ORIGINAL ARTICLE

Combining Mini-Mental State Examination and Montreal Cognitive Assessment for assessing the clinical efficacy of cholinesterase inhibitors in mild Alzheimer's disease: a pilot study

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Abstract
Current drugs for Alzheimer's Disease (AD), such as cholinesterase inhibitors (ChEIs), exert only symptomatic activity. Different psychometric tools are needed to assess cognitive and non-cognitive dimensions during pharmacological treatment. In this pilot study, we monitored 33 mild-AD patients treated with ChEIs. Specifically, we evaluated the effects of 6 months (Group 1 = 17 patients) and 9 months (Group 2 = 16 patients) of ChEIs administration on cognition with the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Frontal Assessment Battery (FAB), while depressive symptoms were measured with the Hamilton Depression Rating Scale (HDRS). After 6 months (Group 1), a significant decrease in MoCA performance was detected. After 9 months (Group 2), a significant decrease in MMSE, MoCA, and FAB performance was observed. ChEIs did not modify depressive symptoms. Overall, our data suggest MoCA is a potentially useful tool for evaluating the effectiveness of ChEIs.

Keywords Cognitive decline · Alzheimer's Disease · MMSE · MoCA · Cholinesterase inhibitors · Psychometric tools

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Introduction

Currently available drugs for Alzheimer's Disease (AD), such as cholinesterase inhibitors (ChEIs), exert only a symptomatic effect by slowing the progression of cognitive decline [1]. In this scenario, the response of AD patients to treatment with ChEIs should be measured for tailored interventions. A recent meta-analysis [2] focused on the use of the Mini-Mental State Examination (MMSE) [3] as the main tool to assess the effects of the ChEIs on cognitive decline in dementia. However, the same authors pointed out the limitations of the MMSE for its poor convergent validity and the floor/ceiling effect [2]. Accordingly, there is a need to include other psychometric instruments for assessing the clinical effectiveness of ChEIs in AD.

For instance, the Montreal Cognitive Assessment (MoCA) [4] is a global measure of cognition that has shown high sensitivity and specificity in detecting Mild Cognitive Impairment (MCI), while other specific cognitive domains and neuropsychiatric symptoms should be considered to

Table 1 Demographic characteristics of samples

	No.	Age (Mean ± SD)	Years of Education (Mean ± SD)	Sex	
Group 1	17	76.29 ± 6.87	7.29 ± 3.39	*Females*	14
				Males	3
Group 2	16	76.38 ± 5.965	9.19 ± 5.72	*Females*	11
				Males	5

give clearer a picture into person's intrinsic capacity [5], in particular executive functions [6] and affective symptoms such as depression [7].

Given the importance of identifying the most sensitive tools to monitor the outcome of ChEIs treatment, the aim of this pilot study was to compare the performance of the MMSE, MoCA, Frontal Assessment Battery (FAB) [8], and Hamilton Depression Rating Scale (HDRS) [9] in assessing the effects of ChEIs effects in mild AD. Therefore, a sample of 33 patients who underwent a psychometric assessment at the beginning of pharmacological treatment (T_0), and after 6 (Group 1) or 9 months (Group 2) of drug intake (T_1) was enrolled.

Materials and methods

Participants

The study involved 33 participants with mild AD, recruited from the U.O.S. Centro Alzheimer e Psicogeriatria, ASP3, Catania, Italy. The diagnosis of probable AD was made according to National Institute on Aging and the Alzheimer's Association guidelines [10]. Inclusion criteria regarded an adjusted MMSE score ≥ 16, and ≤ 25, while exclusion criteria concerned the presence of other neurological and/or psychiatric conditions. The entire sample was divided into two AD subgroups with different follow-up: Group 1 (17 participants) was screened before (T_0) and after (T_1) 6 months of drug treatment, while Group 2 (16 participants) was screened before (T_0) and after (T_1) 9 months of drug treatment (Table 1).

Procedure

The study was conducted in accordance with the Declaration of Helsinki and guidelines set by the Ethical Council of

AIP (Italian Association of Psychology). The protocol was approved by the Internal Ethics Review Board of the Department of Educational Sciences (Section of Psychology) of the University of Catania (Ierb-Edunict-2023.05.23/02). After signing an informed consent, each participant was tested by an expert neuropsychologist twice (T_0 and T_1) in a single session of about 20 min each. All patients were treated with ChEIs (donepezil 10 mg/die or rivastigmine patch 9.5 mg/die) for at least 6 (Group 1) and 9 (Group 2) months.

Measures

The psychometric protocol consisted of: (1) the Italian version of the MMSE [3]; (2) the Italian version of the MoCA [4]; (3) the Italian version of the FAB [8], a global measure to evaluate executive functioning; and (4) the Italian version of the HDRS [9] for the assessment of depressive symptoms.

Data analysis

Given the sample size and the distribution of variables, statistical analysis was carried out using non-parametric tests with SPSS version 27 (IBM). The Mann-Whitney U test for independent samples and Wilcoxon W test for paired data were used. Performance between baseline (T_0) and follow-up (T_1) at 6 months (Group 1) or 9 months (Group 2) during ChEIs treatment was compared. For all analyses, significance level was set at $p < 0.05$ with related effect-sizes.

Results

Participants of Group 1 and Group 2 did not differ at T_0 in MMSE (U = 126; $p = 0.73$; $r_g = 0.07$), MoCA (U = 132; $p = 0.9$; $r_g = 0.02$), FAB (U = 129; $p = 0.81$; $r_g = 0.05$), and HDRS (U = 126; $p = 0.73$; $r_g = 0.07$), nor in years of education (U = 119; $p = 0.51$; $r_g = 0.12$).

Firstly, the effect of ChEIs treatment on cognitive performance and depressive symptoms in Group 1 after 6 months was evaluated (Table 2). The comparison between T_0 and T_1 showed no statistically significant differences in MMSE scores. Similarly, no statistically significant change in FAB scores was found after 6 months of ChEIs treatment. In contrast, a significant reduction in MoCA scores was found

Table 2 Descriptive statistics and changes in Group 1

Measure	Baseline (T_0) Mean ± SD	6 months (T_1) Mean ± SD	Wilcoxon W	p	r_c
MMSE	20.42 ± 2.278	21.34 ± 3.291	20	0.143	-0.48
MoCA	16.47 ± 3.815	14.58 ± 4.634	75	0.042	0.64
FAB	10.65 ± 3.457	9.765 ± 3.413	88.5	0.11	0.47
HDRS	12.12 ± 7.999	10.47 ± 6.463	62.5	0.247	0.37

between T_0 and T_1. The use of ChEIs for 6 months had no impact on depressive symptoms.

Secondly, the effect of ChEIs treatment on cognitive performance and depressive symptoms in mild AD after 9 months in Group 2 was examined (Table 3). Interestingly, the comparison between T_0 and T_1 scores showed significant differences in all psychometric tools evaluating cognitive functioning (MMSE, MoCA, and FAB). In particular, the MMSE showed the highest significance, followed by FAB and MoCA. Again, there were no significant differences between T_0 and T_1 concerning HDRS scores.

Discussion

There is a surprising lack of data on the validity of MoCA and FAB in monitoring the effects of drug treatment with ChEIs [11]. Therefore, in the present pilot study the efficacy of MoCA and FAB, compared to the MMSE, in assessing the effect of ChEIs on cognitive decline was evaluated. Furthermore, we also tested whether the HDRS was able to detect any changes in depressive symptoms after taking ChEIs. As a preliminary check, we ensured that Group 1 and Group 2 started with the same cognitive and affective condition.

The comparison between T_0 and T_1 in Group 1 showed that there were no significant differences in MMSE scores after 6 months of treatment. When we used also the MoCA and FAB, a clinically relevant difference between T_0 and T_1 was found only for the former, but not for the latter; this suggests that MoCA is a more sensitive instrument in detecting a slight worsening in AD patients treated with ChEIs, compared to MMSE and FAB [12, 13]. These results were confirmed by the analysis of the data collected in Group 2, where after 9 months of ChEIs treatment there was a significant decrease in MMSE, MoCA and FAB performance.

The results described above are consistent with those in the literature. For instance, the meta-analysis by Ciesielska et al. found that the MoCA is superior than MMSE as a screening tool for MCI [14]. Furthermore, other authors have shown that MoCA is a very useful psychometric tool not only for MCI, but also for the detection of the early stages of AD [15]. For example, Cecato et al. conducted a cross-sectional study of 136 community-dwelling elderly participants using MMSE and MoCA to evaluate which test was better able to discriminate between healthy controls, MCI

and AD. They found that some subtests of the MoCA (i.e., rhino naming, serial 7s, clock drawing, word recall and orientation subtests) differentiated participants with MCI from AD patients [16]. MoCA has also been identified as a well-established tool to track very slight changes in cognition during different treatments, like electroconvulsive therapy [17] and second-generation antidepressants [18], supporting its effective use for monitoring the outcome of clinical protocols. Our study confirms and strengthen these data, also suggesting that MoCA could be a promising tool to better evaluate response to ChEIs, particularly during the first six months of treatment. Despite the limited psychometric profile of our sample, we could hypothesize that MoCA tracked these significant changes because it focuses also on executive deficits, unlike MMSE, and takes into account several different cognitive functions, unlike FAB [19].

One of the main advantages of this pilot study was the comparison of different tests for monitoring the effects of ChEIs in AD. Furthermore, two different follow-up times (i.e., 6 and 9 months) were considered. However, some methodological issues deserve to be mentioned. Firstly, the small sample size certainly limited our inferential power and did not allow to properly estimating ChEIs effects on AD (e.g., the effect on depressive symptoms). Moreover, not all enrolled patients performed a comprehensive neuropsychological assessment at baseline, making it impossible to assess which cognitive aspects were best captured by the MoCA instead of MMSE as a measure of global cognitive impairment. Secondly, the use of a relatively short follow-up is to be considered another limitation of the study (i.e., favorable early cognitive effects may not be maintained in the long term, and late treatment-related side effects may be discovered). Therefore, future studies on this topic should compare an experimental and a control group using a longer follow-up. Finally, although diagnoses of probable AD were carried out by using current criteria, residual confounding (e.g., medical comorbidity, use of other drug classes) should be taken into account.

Conclusion

The present pilot study suggests the use of MoCA as a preferred global cognition tool for evaluating the effect of treatment with ChEIs in patients with mild AD. Furthermore, the data from the present research suggest the inclusion of

Table 3 Descriptive statistics and changes in Group 2

Measure	Baseline (T_0) Mean ± SD	9 months (T_1) Mean ± SD	Wilcoxon W	p	r_c
MMSE	20.47 ± 2.6	17.72 ± 2.241	136	< 0.001	1.0
MoCA	16.14 ± 3.3	12.94 ± 3.431	108	0.007	0.8
FAB	10.93 ± 2.718	8.363 ± 2.957	110	0.005	0.83
HDRS	12.94 ± 7.672	13.56 ± 10.88	61.5	0.755	-0.09

MoCA as an outcome measure in future clinical trials aimed at evaluating the efficacy of cognitive enhancers in mild AD patients. Considering the clinical relevance of early detection of AD, and the efficacy of treatment with ChEIs, the use of combined psychometric tools such as MMSE and MoCA for rapid assessment of the degree of cognitive impairment may be a relevant option to facilitate early treatment and improve the quality of life of patients with AD [20, 21].

Data availability The data presented in this study are available on request from the corresponding authors.

Declarations

Conflict of interest The authors report no conflicts of interest.

Statement of human rights The study was approved by the Internal Ethics Review Board of the Department of Educational Sciences (Section of Psychology) of the University of Catania (protocol number Ierb-Edunict-2023.05.23/02). The study was conducted in accordance with the Good Clinical Practice (CGP) guidelines, the ethical standards of the Helsinki Declaration (1975), and its subsequent amendments.

Informed consent Informed consent was obtained from all participants, their caregivers, or their legal representants. Data were processed and treated in compliance with the EU Regulation 2016/679.

References

1. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, Burns A, Dening T, Findlay D, Holmes C et al (2015) Nursing Home Placement in the Donepezil and Memantine in moderate to severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses. Lancet Neurol 14. https://doi.org/10.1016/S1474-4422(15)00258-6

2. Knight R, Khondoker M, Magill N, Stewart R, Landau SA (2018) Systematic review and Meta-analysis of the effectiveness of acetylcholinesterase inhibitors and memantine in treating the cognitive symptoms of Dementia. Dement Geriatr Cogn Disord *45*

3. Magni E, Binetti G, Bianchetti A, Rozzini R, Trabucchi M (1996) Mini-mental state examination: a normative study in Italian Elderly Population. Eur J Neurol 3:198–202. https://doi.org/10.1111/j.1468-1331.1996.tb00423.x

4. Santangelo G, Siciliano M, Pedone R, Vitale C, Falco F, Bisogno R, Siano P, Barone P, Grossi D, Santangelo F et al (2015) Normative Data for the Montreal Cognitive Assessment in an Italian Population Sample. Neurol Sci 36:585–591. https://doi.org/10.1007/s10072-014-1995-y

5. López-Ortiz S, Caruso G, Emanuele E, Menéndez H, Peñín-Grandes S, Guerrera CS, Caraci F, Nisticò R, Lucia A, Santos-Lozano A et al (2024) Digging into the intrinsic Capacity Concept: can it be Applied to Alzheimer's Disease? Prog Neurobiol 234:102574. https://doi.org/10.1016/j.pneurobio.2024.102574

6. Junquera A, Garcia-Zamora E, Olazaran J, Parra MA, Fernandez-Guinea S (2020) Role of executive functions in the Conversion from mild cognitive impairment to Dementia. J Alzheimer's Disease 77. https://doi.org/10.3233/JAD-200586

7. Platania GA, Guerrera CS, Sarti P, Varrasi S, Pirrone C, Popovic D, Ventimiglia A, De Vivo S, Cantarella RA, Tascedda F et al (2023) Predictors of functional outcome in patients with Major Depression and bipolar disorder: a Dynamic Network Approach to identify distinct patterns of interacting symptoms. PLoS ONE 18:e0276822. https://doi.org/10.1371/journal.pone.0276822

8. Appollonio I, Leone M, Isella V, Piamarta F, Consoli T, Villa ML, Forapani E, Russo A, Nichelli P (2005) The Frontal Assessment Battery (FAB): normative values in an Italian Population Sample. Neurol Sci 26. https://doi.org/10.1007/s10072-005-0443-4

9. Fava GA, Kellner R, Munari F, Pavan L (1982) The Hamilton Depression Rating Scale in normals and depressives. Acta Psychiatr Scand 66:26–32. https://doi.org/10.1111/j.1600-0447.1982.tb00911.x

10. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R et al (2011) The diagnosis of Dementia due to Alzheimer's Disease: recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic guidelines for Alzheimer's Disease. Alzheimer's Dement 7. https://doi.org/10.1016/j.jalz.2011.03.005

11. Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R, Montero-Odasso M, Rockwood K, Rosa-Neto P, Seitz D et al (2020) Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of Dementia. Alzheimer's Dement 16. https://doi.org/10.1002/alz.12105

12. Limongi F, Noale M, Bianchetti A, Ferrara N, Padovani A, Scarpini E, Trabucchi M, Maggi S, Antonucci S, Arena MG et al (2019) The instruments used by the Italian centres for Cognitive disorders and Dementia to diagnose mild cognitive impairment (MCI). Aging Clin Exp Res 31. https://doi.org/10.1007/s40520-018-1032-8

13. Boccardi V, Bubba V, Murasecco I, Pigliautile M, Monastero R, Cecchetti R, Scamosci M, Bastiani P, Mecocci P (2021) Serum alkaline phosphatase is elevated and inversely correlated with cognitive functions in Subjective Cognitive decline: results from the ReGAl 2.0 project. Aging Clin Exp Res 33. https://doi.org/10.1007/s40520-020-01572-6

14. Ciesielska N, Sokołowski R, Mazur E, Podhorecka M, Polak-Szabela A, Kędziora-Kornatowska K (2016) Is the Montreal

Cognitive Assessment (MoCA) Test Better Suited than the Mini-mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. Psychiatr Pol 50. https://doi.org/10.12740/pp/45368

15. Aiello EN, Pasotti F, Appollonio I, Bolognini N (2022) Trajectories of MMSE and MoCA scores across the healthy adult lifespan in the Italian Population. Aging Clin Exp Res 34. https://doi.org/10.1007/s40520-022-02174-0

16. Cecato JF, Martinelli JE, Izbicki R, Yassuda MS, Aprahamian IA (2017) Subtest Analysis of the Montreal Cognitive Assessment (MoCA): which Subtests can best discriminate between healthy controls, mild cognitive impairment and Alzheimer's Disease? Int Psychogeriatr 29. https://doi.org/10.1017/S104161021600212X

17. Hebbrecht K, Giltay EJ, Birkenhäger TK, Sabbe B, Verwijk E, Obbels J, Roelant E, Schrijvers D, Van Diermen L (2020) Cognitive change after Electroconvulsive Therapy in Mood disorders measured with the Montreal Cognitive Assessment. Acta Psychiatr Scand 142. https://doi.org/10.1111/acps.13231

18. Guerrera CS, Platania GA, Boccaccio FM, Sarti P, Varrasi S, Colliva C, Grasso M, De Vivo S, Cavallaro D, Tascedda F et al (2023) The Dynamic Interaction between symptoms and pharmacological treatment in patients with major depressive disorder: the role of Network Intervention Analysis. BMC Psychiatry 23. https://doi.org/10.1186/s12888-023-05300-y

19. De Roeck EE, De Deyn PP, Dierckx E, Engelborghs S (2019) Brief Cognitive Screening Instruments for Early Detection of Alzheimer's Disease: A Systematic Review. *Alzheimers Res Ther 11*

20. Castellano S, Platania GA, Varrasi S, Pirrone C, Di Nuovo S (2020) Assessment Tools for Risky Behaviors: Psychology and Health. *Health Psychol Res 8*

21. Coco M, Buscemi A, Guerrera CS, Licitra C, Pennisi E, Vettor V, Rizzi L, Bovo P, Fecarotta P, Dell'Orco S et al (2019) October. Touch and Communication in the Institutionalized Elderly. In Proceedings of the 2019 10th IEEE International Conference on Cognitive Infocommunications (CogInfoCom); IEEE, ; pp. 451–458