically significant differences on the ADAS-cog individual item scores, *P* values for differences between treatment groups were calculated for each item using the van Elteren test blocking for country. The data were not corrected for multiple comparisons.

In addition to using the ADAS-cog domains of language, memory, and praxis previously identified by the earlier factor analysis,[3] a new factor analysis was performed to establish a "best fit" for individual items to cognitive domains in the current study population and to test whether the grouping of the ADAS-cog items differs in different populations with AD. For this new factor analysis, PROC FACTOR in SAS was used. Initial common factor extraction was performed using the principal component method. Estimates of loadings were obtained using varimax rotation. Although the study was not powered to detect statistically significant differences on the newly fitted or previously identified cognitive domains,[3] *P* values for differences between treatment groups were calculated for each domain using an analysis of covariance (ANCOVA) model, with treatment and country as factors and baseline as a covariate.

Results

In the original analysis, baseline and week 24 ADAS-cog data were provided by 248, 262, 253, and 281 patients receiving 9.5 mg/24 h rivastigmine patch, 17.4 mg/24 h rivastigmine patch, 12 mg/d rivastigmine capsules, and placebo, respectively.[5] Approximately two thirds of the study population was female, the mean age was approximately 74 years, and the mean baseline MMSE score was approximately 16.5, suggesting a moderate degree of dementia severity.[5]

At baseline, patients in all treatment groups showed a similar profile of cognitive impairment across the 11 ADAS-cog items (Figure 1). Greatest baseline impairment appeared to be seen in tasks of word recall, orientation, and word recognition. Other items were relatively well preserved at study entry.

The rivastigmine treatment groups, particularly the 9.5 mg/24 h and 17.4 mg/24 h rivastigmine patch groups, showed improvements over placebo in the mean changes between baseline and week 24 on all ADAS-cog item scores (Figure 2). These differences were statistically significant for the 9.5 mg/24 h rivastigmine patch versus placebo on 3 items (word recall, naming objects or fingers, and ideational praxis; all Ps < .05), and for the 17.4 mg/24 h rivastigmine patch versus placebo on 9 items (word recall, following commands, constructional praxis, naming objects or fingers, ideational praxis, word recognition, recall of test instructions, spoken language ability, and word-finding difficulty items; all Ps < .05). The rivastigmine capsule group showed significant differences when compared to placebo on 4 ADAS-cog items (word recall, constructional praxis, ideational praxis, and recall of test instructions items; all Ps < .05). Importantly, significant differences in ADAS-cog item scores also emerged between the 17.4 mg/24 h rivastigmine patch and both the 9.5 mg/24 h rivastigmine patch and 12 mg/d rivastigmine capsule groups. The 17.4 mg/24 h rivastigmine patch group showed a significant reduction on spoken language ability score over 24 weeks relative to the 9.5 mg/24 h rivastigmine patch group and on word recognition and word-finding difficulty relative to the 12 mg/d rivastigmine capsule group (all Ps < .05).

The word recall task of the ADAS-cog consists of 3 trials where the patient reads and recalls the same 10 words. At week 24, the rivastigmine-treated groups, particularly the 17.4 mg/24 h rivastigmine patch group, tended to recall more words in each trial than the placebo group (Figure 3). All 4 treatment groups showed a tendency to improve in task performance over the 3 trials, with similar changes in score between trial 1 and trial 3. There were no significant treatment differences detected in the trial 1 to trial 3 improvements between baseline and week 24.

The 9.5 mg/24 h and 17.4 mg/24 h rivastigmine patch groups showed statistically significant effects versus placebo on the previously determined language, memory, and praxis ADAS-cog domains (Figure 4). The 12 mg/d rivastigmine capsule group was significantly superior to placebo on the memory and praxis domains, but not the language domain.

The new factor analysis using the current data set identified 2 ADAS-cog domains, termed direct cognitive assessments and

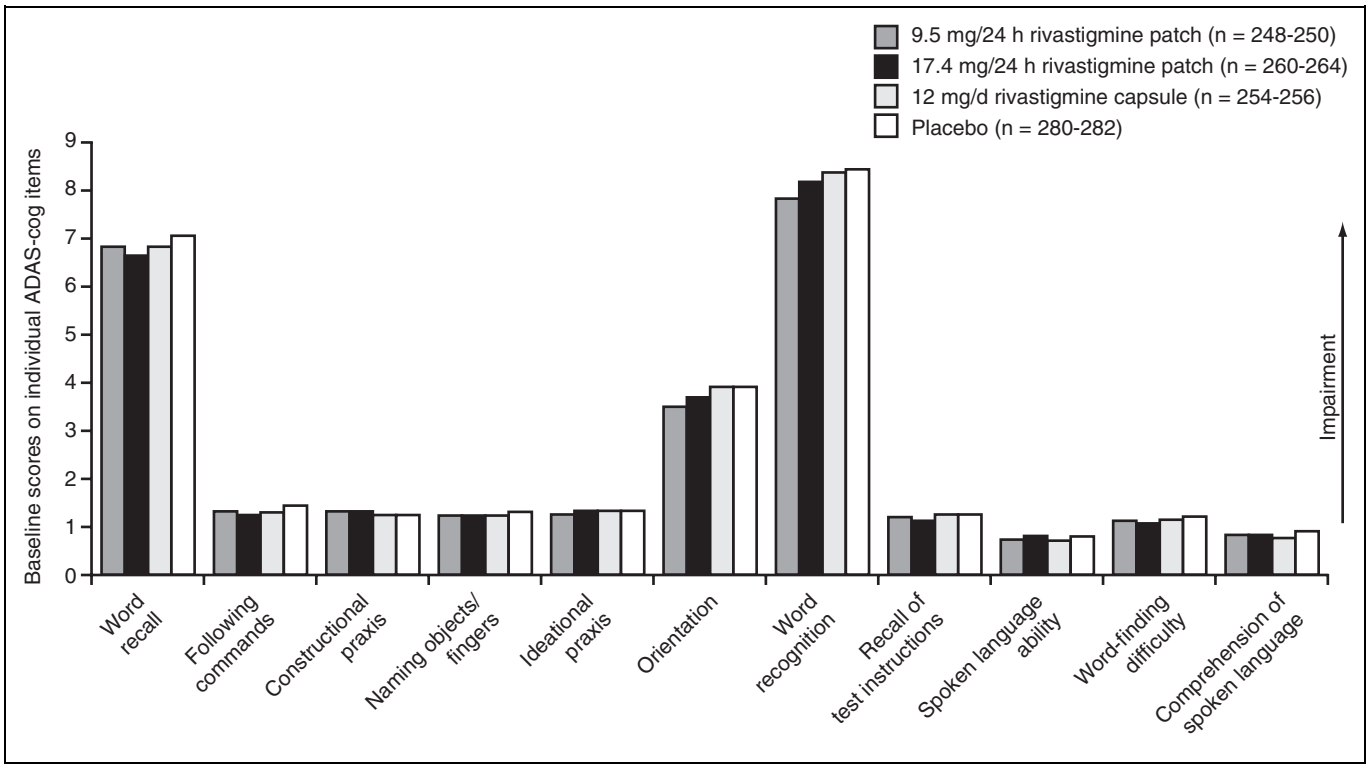

Figure 1. Mean baseline scores on individual ADAS-cog items by treatment group (ITT-LOCF population). Items are scored from 0 to 5, except for word recall (0 to 10), orientation (0 to 8), and word recognition (0 to 12). Higher scores indicate more severe impairment. ADAS-cog indicates Alzheimer's disease Assessment scale–cognitive subscale; ITT, intent-to-treat; LOCF, last observation carried forward.

subjective rater assessments. Direct cognitive assessments included the word recall, following commands, constructional praxis, naming objects or fingers, ideational praxis, orientation questions, and word recognition items. Subjective rater assessments included the recall of test instructions, spoken language ability, word-finding difficulty, and comprehension of spoken language items. All rivastigmine treatment groups provided statistically significant benefits on direct cognitive assessments, but only the 17.4 mg/24 h rivastigmine patch provided significant benefit on subjective rater assessments (Figure 5).

Discussion

This is the first time that the findings from the ADAS-cog individual item scores from the primary rivastigmine patch study[5] have been published. Previous exploratory analyses of rivastigmine capsule studies have shown that treatment with 6 to 12 mg/d rivastigmine is associated with significant improvements on the memory, language, and praxis domains of the ADAS-cog.[17] The current analyses show that rivastigmine patch is associated with broad improvements in cognitive performance in patients with mild-to-moderate AD. All rivastigmine groups (patches and capsules) showed significant effects on memory and praxis domains of cognition. Both rivastigmine patch groups also showed significant effects on the language domain, but unlike the previous analysis, rivastigmine capsule did not show a significant improvement on the language domain score.[17] Further research is needed to clarify the effects of rivastigmine capsules on the language domain of the ADAS-cog.

This breadth of treatment effects may not support a clear-cut brain region selectivity of rivastigmine. Alternatively, it may mean that different ADAS-cog items are not sufficiently distinct or sensitive to detect or distinguish specific effects that may be related to distinct brain regions. In this study, the greatest effects tended to be observed on the memory domain (rather than language and praxis), but additional studies are required to provide a detailed view of the regions of the brain affected by rivastigmine and other cholinesterase inhibitors.

The analyses of word recall scores by trial highlight the potential effect of cholinesterase inhibitors on learning. Across the 3 trials, there was an increase in word list learning that was unaffected by rivastigmine treatment. However, patients on rivastigmine tended to recall more words than those on placebo, suggesting that cholinesterase inhibitors may influence memory, possibly by affecting the overall level of attention devoted to learning.

Reflecting the dose–response relationship seen with rivastigmine,[8] the larger patch (17.4 mg/24 h) tended to show greatest effects on individual ADAS-cog items. A tendency for superior efficacy with both doses of the rivastigmine patch versus capsules was also observed. Previous authors have described data from the primary study showing that about

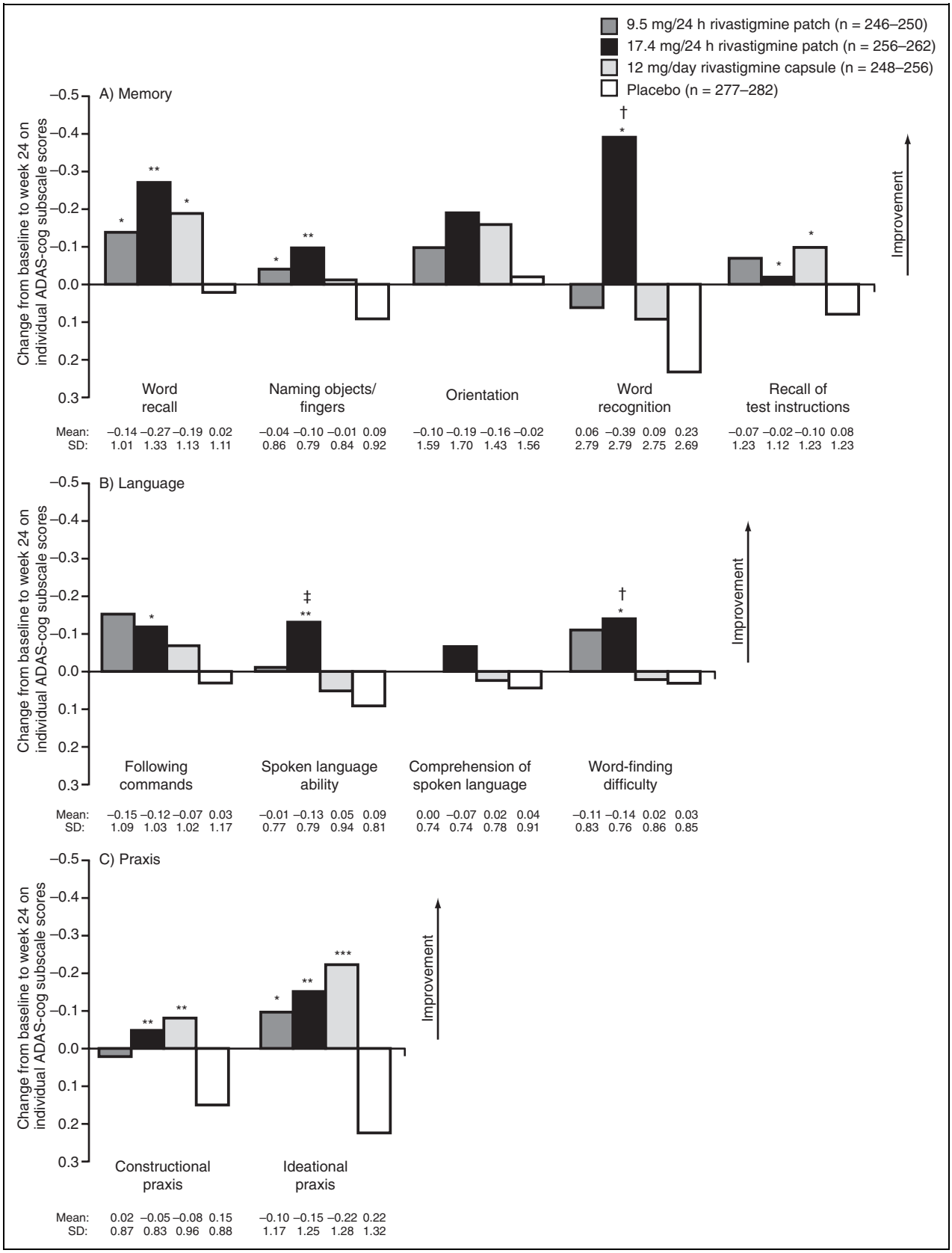

Figure 2. Baseline to week 24 changes on individual ADAS-cog items by treatment group (ITT-LOCF population). *$P < .05$, **$P < .01$, ***$P < .001$, rivastigmine treatment versus placebo; †$P < .05$, 17.4 mg/24 h rivastigmine patch versus 12 mg/d rivastigmine capsule; ‡$P < .05$, 17.4 mg/24 h rivastigmine patch versus 9.5 mg/24 h rivastigmine patch. ADAS-cog indicates Alzheimer's disease Assessment scale—cognitive subscale; ITT, intent-to-treat; LOCF, last observation carried forward.

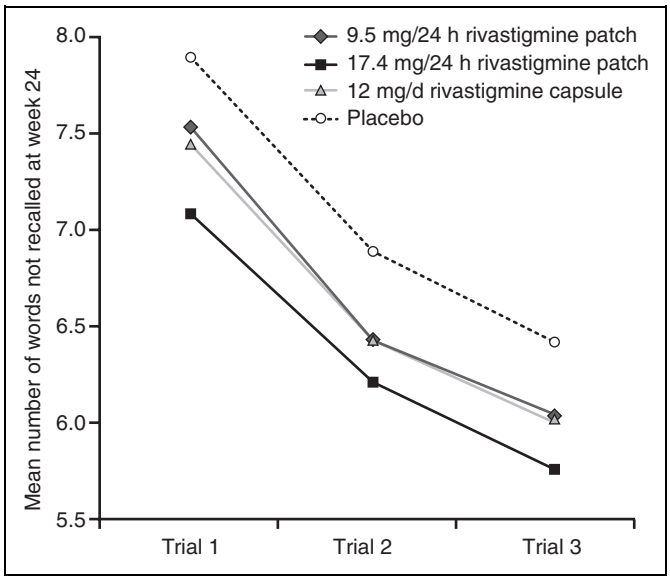

Figure 3. The mean number of words not recalled on each trial of the ADAS-cog word recall task by treatment group at week 24 (ITT-LOCF population). ADAS-cog indicates Alzheimer's disease Assessment scale–cognitive subscale; ITT, intent-to-treat; LOCF, last observation carried forward.

50% more patients in the 9.5 mg/24 h rivastigmine patch group reached target dose, compared with the capsule group.[18] The reduced rates of nausea and vomiting with the patch[5] may permit easier use of higher doses, which in turn may lead to greater clinical effectiveness in some patients. Therefore, a tendency for superior efficacy in both patch groups versus capsules might again be explained by the dose–response relationship seen with this drug.

The current factor analysis allocated the 11 ADAS-cog items to 2 domains, rather than the 3 domains previously published.[3] The "new" direct cognitive assessments domain comprised all of the items that had previously been allocated to the memory and praxis domains, except recall of test instructions, which was replaced by following commands. The "new" subjective rater assessments domain comprised all of the items that had previously been allocated to the language domain, except following commands, which was replaced by recall of test instructions. The fact that the 9.5 mg/24 h group did not show a significant difference versus placebo on subjective rater assessments (yet revealed a significant difference on the previously defined language domain), suggests that the switching of the 2 items—following commands and recall of test instructions—had a meaningful impact on the results. In particular, this might mean that subjective assessments are more difficult to assess reliably, reducing their sensitivity to treatment effects. Indeed, these assessments tend to be the ones that require the most attention in training raters for clinical trials.

The findings also have meaningful clinical implications. Although rivastigmine demonstrated broad effects on various aspects of cognitive performance in this study, clinicians attempting to determine whether patients are responding to rivastigmine treatment may find it useful to focus on specific aspects. For example, word recall and ideational praxis, which improved over baseline versus placebo in all rivastigmine groups (patches and capsules), might provide useful measures for assessing treatment response. However, treatment effects on comprehension and constructional praxis may show a tendency for stabilization, rather than marked improvements over baseline. Such effects might underlie, or contribute to, other clinical effects reportedly seen with the rivastigmine patch on activities of daily living or global performance.[5] As well as considering these findings in terms of assessing treatment response, it might be important to explain the likely treatment effects on different cognitive domains to patients and caregivers, to manage expectations. In a progressive neurodegenerative condition such as AD, delaying the worsening of troublesome symptoms can be as important—over the long term—as providing transient symptomatic improvements. Understanding the likely benefits of treatment may result in greater satisfaction on the part of the patient and caregiver and may encourage them to adhere to treatment regimens for longer.[19]

The current analysis is limited by its retrospective nature. The study was not powered to detect significant differences on individual item scores or domains, and data were not corrected for multiple comparisons due to the exploratory nature of the analyses. These factors affect the robustness of the data, which must be interpreted with caution. Although many cases of statistical significance versus placebo have been reported, further research is required to confirm these findings and to confirm the clinical relevance of the treatment differences observed. Nevertheless, the data have credence for hypothesis formation, which was the original objective.

In conclusion, rivastigmine patch was associated with improved cognitive function in patients with mild-to-moderate AD, including broad effects on memory, praxis, and language domains of cognition. Of these 3 domains, the strongest treatment effects tended to be seen on memory.

Acknowledgments

The development of this review article was supported by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. All authors contributed to the content, drafting, critical revision and approval of this review article. Xiangyi Meng performed the statistical analyses on which the article is based. Novartis developed and manufactures rivastigmine transdermal patch, and they sponsored the large multicenter, randomized, double-blind, 24-week study that led to its approval in the USA. Medical writing and editorial assistance in the preparation of this article was provided by Lisa Redrup and Sarah Harding of Alpha-Plus Medical Communications Limited (UK).

Declaration of Conflicting Interests

GTG has received personal compensation for consulting and research funding from Novartis Pharmaceuticals. FAS has received research funding from Pfizer and Forest Laboratories. XM, ST and JTO are employees and stock holders of Novartis Pharmaceuticals Corporation.

Funding

The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article: This study was supported by Novartis Pharmaceuticals Corporation, East Hanover, NJ. Medical

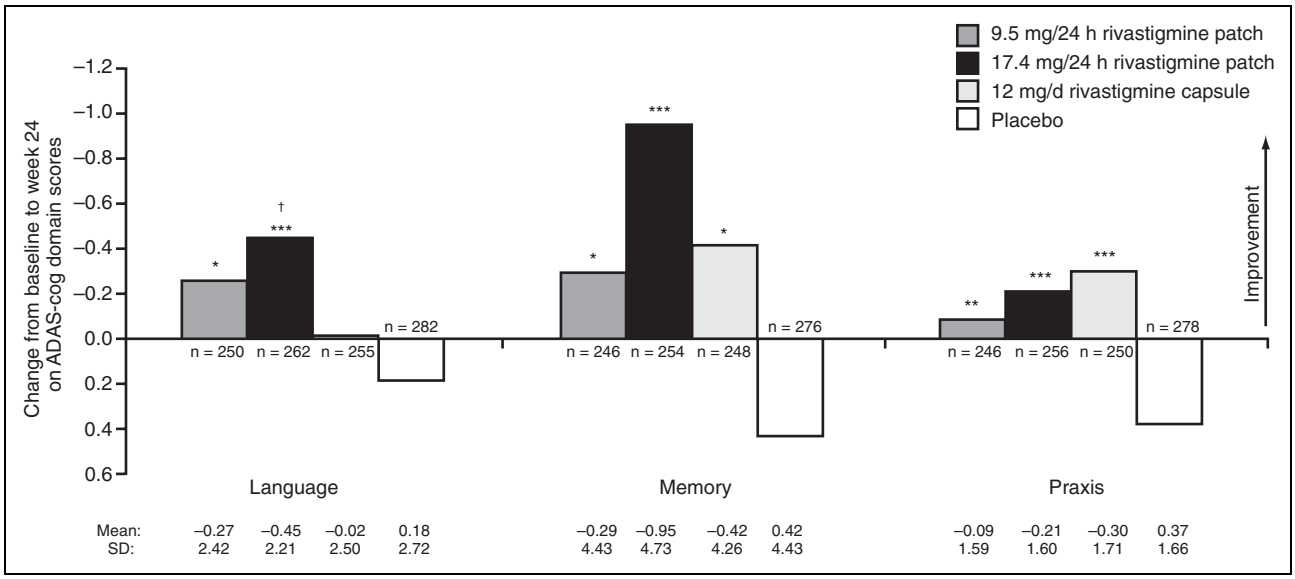

Figure 4. Baseline to week 24 changes by treatment group on the ADAS-cog domains identified by a previous factor analysis[3] (ITT-LOCF population). *$P < .05$, **$P < .01$, ***$P < .001$, rivastigmine treatment versus placebo; †$P < .05$, 17.4 mg/24 h rivastigmine patch versus 12 mg/d rivastigmine capsule. Language domain: following commands, spoken language ability, word-finding difficulty, and comprehension of spoken language items. Memory domain: word recall, naming objects/fingers, orientation questions, word recognition, and recall of test instruction items. Praxis domain: constructional praxis and ideational praxis items. ADAS-cog indicates Alzheimer's disease Assessment scale—cognitive subscale; ITT, intent-to-treat; LOCF, last observation carried forward.

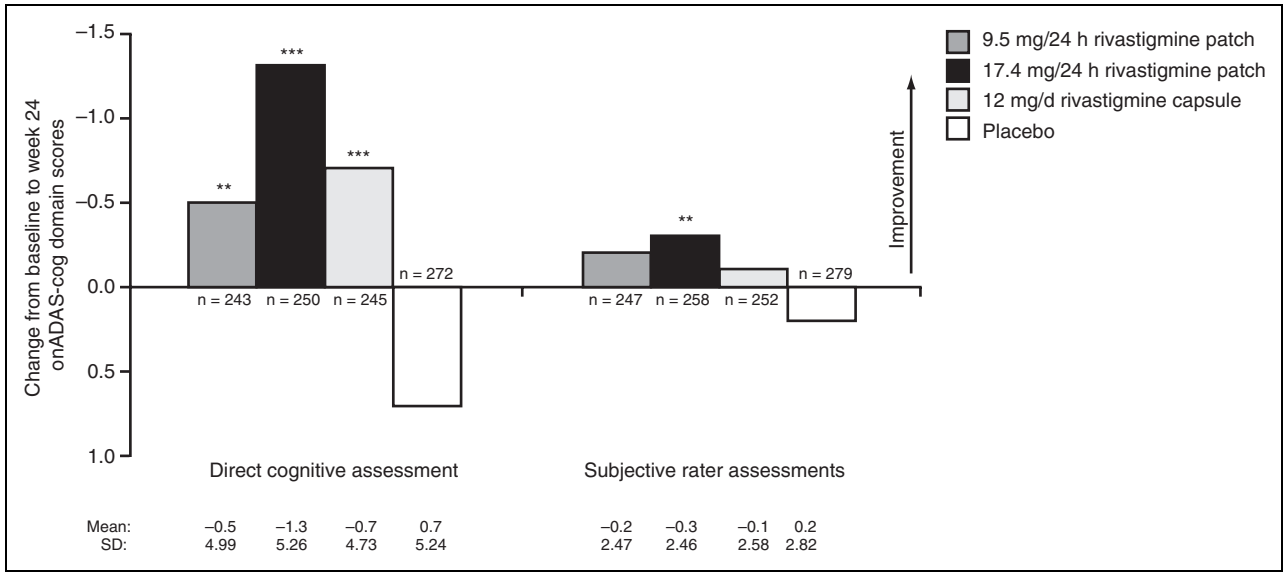

Figure 5. Baseline to week 24 changes by treatment group on the ADAS-cog domains identified by a new factor analysis of the current data set (ITT-LOCF population). **$P < .01$, ***$P < .001$, rivastigmine treatment versus placebo. Direct cognitive assessments: word recall, following commands, constructional praxis, naming objects/fingers, ideational praxis, orientation questions, and word recognition items. Subjective rater assessments: recall of test instructions, spoken language ability, word-finding difficulty, and comprehension of spoken language items.

writing and editorial assistance were provided by Alpha-Plus Medical Communications Ltd (UK), which was sponsored by Novartis Pharmaceuticals Corporation.

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