Activities of Daily Living in Moderate-to-Severe Alzheimer Disease: An Analysis of the Treatment Effects of Memantine in Patients Receiving Stable Donepezil Treatment

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Abstract: In moderate-to-severe Alzheimer disease (AD), there are significant losses of activities of daily living (ADL). In a recent prospective, randomized, placebo-controlled trial, memantine treatment lessened the overall functional decline in AD patients already on stable donepezil therapy. In this trial, patients (n = 404) with Mini-Mental State Examination scores of 5 to 14 receiving stable donepezil treatment were randomized to double-blind treatment with memantine (10 mg b.i.d.; n = 203) or placebo (n = 201). A primary outcome measure was the 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL$_{19}$). To further evaluate the treatment effects of memantine on function, we performed post hoc analyses of ADCS-ADL$_{19}$ data from this trial, including ADL items and new subscales derived from factor analysis. Using mixed model analyses, patients receiving memantine had statistically significant less decline in total ADCS-ADL$_{19}$ scores compared with placebo. An item analysis revealed statistically significant benefits of memantine on grooming, toileting, conversing, watching television, and being left alone. Statistically significant improvements were noted in subscales evaluating higher-level functions and connectedness/autonomy with memantine compared with placebo. These post hoc analyses in moderate-to-severe AD patients receiving stable donepezil treatment suggest that memantine may impact overall functional levels, and some of the cognitive processing underlying ADL performance.

Key Words: Alzheimer disease (AD), activities of daily living (ADL), randomized placebo-controlled trial (RCT), memantine, donepezil, treatment

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Alzheimer disease (AD) is accompanied by increased functional disability over time,[1] associated with loss of independence, caregiver burden,[2] and institutionalization.[3,4] Scales to assess function include the Disability Assessment for Dementia (DAD)[5] and the Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory (ADCS-ADL).[6] These instruments allow more detailed assessment, characterize both rates and patterns of decline, and can be used to evaluate treatment efficacy. Whereas the evolution of functional disability in mild-to-moderate AD is well characterized,[6,7] the patterns of loss in moderate-to-severe AD are less completely delineated. As AD progresses from mild-to-moderate stages, losses in basic or physical activities of daily living (ADL) take greater precedence over those of instrumental ADL (IADL). One post hoc analysis found that a key transition point from mild-to-moderate AD is a Mini-Mental State Examination (MMSE) score of 16.[7] In moderate-to-severe AD, the deterioration in basic ADL accelerates while IADL decline slows, as there are fewer residual functional tasks that remain intact.

The impact of currently approved AD treatments on IADL and basic ADL losses in moderate-to-severe AD remains to be fully characterized. A 6-month

randomized placebo-controlled trial of de novo patients treated with donepezil in moderate-to-severe AD (MMSE range 5 to 17) found an overall functional stabilization with donepezil compared with a significant decline in the placebo group,[8] with a particularly beneficial effect on the initiation component of completing ADL as measured by the DAD.[9]

Memantine is a moderate-affinity, uncompetitive *N*-methyl-D-aspartate-receptor antagonist approved in the United States, Canada, and Europe for the treatment of moderate-to-severe AD.[10,11] Efficacy and safety of memantine in moderate-to-severe AD have been established in several clinical trials (additional information also available at www.forestclinicaltrials.com).[12–14]

A recent placebo-controlled trial evaluated memantine in patients with moderate-to-severe AD receiving stable donepezil treatment.[10] The 19-item ADCS-ADL inventory (ADCS-ADL$_{19}$) was a coprimary outcome measure. In this report, ADCS-ADL$_{19}$ data are further analyzed to investigate the impact of memantine on individual and grouped ADL items.

METHODS

Patients and Study Design

The data reported are secondary post hoc analyses of a prospective, randomized, double-blind, placebo-controlled, 24-week study of memantine in combination with donepezil in community-dwelling patients with moderate-to-severe AD conducted at 37 US sites. For a more detailed description of the study design, please refer to Tariot et al.[10] Briefly, 404 patients were diagnosed with probable AD, according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria. Study inclusion criteria were MMSE score of 5 to 14, age at least 50 years old, a recent magnetic resonance imaging or computed tomography scan consistent with AD diagnosis, ongoing donepezil therapy for more than 6 months before entrance into the trial and at a stable dose (5 to 10 mg/d) for at least 3 months. Caregivers were knowledgeable about the patients, accompanied them to research visits, and oversaw the administration of the investigational drug during the trial. Patients were medically stable and ambulatory. Stable doses of concomitant medications including psychotropics were permitted. Written informed consent was obtained from caregiver and patient (if possible), or a legally acceptable representative, before initiating study-specific procedures. The study was reviewed and approved by each site's institutional review board.

Patients were randomized to double-blind treatment with placebo or memantine after a 1-week to 2-week single-blind placebo lead-in. Memantine was titrated in 5-mg weekly increments beginning at 5 mg/d to a maintenance dose of 20 mg/d at week 4. Medication was administered in divided doses twice daily. All patients continued stable doses of donepezil throughout the study.

Outcome Measures

The primary measure for these analyses was the ADCS-ADL$_{19}$ (1 of 2 prospectively defined primary outcome measures). Designed specifically for moderate-to-severe AD, the ADCS-ADL$_{19}$ was developed from a subset of 45 ADL items that were originally evaluated in a sample of 242 patients with probable AD.[6] The 19-item version has been shown to be a valid and reliable measure of functional decline in this patient population.[15] The ADCS-ADL$_{19}$ is administered as an interview with the caregiver and is focused on the performance of each ADL during the prior 4 weeks.[6] Possible scores range from 0 to 54. For each ADL item, 0 reflects inability to perform an activity or the need for extensive help, and the highest score represents complete independence. The ADCS-ADL$_{19}$ was administered at baseline and at weeks 4, 8, 12, 18, and 24.

Cognitive, behavioral, and global outcome measures were obtained.[10] The coprimary outcome measure was the Severe Impairment Battery.[16,17] The Neuropsychiatric Inventory[18,19] and the Behavioral Rating Scale for Geriatric Patients[20] assessed behavioral symptomatology, and the Clinician's Interview-Based Impression of Change With Caregiver Input (ADCS version)[21] assessed the patient globally.

Statistical Analyses

All randomized patients receiving at least 1 dose of medication were included in safety, demographics, and baseline analyses (n = 403). Efficacy analyses were derived from the intent-to-treat population (n = 395), which included randomized patients receiving more than 1 dose of medication and completing at least 1 postbaseline primary assessment.

Observed case (OC) and mixed model repeated measures (MMRM) approaches are reported. An advantage of MMRM analyses over both OC and the traditional last observation carried forward approach is that they use all available data to impute performance at end point. The MMRM analyses used treatment group, week, center, and treatment group-by-week interaction as factors and baseline scores as covariates. An unstructured covariance matrix was used for the repeated measures and corrected least squares means are reported.

For responder analyses, a generalized estimating equations (GEE) approach, an adaptation of generalized linear modeling, was used.[22] The GEE method takes into account the correlation between repeated observations on individual subjects that occurs when subjects are evaluated with the same outcome measures over time. For these analyses, an unstructured covariance matrix was used to model the correlation over time. The difference in the proportion of responders between groups, termed absolute risk reduction (ARR), was analyzed for significance using a Wald χ^2 test at the $\alpha = 0.05$ level of significance with no adjustments for multiple comparisons.[23]

Finally, an additional measure of treatment effect, the number needed to treat (NNT), was calculated. It is the inverse of the ARR and is considered useful in

TABLE 1. ADCS-ADL$_{19}$ Items and Factor Loading[6]

Factors (Eigenvalue)	Factor 1 ADL (6.42)	Factor 2 Higher-level Functions (1.53)	Factor 3 Simple Motor Skills/Praxis (1.18)	Factor 4 Connectedness/ Autonomy (1.14)
Items (scoring range)				
Eating (0-3)	**0.53**	0.33	0.32	0.08
Walking (0-3)	**0.72**	−0.22	0.05	0.19
Toileting (0-3)	**0.71**	0.24	0.08	0.09
Bathing (0-3)	**0.51**	0.40	0.11	0.32
Grooming (0-3)	**0.58**	0.35	0.21	0.16
Dressing (0-4)	**0.73**	0.23	0.27	0.13
Using a telephone (0-5)	0.10	0.34	0.04	**0.66**
Watching television (0-2)	0.08	0.45	0.12	**0.49**
Conversing (0-3)	0.05	**0.75**	−0.02	0.18
Clearing a table (0-3)	**0.50**	0.33	0.21	0.08
Finding belongings (0-3)	0.34	**0.54**	0.20	0.02
Obtaining a beverage (0-3)	0.33	**0.50**	0.17	0.32
Disposing of litter (0-3)	0.40	0.26	**0.42**	0.30
Traveling outside the house (0-4)	0.25	−0.17	0.14	**0.74**
Being left alone (0-1)	0.10	0.16	0.06	**0.73**
Turning a faucet on (0-1)	0.13	0.11	**0.86**	0.08
Turning a faucet off (0-1)	0.16	0.11	**0.85**	0.05
Turning a light on (0-1)	0.33	0.05	**0.42**	0.20
Turning a light off (0-1)	0.26	**0.42**	0.29	0.00

ADCS-ADL$_{19}$, Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory (19 items; range 0-54). Higher score indicates better function.

rendering research trial data meaningful for clinical decision making.[15] In this case, the NNT is the number of patients who need to be treated for one additional patient to respond according to a specified criterion.[24]

Change in the total score of the ADCS-ADL$_{19}$ was first analyzed using MMRM and OC approaches. Next, the distribution of change scores for each treatment group was examined based on 5-point intervals. A Cochran-Mantel-Haenszel test controlling for study center was performed on the treatment distributions. Finally, a series of responder analyses was performed using different thresholds of response and tested with GEEs.

Four subscales were derived from a factor analysis on the covariance matrix using a varimax rotation, and factors retained had eigenvalues of at least 1 (Table 1). Subscales took the sum of each item that loaded at 0.30 or greater; items that loaded on multiple factors were included on the factor with the highest loading. Change was analyzed using MMRM and OC approaches, and a responder analysis (defined as no change or improvement) was performed with GEE. Because of the hypothesis-generating aspect of these analyses, all testing was conducted at $P \leq 0.05$, with no adjustment for multiple comparisons using SAS version 9.1.3.

RESULTS

Table 2 shows the demographics and clinical characteristics of the study population of 404 patients (placebo: 201; memantine: 203).[10] More patients (85%) receiving memantine completed the study than those receiving placebo (74.6%). Patients receiving memantine demonstrated significantly better total scores on the ADCS-ADL$_{19}$ at week 24 than patients receiving placebo (Fig. 1) (least square mean difference between placebo and memantine [95% confidence intervals]: MMRM, −1.2 [−1.99, −0.36], $P = 0.005$; OC, −1.6 [−2.9, −0.3], $P = 0.02$).[10]

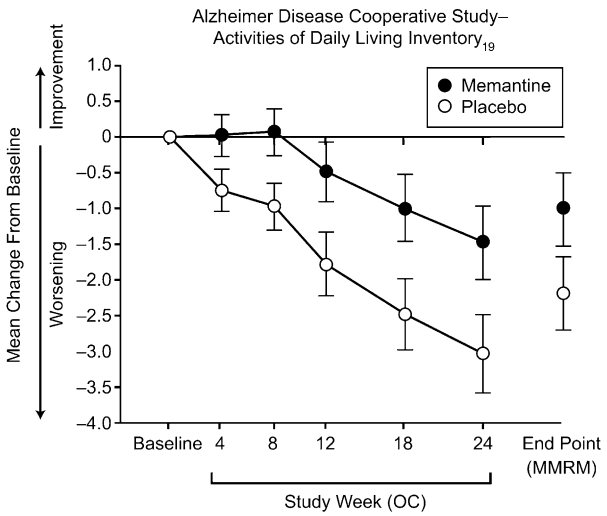
When examining change on the ADCS-ADL$_{19}$, patients receiving memantine showed more improvement (≥ 0 points), whereas patients receiving placebo showed greater worsening (particularly with loss of ≥ 6 points) (Fig. 2). However, a statistically significant difference was not observed between these 2 treatment distributions ($P = 0.141$). For stabilization or improvement (≥ 0 points on the ADCS-ADL$_{19}$ total score) in the OC analysis, the NNT was 10.

When treatment response was defined as no change or improvement relative to baseline, memantine yielded higher rates of improvement than placebo for most ADCS-ADL$_{19}$ increments (Table 3). The ARR between memantine and placebo ranged from 4.4% to 10.4% in

TABLE 2. Baseline Patient Demographics and Clinical Characteristics[10*]

Characteristic	Placebo (n = 201)	Memantine (n = 202)
Men, N (%)	67 (33)	74 (37)
Mean age (y) (SD)	75.5 (8.73)	75.5 (8.45)
Mean weight (kg) (SD)	66.4 (14.12)	70.7 (14.31)†
Mean MMSE (SD)	10.2 (2.98)	9.9 (3.13)
Mean duration of donepezil treatment (wk) (SD)	129 (70.3)	126 (64.9)
Mean donepezil dose (mg) (SD)	9.49 (1.88)	9.25 (1.79)
Mean baseline ADCS-ADL$_{19}$ (SD)	36.2 (9.32)	35.9 (9.75)

*Data are no. (%) unless otherwise specified.
†$P = 0.003$.



No. of Patients							
Memantine	198	198	190	185	181	172	198
Placebo	197	195	182	170	163	152	195
LS Mean Difference		−0.8	−1.1	−1.3	−1.4	−1.6	−1.2
P Value		.03	.01	.02	.03	.02	.005

FIGURE 1. Mean change from baseline of ADCS-ADL$_{19}$.

favor of memantine and was significant for each increment, except for ≥ 4 points (OC) and for at least 8 points (OC/MMRM). The NNT ranged from 10 to 23 (OC).

Within the placebo group, the largest declines in change scores were found on ADL skills of toileting, grooming, and dressing, as well as being left alone (Table 4). Overall in the placebo group, there were 5 items whose mean item scores did not change and 14 items that evidenced decline at 24 weeks. No ADCS-ADL$_{19}$ items improved. Within the memantine group, there were 3 individual items whose mean scores improved, 8 items that did not change, and 8 items that declined. Results of the MMRM analysis revealed a significant treatment effect for memantine on 5 items: toileting ($P = 0.030$), grooming ($P = 0.019$), watching

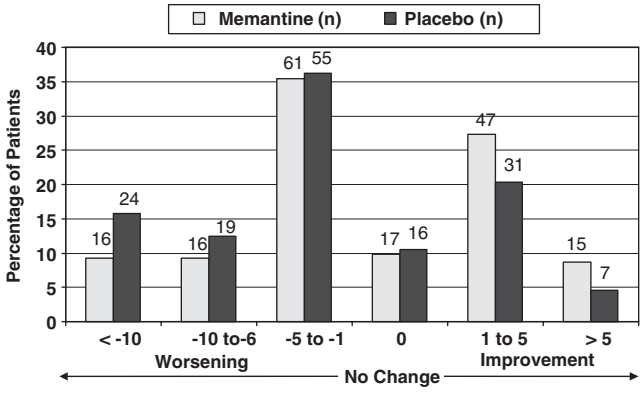


FIGURE 2. Distribution of ADCS-ADL$_{19}$ total scores at end point (OC analysis).

television ($P = 0.009$), conversing ($P = 0.048$), and being left alone ($P = 0.034$). On the basis of OC analysis, treatment with memantine demonstrated significant benefit compared with placebo on 3 items: grooming ($P = 0.002$), watching television ($P = 0.008$), and finding belongings ($P = 0.011$).

When examining change on the ADCS-ADL$_{19}$ subscales, the higher-level subscale functions showed significant benefit for memantine compared with placebo at week 24 (MMRM: $P = 0.015$; OC: $P = 0.011$). Similarly, the subscale connectedness/autonomy significantly favored memantine (MMRM: $P = 0.015$; OC: $P = 0.033$) (Table 4). A similar pattern emerged with responder analyses whereby both subscales reached statistical significance: higher-level functions (61.6% vs. 48.0%, GEE: $P = 0.04$; OC: $P = 0.008$) and connectedness/autonomy (57.0% vs. 46.7%, GEE: $P = 0.01$; OC: $P = 0.053$).

DISCUSSION

The current study provides important data on the patterns of functional decline that occur in patients with moderate-to-severe AD who were followed over a 6-month period. These results indicate that with a history of 2.5 years (on average) of donepezil treatment, patients will either decline or remain unchanged on every individual ADL item over 6 months, while no individual skill seems to improve. The response pattern with memantine is different. There are a greater number of individual items that, on average, remain unchanged, whereas in contrast to placebo, there are individual items that improve.

On the basis of the ADL total score, memantine showed relatively consistent benefit over placebo. For responder analyses, the benefit of memantine was maintained throughout using the GEE approach (from no change/improvement using responder definition up to 4 points or more), with similar response using an OC approach. On the whole, these findings suggest that memantine has the potential to offer benefit across a range of functional abilities in moderate-to-severe AD.

Subscales help clarify the pattern of ADL changes. The ADL factor includes the usual items of eating, toileting, and grooming, activities previously recognized and used as outcome measures.[25] The simple motor skills/praxis factor allows for evaluation of the breakdown of motor skills and sequences that impact on caregiving. These items require a caregiver to take over functions no longer performed independently, adding to time spent assisting with ADL. The connectedness/autonomy component touches on the important dimension of retaining aspects of functional autonomy in moderate-to-severe AD. The ability to be left alone, to travel outside the home, and to engage in some activities inside the home all carry important implications for the quality of life for both patient and caregiver. Similarly, higher-level functions such as conversing, obtaining a beverage, and finding belongings touch on spontaneous actions in daily

TABLE 3. ADCS-ADL$_{19}$ Response Rate for Selected Degrees of Functional Improvement

	Observed Cases				
	Response Rate				
ADCS-ADL$_{19}$ Improvement	**Memantine**	**Placebo**	**ARR**	**NNT**	***P* GEE/OC**
≥ 0 points	46.0% (n = 79/172)	35.5% (n = 54/152)	10.4%	10	0.011/0.052
> 0 points	36.0% (n = 62/172)	25.0% (n = 38/152)	11.0%	9	0.023/0.035
≥ 4 points	15.7% (n = 27/172)	9.9% (n = 15/152)	5.8%	17	0.004/0.113
≥ 8 points	6.4% (n = 11/172)	2.0% (n = 3/152)	4.4%	23	NC/0.063

NC indicates not able to be calculated.

activities that reflect one's engagement and forming of intention.

The present analysis shows that the memantine treatment was associated with significant benefit on the connectedness/autonomy and higher-level functioning factors or item subgroups. The impact on these domains suggests that treatment with memantine relates to improving spontaneity and engagement in ADL, as well as preserving and improving residual functional autonomy. These results help to translate memantine's benefits on ADL into a more qualitative understanding of the clinical meaningfulness of treatment.

These analyses have limitations in that they are post hoc and the trial from which data were derived did not include an item or factor analysis a priori. There was no effort to control for repeated testing, which was necessary owing to the hypothesis-generating nature of these analyses. These results have potential for bias, having been taken from one of three 6-month trials of memantine conducted in moderate-to-severe AD. Future prospective studies are recommended to confirm these findings. Nonetheless, these data support the potential importance of ADL as an outcome in moderate-to-severe AD and underscore the potential role of ADL as a clinically meaningful primary outcome measure.

In conclusion, these data suggest that memantine seems to be associated with an overall benefit in function in patients treated with stable donepezil.

TABLE 4. Individual Items of the ADCS/ADL$_{19}$: Mean Scores (SD) at Baseline and 24 Weeks of Treatment With Memantine or Placebo (ITT Population)

	Placebo (N = 197)		Memantine (N = 198)		Week 24 OC		Overall MMRM	
	Baseline (SD)	**Week 24 (SD)**	**Baseline (SD)**	**Week 24 (SD)**	**LS Mean Difference (95% CI)**	***P***	**LS Mean Difference (95% CI)**	***P***
ADCS-ADL$_{19}$ Items								
Eating	2.8 (0.45)	2.7 (0.54)	2.7 (0.54)	2.6 (0.56)	0.0 (−0.1, 0.1)	0.518	0.0 (−0.06, 0.06)	0.9739
Walking	2.9 (0.48)	2.8 (0.52)	2.9 (0.46)	2.8 (0.6)	0.0 (−0.1, 0.1)	0.886	0.0 (−0.07, 0.04)	0.5764
Toileting	2.6 (0.79)	2.3 (1.05)	2.5 (0.9)	2.5 (0.93)	−0.2 (−0.3, 0.0)	0.051	0.1 (0.01, 0.20)	0.0301
Bathing	1.9 (0.97)	1.7 (1.07)	2.0 (0.94)	1.8 (1.03)	−0.1 (−0.3, 0.1)	0.241	0.0 (−0.06, 0.15)	0.3617
Grooming	2.2 (0.9)	1.9 (1.13)	2.1 (0.96)	2.2 (0.96)	−0.3 (−0.5, −0.1)	0.002	0.1 (0.02, 0.26)	0.0192
Dressing	3.0 (1.2)	2.7 (1.43)	2.9 (1.24)	2.7 (1.4)	0.0 (−0.3, 0.2)	0.825	0.1 (−0.06, 0.23)	0.2318
Using a telephone	1.9 (1.08)	1.7 (1.12)	1.9 (1.09)	1.7 (1.07)	−0.1 (−0.2, 0.1)	0.591	0.0 (−0.09, 0.15)	0.5876
Watching television	1.4 (1.29)	1.2 (1.26)	1.4 (1.35)	1.5 (1.34)	−0.3 (−0.5, −0.1)	0.008	0.2 (0.05, 0.37)	0.0092
Conversing	2.2 (1.10)	2.0 (1.2)	2.2 (1.14)	2.2 (1.10)	−0.2 (−0.4, 0.0)	0.123	0.1 (0.00, 0.27)	0.0478
Clearing a table	2.2 (1.11)	2.1 (1.23)	2.4 (1.09)	2.2 (1.18)	0.0 (−0.2; 0.2)	0.888	0.0 (−0.15, 0.12)	0.8428
Finding belongings	1.9 (1.05)	1.8 (1.12)	2.0 (1.06)	2.1 (1.05)	−0.3 (−0.5, −0.1)	0.011	0.1 (−0.04, 0.22)	0.1636
Obtaining a beverage	1.5 (1.10)	1.4 (1.13)	1.4 (1.12)	1.4 (1.11)	−0.1 (−0.3, 0.1)	0.312	0.1 (−0.05, 0.17)	0.2727
Disposing of litter	2.4 (1.02)	2.4 (1.06)	2.3 (1.11)	2.3 (1.04)	0.0 (−0.2, 0.2)	0.715	0.0 (−0.11, 0.13)	0.9040
Traveling outside house	2.2 (0.85)	2.1 (0.81)	2.2 (0.87)	2.1 (0.80)	0.0 (−0.1, 0.2)	0.923	0.0 (−0.10, 0.08)	0.8115
Being left alone	1.6 (1.19)	1.3 (1.20)	1.5 (1.18)	1.5 (1.21)	−0.2 (−0.4, 0.0)	0.107	0.1 (0.01, 0.27)	0.0343
Turning a faucet on	0.9 (0.25)	0.9 (0.32)	0.9 (0.22)	0.9 (0.26)	0.0 (−0.1, 0.0)	0.175	0.0 (−0.02, 0.06)	0.2980
Turning a faucet off	0.9 (0.29)	0.9 (0.34)	0.9 (0.30)	0.9 (0.31)	0.0 (−0.1, 0.0)	0.522	0.0 (−0.02, 0.06)	0.4075
Turning a light on	0.9 (0.29)	0.9 (0.35)	0.9 (0.27)	0.9 (0.31)	0.0 (−0.1, 0.0)	0.269	0.0 (−0.02, 0.06)	0.3115
Turning a light off	0.6 (0.48)	0.6 (0.50)	0.7 (0.47)	0.6 (0.49)	0.0 (−0.1, 0.1)	0.330	0.0 (−0.01, 0.11)	0.1338
ADCS-ADL$_{19}$ Subscales								
ADL	17.7 (4.2)	16.2 (5.4)	17.6 (4.5)	16.8 (5.1)	0.5 (−0.2, 1.1)	0.194	0.4 (−0.01, 0.81)	0.0567
Higher-level functions	6.3 (2.6)	5.7 (2.9)	6.2 (2.7)	6.2 (2.7)	0.6 (0.1, 1.0)	0.011	0.3 (0.06, 0.60)	0.0151
Simple motor skills/praxis	5.2 (1.4)	5.1 (1.6)	5.1 (1.5)	5.1 (1.5)	0.1 (−0.2, 0.3)	0.590	0.1 (−0.10, 0.25)	0.4257
Connectedness/autonomy	7.1 (3.1)	6.3 (3.2)	7.0 (3.2)	6.8 (3.3)	0.5 (0.0, 1.0)	0.033	0.4 (0.08, 0.69)	0.0149

CI indicates confidence interval; ITT, intent to treat; LS, least squares.

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