

RESEARCH ARTICLE

Combined treatment with *Ginkgo biloba* extract EGb 761 plus acetylcholinesterase inhibitors improved cognitive function and neuropsychiatric symptoms in patients with mild cognitive impairment

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Abstract

Introduction: Mild cognitive impairment (MCI) is a neurocognitive state between normal aging and dementia. There is currently no approved treatment for MCI, with acetylcholinesterase inhibitors (AChEI) being the commonly prescribed drugs. The *Ginkgo biloba* extract EGb 761 is an herbal remedy used for cognitive disorders, including dementia. This study aims to explore the potential synergistic effect of combination therapy with EGb 761 plus AChEI in patients with amnesic MCI in a real-life setting.

Methods: We retrospectively identified 133 patients with amnesic MCI who were attending a memory clinic. Patients had received treatment with any of the following drugs: *G. biloba* extract EGb 761, donepezil, galantamine, or rivastigmine at their standard doses. Subjects were divided into three treatment groups: EGb 761, AChEI, and EGb 761+AChEI. Patients were assessed by Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test (RAVLT), Symbol Digit Modalities Test, Boston Naming Test, Trail Making Test (TMT Parts A and B), Letter and Category Fluency Test (LFT, CFT), Neuropsychiatric Inventory (NPI), and Interview for Deterioration in Daily Living. Mixed-effects model analysis was carried out to evaluate changes in cognitive, functional, and behavioral outcomes over a 12-month follow-up.

Results: After 12 months, EGb 761+AChEI showed significant improvement in MMSE, RAVLT, CFT, TMT A-B, and NPI compared to AChEI and in MMSE and RAVLT compared to EGb 761. At 12 months, EGb 761 was superior to AChEI on the CFT, TMT A-B, and NPI.

Discussion: Our findings suggest that combined therapy with EGb 761 plus AChEI may provide added cognitive and functional benefits in patients with MCI and provides additional real-world evidence for the combined use of EGb 761 and anti-dementia drugs in patients with MCI. This study can serve as a model for the design of clinical

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trials that help to support the combined use of EGb 761 and anti-dementia drugs in patients with MCI.

KEYWORDS

acetylcholinesterase inhibitors, dementia, *Ginkgo biloba* extract EGb 761, mild cognitive impairment, neurodegenerative disease

1 | INTRODUCTION

Mild cognitive impairment (MCI) represents the preclinical, transitional stage between healthy aging and dementia. The term was initially introduced in the late 1980s by Reisberg et al. to identify patients in this intermediate phase, with Petersen et al. proposing the first clinical criteria in 1999.¹

The prevalence of MCI in the population aged 60 and over varies widely, showing a wide range of incidence depending on the age of the population examined, study setting, subject selection, variation in MCI diagnostic criteria and differences in the assessment approach between different studies, with results ranging from 5.9 to 31.3.^{2,3} In addition to age, numerous risk factors influence its evolution, including genetics, comorbidities, and vascular risk factors such as hypertension or diabetes, depression, and tobacco use.^{4,5} An estimated 40% to 60% of individuals 58 years of age and older with MCI have underlying Alzheimer's disease (AD) pathology.⁶

The diagnosis of MCI includes concern about a change in cognition in comparison with the person's previous level ascertained by the patient; observations from a reliable observer who knows the patient well or a skilled health professional; lower performance in one or more cognitive domains that is greater than would be expected taking into account the patient's age and educational background. However, activities of daily living should be preserved, as a differentiation from dementia. For an accurate diagnosis, it is essential that the evaluator perform a comprehensive evaluation of the patient's history derived from reliable informants focused on detecting clinical signs, along with the use of the necessary and sufficient clinical and neuropsychological assessment instruments. When repeated evaluations are available, the development over time becomes monitored. This change can be manifested in different cognitive domains, such as memory, executive function, attention, language, and visuospatial skills.^{7,8}

The International Working Group on MCI⁸ proposed classifying MCI into two subtypes: amnesic MCI (aMCI, where memory is significantly impaired) and non-amnesic MCI (naMCI, where memory remains intact), each of which may involve deterioration in a single cognitive domain or in multiple cognitive domains. These different subtypes of MCI are highly heterogeneous in terms of etiology, presentation, and prognosis. Although the progression of different MCI subtypes into a particular type of dementia is not well known, there is evidence that patients with the aMCI subtype are at a high risk of progression to AD probably representing the prodromal stage of AD.⁹ Its early diagnosis could serve as an appropriate target for early intervention and therapy development.¹⁰

There are currently approved treatments for mild to moderate dementia due to AD, but there is still no specific drug approved by the US Food and Drug Administration (FDA) for the treatment of MCI, with acetylcholinesterase inhibitors (AChEI) being the most commonly used drugs to treat MCI symptoms even though they have not shown positive results in MCI^{7,11} with only modest benefits for secondary outcome measures. Given that MCI, particularly in its amnesic form, is often a precursor to AD, it is not surprising that clinicians often choose to offer AChEI for patients diagnosed with MCI.⁷

The *Ginkgo biloba* special extract EGb 761 has been used widely in the treatment of cognitive disorders, including AD and cerebrovascular disease.^{12–14} The European Medicines Agency (EMA) supports its use to improve the age-related cognitive impairment (worsening of mental abilities) and quality of life of adults with mild dementia, and it is recommended in guidelines for the treatment of cognitive disorders, including AD and MCI.^{12,13,15} The *G. biloba* extract EGb 761 has a positive effect on cognitive and neurological function based on the improvement of vascular flow, anti-oxidant effect, anti-inflammatory action, anti-apoptotic action, thereby enhancing neuroplasticity, modulation of amyloid aggregation, and the defense against mitochondrial dysfunction, which would confer neuroprotective properties.^{16,17} These mechanisms are considered to contribute to cognitive improvement, impeding the evolution of neurodegenerative diseases. EGb 761 has been used widely in the treatment of cognitive disorders, and several studies show its clinical efficacy in the treatment of dementia.^{18–21} Specifically, EGb 761 has been shown to produce cognitive improvement in both AD and vascular dementia.^{21,22}

The efficacy of EGb 761 in the treatment of cognitive impairment and behavioral symptoms associated with MCI has been showed in several clinical trials, which have yielded results suggesting that EGb 761 may improve such symptoms.^{23,24} However, there is no evidence to support the efficacy of the combination of EGb 761 and AChEI in the treatment of MCI. Therefore, given that there is no approved treatment for MCI, it may be of interest to explore a future option for combination therapy of EGb 761 with AChEIs. To this end, further evidence is needed to evaluate the role of EGb 761 as an add-on therapy to the prevalent use of AChEIs in MCI in clinical practice.

We hypothesized that combined treatment with EGb 761 plus AChEIs could lead to a synergistic effect that would provide cognitive, behavioral, and functional benefits in patients with MCI. Thus the aim of this study is to evaluate the effectiveness of EGb 761 alone and the added effects of a combination therapy of EGb 761 plus AChEIs in patients with MCI in a real-life setting. To this end, we carried out a

RESEARCH-IN-CONTEXT

- 1. Systematic Review:** We reviewed the literature using traditional (e.g., PubMed) sources as well as Google keyword searches. Prior studies have explored the development of appropriate interventions for mild cognitive impairment (MCI) including the *Ginkgo biloba* extract EGb 761 and acetylcholinesterase inhibitors (AChEI). However, outcomes are controversial and no pharmacological treatment is currently available for MCI. (We included the relevant citations.)
- 2. Interpretation:** Our findings showed that EGb 761 was associated with a reduction in cognitive impairment and neuropsychiatric burden in patients with amnesic MCI. Activities of daily living were stabilized. Moreover, EGb 761 was superior to AChEI in improving cognitive performance and neuropsychiatric symptoms in most of the assessment tests performed. Similarly, the results of the combined treatment of EGb 761 plus AChEI was superior to the use of both drugs separately.
- 3. Future Directions:** This study can serve as a model for the design of future long-term randomized controlled trials that help to support the combined use of EGb 761 and anti-dementia drugs in amnesic MCI patients.

retrospective analysis of service provision data over a 12-month period from the Instituto Andaluz de Neurociencia (IANEC) in a sample of people with aMCI.

2 | METHODS**2.1 | Patient selection**

We retrospectively identified patients with a diagnosis of aMCI who attended the Memory Clinic of the Instituto Andaluz de Neurociencia (IANEC), Málaga, Spain, between January 2018 and December 2020. A consensus diagnosis was determined using the standardized clinical criteria for aMCI.²⁵

The diagnosis of aMCI was recorded on each participant's medical history issued by a neurologist, neuropsychologist, or psychiatrist. The data were collected by clinical researchers from the patient medical records, including treatment they were taking as prescribed by their physician with EGb 761 or AChEI alone or combined with both drugs, physical examination, neurological and psychiatric examination, neuropsychological assessment, and magnetic resonance imaging (MRI). Usually, after a diagnosis of aMCI, patients are evaluated every 6 months, with these examinations being a part of the regular assessments that patients undergo at the IANEC, as part of their follow-up clinical evaluations. Information on demographic and clinical charac-

teristics was collected. At the study inclusion visit, data were recorded regarding gender, age, educational level, MCI diagnosis, personal and family history, personal psychiatric history, general medication, and anti-dementia drugs.

The exclusion criteria were the presence of dementia; focal neurological signs; presence of focal vascular signs such as hematomas or strokes; normal pressure hydrocephalus; patients with epilepsy or inflammatory brain disease, severe psychiatric disorders (e.g., psychosis, major depression, and bipolar disorder) or substance abuse; absence of a reliable informant; absence of a complete medical history to assess the study variables; significant temporal lobe or hippocampal atrophy reflected on MRI by a Scheltens²⁶ index of two or greater; and presence of a sensory disorder (e.g., severe vision and hearing impairment).

Patients with MCI who received fixed and adjusted treatment for 12 months with any of the following drugs and doses were considered as candidates: EGb 761 (240 mg daily), donepezil (5 or 10 mg daily), galantamine (16 or 24 mg daily), or rivastigmine patch (9.5 or 13.3 mg daily). Subjects were divided into three groups according to the treatment they had received: EGb 761 only, AChEI only, or EGb 761 plus AChEI.

During the study period, a total of 324 patients with aMCI were identified. From these 324 subjects, 52 potential participants were excluded because they had insufficient documentation in their medical record, 39 were unable to be contacted, 29 refused to participate, and 71 satisfied the exclusion criteria.

The sample size in this retrospective pilot study was not ascertained a priori. The study was approved by the ethics committee of the Instituto Andaluz de Neurociencia, Málaga, Spain, and informed consent was obtained from patients or their representative caregivers.

2.2 | Assessment

Drug effects on cognition, behavior, and functional performance were evaluated at baseline 6 and 12 months using the following neuropsychological tests:

The Mini-Mental State Examination (MMSE) is the most commonly used test for the screening of cognitive functioning. Possible scores range from 0 to 30 points, and higher scores indicate better cognitive function.²⁷

The Rey Auditory Verbal Learning Test (RAVLT) is a verbal list-learning and memory test to assess verbal episodic memory. The RAVLT consists of five repeated learning trials of the same 15-word list, with immediate and delayed recall trials after 3 and 30 minutes, respectively, as well as recognition tests. In this study we used the total sum of words recalled across the five trials to measure total encoding.²⁸

The Symbol Digit Modalities Test (SDMT) is a widely used measure of information processing speed. The subject is presented with a page headed by a key that pairs the single digits 1 to 9 with nine symbols. Rows below contain only symbols; the subject's task is to write or orally

report the correct number in the spaces below. After completing the first 10 items with guidance, the subject is timed to determine how many responses can be made in 90 seconds.²⁹

The Boston Naming Test (BNT) is the best-known neuropsychological test used widely for evaluating linguistic ability; the test includes object naming and word retrieval. In this study we used the abbreviated 15-item version.³⁰

The Trail Making Test (TMT) is a tool that is used for the assessment of the ability to flexibly switch attention between competing task-set representations. The TMT comprises two task components: TMT Part A (TMT-A) and TMT Part B (TMT-B). The TMT-A requires the participant to draw lines and connect circled numbers in a numerical sequence. In the TMT-B, the participant is asked to draw lines to connect circled numbers and letters in an alternating numeric and alphabetic sequence. The participant is instructed to complete both task components as fast and accurately as possible without lifting the pen from the worksheet.³¹

Letter fluency test (LFT), and Category fluency test (CFT) were used to assess verbal fluency. Both tests involve the activation of multiple cognitive processes engaging verbal knowledge and executive function to inhibit repetitions. In the LFT, subjects were instructed to say as many words as possible that begin with the letter "P" for 1 minute. In the CFT, the subjects were asked to list as many animals as possible within 1 minute.³²

The study of behavioral and psychological symptoms of dementia (BPSD) was carried out using the Neuropsychiatric Inventory (NPI). The NPI is composed of 12 subscales that evaluate the most commonly occurring BPSD in patients with AD. A composite score for each subscale was obtained by multiplying frequency by severity, with a maximum of 12 points. A total NPI composite score can be obtained ranging from 0 to 144 points.³³

The patients' performance on activities of daily life was assessed using the Interview for Deterioration in Daily Living (IDDD). Possible scores range from 33 to 99 points, where higher scores indicate worse functional ability.³⁴

2.3 | Statistical analysis

Demographic variables were reported using the mean and standard deviation (SD) in the case of quantitative variables; and number and percentage in the case of qualitative. Baseline differences between the two treatment groups were assessed by an analysis of variance (ANOVA) or non-parametric tests, as appropriate.

A Mixed Model for Repeated Measures (MMRM) analysis was carried out to evaluate changes in cognitive, functional, and neuropsychiatric scores, and to handle missing value in some of the follow-up assessments. The effect of time (between the mean baseline measurements and each time point), treatment, and treatment-by-time interactions were evaluated. Post hoc analyses for multiple comparisons were conducted using Bonferroni's correction.

All analyses were conducted with SPSS Statistics (Version 25.0) and the significance level was set at $p \leq 0.05$.

3 | RESULTS

A total of 133 patients met the inclusion criteria and their data were available for analysis (98 female, 35 male). Patients had a mean age of 75.66 ± 5.71 years (range 64 to 84) and mean years of education of 6.53 ± 1.92 (range 4 to 15). All patients were Caucasian. At baseline, patients treated with EGb 761 only ($n = 54$) did not differ from those treated with AChEI only ($n = 31$) or with EGb 761 plus AChEI ($n = 48$) except for sex and duration of MCI, with women comprising approximately three-quarters of the study population (73.68%) ($p = 0.001$) and the duration of MCI lasting longer in the combined treatment group (35.17 ± 11.96 months) than in EGb 761 treatment group (30.44 ± 10.60 months) and AChEI group (29.42 ± 6.69 months) ($p = 0.025$) (Table 1).

3.1 | Changes in cognitive scores

With regard to the MMSE, the MMRM analysis showed a statistically significant time by treatment effect ($F(2, 130) = 20.628, p < 0.0001$). The EGb 761 plus AChEI group performed better than the AChEI group at the 12-month follow-up (+1.41 points, 95% confidence interval [CI]: 0.55 to 2.27, $p < 0.0001$) and showed improvement as early as 6 months. The EGb 761 plus AChEI group performed better than the EGb 761 group at the 12-month follow-up (+2.12 points, 95% CI: 1.37 to 2.86, $p < 0.0001$) and showed improvement as early as 6 months (Figure 1).

Concerning the RAVLT, the MMRM analysis showed a statistically significant time by treatment effect ($F(2, 130) = 30.572, p < 0.0001$). The EGb 761 plus AChEI group performed better than the AChEI group at the 12-month follow-up (+1.74 points, 95% CI: 0.19 to 3.29, $p = 0.022$). The EGb 761 plus AChEI group performed better than the EGb 761 group at the 12-month follow-up (+1.59 points, 95% CI: 0.25 to 2.92, $p = 0.014$) (Figure 1).

With regard to the CFT, the MMRM analysis showed a statistically significant time by treatment effect ($F(2, 130) = 10.030, p < 0.0001$). The EGb 761 plus AChEI group performed better than the AChEI group at 12-month follow-up (+0.76 points, 95% CI: 0.18 to 1.33, $p = 0.005$). The EGb 761 group performed better than AChEI group at 12-month follow-up (+0.91 points, 95% CI: 0.34 to 1.46, $p < 0.0001$) and showed improvement as early as 6 months (Figure 1). Regarding the LFT, the Mixed Model analysis showed no a statistically significant time by treatment effect ($F(2, 130) = 7.813, p = 0.056$).

With regard to the TMT-A, the MMRM analysis showed a statistically significant time by treatment effect ($F(2, 130) = 49.036, p < 0.0001$). The EGb 761 plus AChEI group performed better than AChEI group at 12 months follow-up (-18.05 points, 95% CI: -30.93 to -5.17, $p = 0.003$). The EGb 761 group performed better than AChEI group at 12 months follow-up (-12.89 points, 95% CI: -25.48 to -2.48, $p = 0.043$) (Figure 1).

Concerning the TMT-B, the MMRM analysis showed a statistically significant time by treatment effect ($F(2, 130) = 21.876, p < 0.0001$). The EGb 761 plus AChEI group performed better than AChEI group

TABLE 1 Demographic and clinical characteristics of patients at baseline

Variable	Overall (n = 133)	EGb761 (n = 54)	AChEI (n = 31)	EGb761+AChEI (n = 48)	p-value ANOVA/ χ^2
Age	75.66 ± 5.71	75.57 ± 5.81	75.32 ± 3.99	75.98 ± 6.57	0.875
Gender					
Male	98 (73.7)	41 (75.9)	20 (64.5)	19 (39.6)	0.001
Female	35 (26.3)	13 (24.1)	11 (35.5)	29 (60.4)	
Marital status					
Married	52 (39.1)	22 (40.7)	10 (32.2)	20 (41.7)	0.931
Single/divorced	11 (8.3)	4 (7.4)	3 (9.7)	4 (8.3)	
Widowed	70 (52.6)	28 (51.9)	18 (58.1)	24 (50.0)	
Duration, months	31.91 ± 10.61	30.44 ± 10.60	29.42 ± 6.69	35.17 ± 11.96	0.025
Education, years	6.53 ± 1.92	6.56 ± 2.01	6.42 ± 2.01	6.58 ± 1.81	0.930
AChEI					
Donepezil	25 (31.6)		9 (29.0)	16 (33.3)	0.235
Rivastigmine	29 (36.8)		12 (38.7)	17 (35.4)	0.164
Galantamine	25 (31.6)		10 (32.3)	15 (31.3)	0.322
MMSE	20.86 ± 2.03	20.94 ± 1.94	21.00 ± 2.03	20.67 ± 2.15	0.716
RAVLT	18.21 ± 3.05	18.48 ± 3.14	18.26 ± 2.25	17.87 ± 3.39	0.605
CFT	8.28 ± 0.86	8.46 ± 0.64	8.26 ± 0.63	8.08 ± 1.13	0.080
LFT	8.62 ± 1.35	8.65 ± 1.08	8.94 ± 1.36	8.40 ± 1.58	0.221
TMT-A	163.91 ± 22.32	162.72 ± 23.27	166.10 ± 21.09	163.83 ± 22.34	0.800
TMT-B	242.82 ± 44.67	242.54 ± 47.39	232.06 ± 43.12	250.08 ± 41.89	0.217
SDMT	24.29 ± 10.20	23.35 ± 9.83	27.39 ± 11.24	23.35 ± 9.73	0.156
BNT	10.18 ± 1.94	9.94 ± 0.88	9.77 ± 1.02	10.17 ± 1.28	0.268
NPI	22.83 ± 4.06	22.17 ± 3.32	22.48 ± 3.36	23.79 ± 5.01	0.112
IDDD	50.60 ± 12.64	51.81 ± 13.23	50.52 ± 13.63	49.29 ± 11.37	0.606

Values are mean ± SD or number (%).

Abbreviations: MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; CFT, Category Fluency Test; LFT, Letter Fluency Test; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; SDMT, Symbol Digit Modalities Test; BNT, Boston Naming Test; NPI, Neuropsychiatric Inventory; IDDD, Interview for Deterioration in Daily Living Activities in Dementia.

at 12 months follow-up (−31.71 points, 95% CI: −49.90 to −13.54, $p < 0.0001$). The EGb 761 group performed better than AChEI group at 12-month follow-up (−45.94 points, 95% CI: −63.73 to −28.17, $p < 0.0001$) and showed improvement as early as 6 months (Figure 1).

With regard to the SDMT, the MMRM analysis showed no statistically significant time by treatment effect ($F(2, 130) = 1.692, p = 0.188$), although analyses for multiple comparisons showed a non-significant trend in favor of the EGb 761 plus AChEI group compared to the AChEI group ($p = 0.054$).

With regard to the BNT, the MMRM analysis showed no statistically significant time by treatment effect ($F(2, 130) = 2.234, p = 0.111$), although analyses for multiple comparisons showed a non-significant trend in favor of the EGb 761 plus AChEI group compared to the AChEI group ($p = 0.058$).

The 12-month results showed within group improvements on all measures for all three treatment groups, except for the AChEI group,

which, when corrected for multiple comparisons, showed no significant changes for TMT-A and SDMT (Table 2).

3.2 | Changes in behavioral scores

With regard to the NPI, the MMRM analysis showed a statistically significant time by treatment effect ($F(2, 130) = 8.842, p < 0.0001$). The EGb 761 plus AChEI group performed better than the AChEI group at 12-month follow-up (−3.71 points, 95% CI: −6.50 to −0.93, $p = 0.005$) and showed improvement as early as 6 months. The EGb 761 group performed better than the AChEI group at 12-month follow-up (−3.57 points, 95% CI: −6.29 to −0.84, $p = 0.006$) and showed improvement as early as 6 months (Figure 1). There were statistically significant improvements on the NPI at 12 months from baseline for all three treatment groups (Table 2).

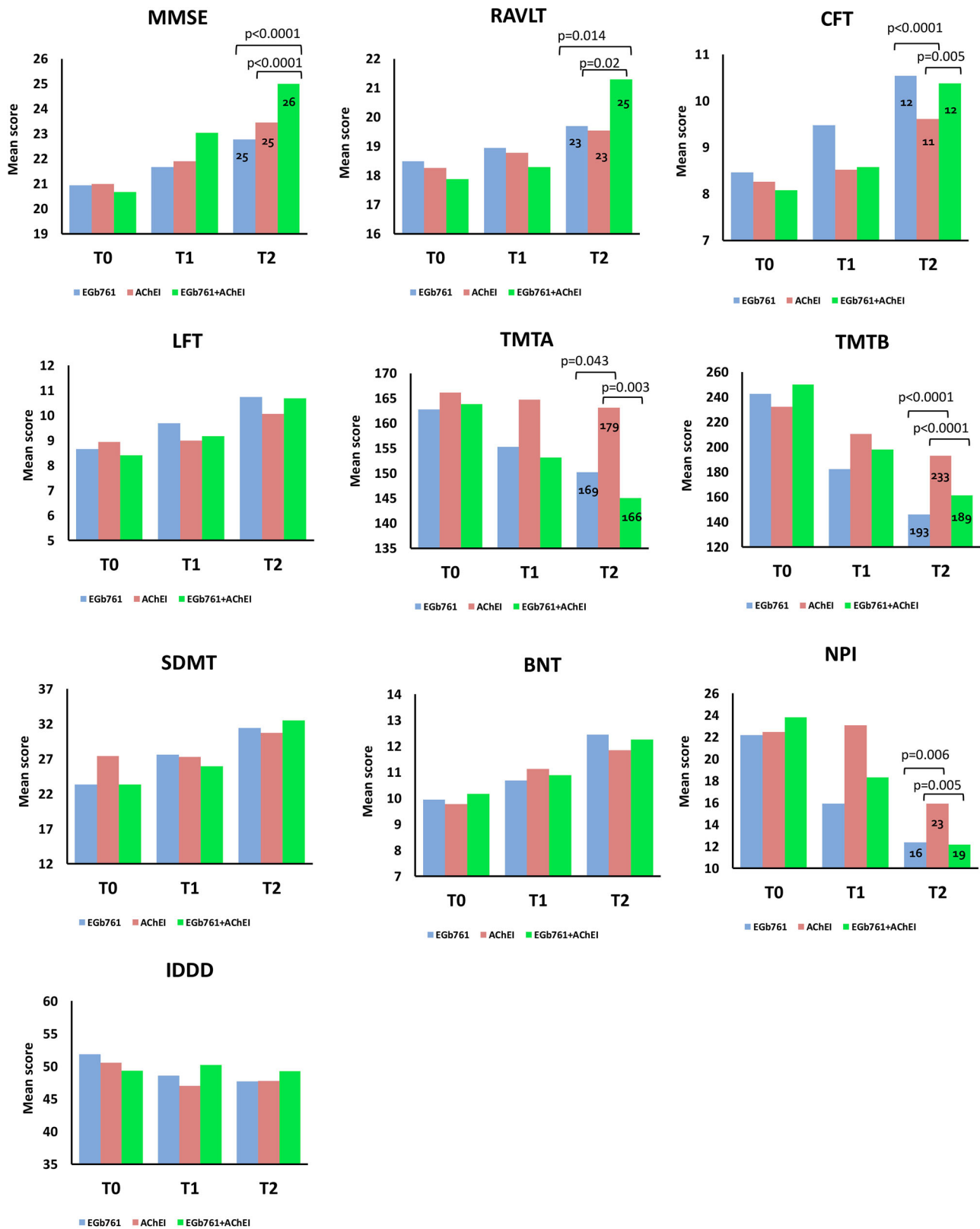


FIGURE 1 Results from the linear mixed model for cognition, behavioral, and functional performances. Numbers in the bars are 90th percentile. T0 baseline, T1 follow-up 6 months, T2 follow-up 12 months. MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; CFT, Category Fluency Test; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; NPI, Neuropsychiatric Inventory

TABLE 2 Rating scale score changes within treatment

Variable	T0	T1	T2	Difference (T0-T2)	p-value
MMSE					
Egb 761	20.94 ± 1.94	21.67 ± 2.04	22.78 ± 2.08	1.84 ± 0.14	<0.0001
AChEI	21.00 ± 2.03	21.90 ± 1.62	23.48 ± 1.31	2.48 ± 0.17	<0.0001
Egb 761+AChEI	20.67 ± 2.15	23.04 ± 1.17	24.90 ± 0.81	4.23 ± 0.79	<0.0001
RAVLT					
Egb 761	18.48 ± 3.14	18.94 ± 2.99	19.70 ± 3.03	1.22 ± 0.19	<0.0001
AChEI	18.26 ± 2.25	18.77 ± 2.62	19.55 ± 1.96	1.29 ± 0.16	<0.0001
Egb 761+ AChEI	17.87 ± 3.39	18.29 ± 3.27	21.29 ± 2.91	3.42 ± 0.56	<0.0001
CFT					
Egb 761	8.46 ± 0.64	9.48 ± 0.86	10.52 ± 1.11	2.06 ± 0.15	<0.0001
AChEI	8.26 ± 0.63	8.52 ± 0.68	9.61 ± 1.05	1.35 ± 0.18	<0.0001
Egb 761+ AChEI	8.08 ± 1.13	8.58 ± 0.98	10.38 ± 0.91	2.30 ± 0.13	<0.0001
LFT					
Egb 761	8.65 ± 1.08	9.69 ± 1.23	10.74 ± 1.38	2.09 ± 0.15	<0.0001
AChEI	8.94 ± 1.36	9.00 ± 1.61	10.06 ± 1.79	1.12 ± 0.21	<0.001
Egb 761+ AChEI	8.40 ± 1.58	9.17 ± 1.58	10.69 ± 1.86	2.29 ± 0.20	<0.0001
TMT-A					
Egb 761	162.72 ± 23.27	155.31 ± 21.43	150.20 ± 22.33	-12.52 ± 0.99	<0.0001
AChEI	166.10 ± 21.09	164.74 ± 21.49	163.10 ± 23.11	-3.00 ± 0.85	0.036
Egb 761+ AChEI	163.83 ± 22.34	153.17 ± 22.90	145.04 ± 23.79	-18.79 ± 0.95	<0.0001
TMT-B					
Egb 761	242.54 ± 47.39	182.30 ± 37.56	147.02 ± 30.25	-95.52 ± 4.60	<0.0001
AChEI	232.06 ± 43.12	210.55 ± 36.88	192.97 ± 33.51	-39.09 ± 5.88	<0.0001
Egb 761+ AChEI	250.08 ± 41.89	197.83 ± 39.01	161.25 ± 34.34	-88.83 ± 5.01	<0.0001
SDMT					
Egb 761	23.35 ± 9.83	27.59 ± 6.88	31.44 ± 8.35	8.09 ± 1.56	<0.0001
AChEI	27.39 ± 11.24	27.26 ± 12.52	30.71 ± 12.26	3.32 ± 2.86	0.497
Egb 761+ AChEI	25.35 ± 9.73	25.96 ± 10.60	32.48 ± 10.54	9.13 ± 1.59	<0.0001
BNT					
Egb 761	9.94 ± 0.88	10.69 ± 1.13	12.41 ± 1.07	2.47 ± 0.49	<0.0001
AChEI	9.77 ± 1.02	11.13 ± 1.43	11.84 ± 1.59	2.07 ± 0.22	<0.0001
Egb 761+ AChEI	10.17 ± 1.28	10.87 ± 1.25	12.25 ± 1.33	2.08 ± 0.18	<0.0001
NPI					
Egb 761	22.17 ± 3.32	15.93 ± 4.71	12.33 ± 4.55	-9.84 ± 0.66	<0.0001
AChEI	22.48 ± 3.36	23.06 ± 5.72	15.90 ± 5.86	-6.58 ± 1.21	<0.0001
Egb 761+ AChEI	23.79 ± 5.01	18.33 ± 5.32	12.19 ± 4.87	-11.60 ± 1.57	<0.0001
IDDD					
Egb 761	51.81 ± 13.23	48.59 ± 16.14	47.70 ± 12.68	-4.11 ± 2.55	0.253
AChEI	50.52 ± 13.63	47.00 ± 11.72	47.77 ± 12.04	-2.75 ± 3.55	0.426
Egb 761+ AChEI	49.29 ± 11.37	50.19 ± 11.67	49.15 ± 11.31	-0.14 ± 2.27	0.865

T0 baseline, T1 follow-up 6 months, T2 follow-up 12 months; Values are mean ± SD.

p-values refers to changes from baseline to month 12.

Abbreviations: MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; CFT, Category Fluency Test; LFT, Letter Fluency Test; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; SDMT, Symbol Digit Modalities Test; BNT, Boston Naming Test; NPI, Neuropsychiatric Inventory; IDDD, Interview for Deterioration in Daily Living Activities in Dementia.

3.3 | Changes in functional scores

Regarding the IDDD, the MMRM analysis showed no statistically significant time by treatment effect ($F(2, 130) = 0.548, p = 0.580$). None of the three treatment groups showed within-group improvements for IDDD (Table 2).

3.4 | Safety analysis

The overall incidence of patients reporting adverse events throughout the study that were considered possibly related to treatment was 28.7% in the EGb 761 group, 46.1% in the AChEI group, and 48.2% in the EGb 761 plus AChEI group. The most commonly reported were insomnia (11%) and headache (13%) for EGb 761; dizziness (24.7%), diarrhea (22.17%), skin rashes (24.22%), fatigue (21.33%), and headaches (24.26%) for the AChEI group; and dizziness (24.23%) and skin rashes (22.24%) in the combined-treatment group.

Most of adverse events in all the three groups were transient, were of mild-to-moderate intensity, and resolved spontaneously. No deaths or serious adverse events occurred during the study. Clinically relevant changes over time or differences between treatment groups were not observed in clinical laboratory test results, vital signs, weight, or electrocardiography (ECG) parameters.

4 | DISCUSSION

This retrospective study was performed to compare the treatment effects of EGb 761, AChEI, and combined treatment with EGb 761 and AChEI in an explorative manner in patients with aMCI. Treatment with *G. biloba* extract EGb 761 for 12 months alone or in combination with AChEI was well tolerated and was associated with a reduction in cognitive impairment and neuropsychiatric burden in patients with aMCI. It seems plausible that the combination of two drugs with different mechanisms of action may result in increased efficacy. These results are particularly relevant, especially considering that there are currently no pharmacological agents approved by the FDA for the treatment of MCI.⁷ Indeed, despite numerous randomized clinical trials being conducted in patients with MCI, none has been able to demonstrate the effectiveness at delaying disease progression.^{35,36} Thus these results could provide physicians with a new approach to the pharmacological management of MCI. In addition, these findings can serve as a model for the design of prospective clinical trials that help to support the combination therapy in patients with MCI.

A statistically significant improvement in favor of EGb 761 plus AChEI compared to AChEI was observed at 12-month follow-up in the MMSE, RAVLT, CFT, TMT-A, TMT-B, and NPI. The EGb 761 plus AChEI group showed improvement as early as 6 months on the MMSE and NPI. The combined treatment appears to benefit performance on a variety of cognitive domains: short memory, verbal episodic memory, linguistic ability, executive functions, selective and sustained attention, and verbal knowledge. These results suggest that the combination of

the two drugs with different mechanisms of action may result in greater efficacy than each of them alone.³⁷

A statistically significant improvement in favor of EGb 761 plus AChEI compared to EGb 761 was observed at 12 months in the MMSE and the RAVLT. The EGb 761 plus AChEI group showed improvement as early as 6 months on the MMSE. A statistically significant improvement in favor of EGb 761 compared to AChEI was observed at 12 months in the CFT, TMT-A, TMT-B, and NPI. The EGb 761 group showed improvement as early as 6 months on the NPI.

The positive response seen in the EGb 761 group alone is consistent with previous results. Indeed, previous studies have shown convincing results on the efficacy of using EGb 761 to improve cognitive function and neuropsychiatric symptoms in patients with MCI and mild to moderate dementia, all together with a good safety profile.^{22,23,38} A review on the neuroprotective and antioxidant effect of EGb 761 on AD and other neurological disorders concluded that EGb 761 may be effective in the treatment and prevention of AD and other age-related, neurodegenerative disorders.³⁹ In the same line, a trial aimed to compare the treatment effects and tolerability of EGb 761, donepezil, and combined treatment in patients with AD and neuropsychiatric features showed that a combination therapy was superior to monotherapy with one of both substances.²⁴ An expert panel on neurocognitive disorders concur that robust evidence supports the inclusion of *G. biloba* extract EGb 761 as part of the treatment armamentarium for AD, vascular dementia, and MCI.⁴⁰

The precise mechanism of action that explains these results is not yet known, but a possible synergistic effect cannot be ruled out. Several studies have shown a cholinergic deficit in subjects with dementia related to reduced acetylcholinesterase activity.^{41,42-44} In this sense, the beneficial effect of AChEIs is based on the characteristic of inhibiting acetylcholinesterase enzyme activity with the potential restoration of physiological acetylcholine levels at the synapse. Thus the enhanced postsynaptic activity promotes a more normal function of the cholinergic system.⁴¹ However, this beneficial effect of AChEIs is not so clear in the case of MCI, showing only a slight efficacy in the treatment of MCI, which makes it difficult to recommend it in these patients.⁴⁵ For example, although trials of AChEIs in persons with MCI have failed to demonstrate efficacy in primary outcome measures, some have shown benefit for secondary outcome measures.⁴⁶⁻⁴⁸

On the other hand, neuroinflammation,⁴⁹ amyloid beta ($A\beta$)1-42 aggregation,⁵⁰ and oxidative stress⁵¹ are important factors involved in age-related degenerative diseases resulting in harmful damage on cellular components. Particularly, oxidative stress appears to be involved in the early phase of AD and MCI and may induce inflammatory signals, identified as key players in neurodegenerative diseases with consequent neuronal death.⁵² Although the molecular basis is not fully understood, EGb 761 appears to have neuroprotective properties. It is a polyvalent free-radical scavenger that improves mitochondrial function, decreases blood viscosity and enhances microperfusion, and decreases $A\beta$ fibrillogenesis.^{16,17} Considered together, the benefit observed in our study with the combined treatment with EGb 761 and AChEIs could be explained by the possible addition of the acetylcholinesterase inhibitory effect exerted by AChEIs together with

the potential antioxidant, anti-inflammatory effects, and even amyloid genesis and phosphorylation of tau protein modulation of EGb 761.¹⁸

Little is currently known about dynamic brain networks involved in high-level cognition and it is a focus of interest to investigate the dynamic functional connectivity of the salience network, the central-executive network, and the default mode network, three core neurocognitive systems that play a central role in cognitive and affective information processing.^{53,54} In this sense, the benefits in different cognitive domains showed in our study could represent a future opportunity to study the possible positive effects of EGb 761 combined with AChEI on network function.

There were no between-group differences for the BNT, LFT, and SDMT. The TMT and the SDMT assess attention, processing speed, and executive functions. Our results showed significant improvements in TMT (Parts A and B) for the combined treatment and EGb 761 alone compared to AChEI. However, contrary to what might be expected, our findings did not show positive results for SDMT. The verbal fluency task is a widely used test that can reveal deficits in executive functions and verbal abilities (such as CFT and LFT). Although evidence suggests that subjects with AD perform worse on category fluency than letter fluency tasks, the pattern in MCI is less well known, and most studies have reported inconsistent results on fluency deficit patterns in aMCI.^{55,56} In addition, there were no differences between groups in the naming task. There could be several explanations for this unexpected findings, but obviously, the small sample size makes interpretations difficult. Therefore, further research is needed to shed light on these contradictory results.

One of the strengths of this study was the long duration of the follow-up, which suggests that the clinical benefit of EGb 761 plus AChEIs may be greater after long-term use. In addition, the patients in the study underwent a comprehensive neuropsychological, behavioral, and functional evaluation with widely used outcome measures focused on reducing observation bias. In addition, our semi-annual evaluations allowed close monitoring of clinical changes.

Some limitations to the study should be considered when interpreting the results. First, given that this was a retrospective study and the participating subjects were not assigned randomly to treatment groups, the results obtained could be affected by this circumstance. Second, this is a study of a single center and, consequently, the number of subjects enrolled was limited and the sample size was small. Therefore, the results should be considered indicative. Moreover, the observational design did not allow us to conclude on causality. On the other hand, we analyzed the AChEIs as a whole, without specifying any of them in particular, which would have allowed us to better quantify the extent of the improvements observed with the treatments under study. It is, therefore, possible that clinical differences may exist if the different AChEIs were studied individually. In this sense, results from Battle et al.⁵⁷ found moderate- to high-certainty evidence that donepezil 5 mg, donepezil 10 mg, and galantamine have a slight beneficial effect on cognition in people with vascular cognitive impairment, although the size of the change is unlikely to be clinically important. The evidence for rivastigmine was less certain. In addition, we did not adjust for the AChEI dose ranges in the statistical analysis. Another lim-

itation was that all subjects were Caucasian and therefore the safety and efficacy of treatments among a small subgroup of people cannot be assumed to generalize to other groups. Finally, we have selected specific tests for the study of the domains under investigation. However, the tests selected are by no means the only possible indices of these domains, and we could reasonably have selected other measures of depression, cognition, or functional performance. In fact, a limitation of the MMSE is its significant ceiling effect, which hampers its usefulness in MCI. Patients who test positive on the brief cognitive assessment should undergo further evaluation with neuropsychological testing, with interpretation based on normative data adequate to formally assess this diagnosis. The diagnosis of MCI is ultimately based on a clinical assessment that determines cognitive function and functional status, and not only on a specific test score.⁷ In addition, as a measure of functional capacity we used the IDDD, which is designed for dementia. The IDDD assesses functional disability in basic activities of daily living (ADLs) and instrumental ADLs (IADLs) in patients with dementia living in the community. According to diagnostic criteria, ADLs are preserved in MCI patients, as opposed to dementia. This could explain why no positive results were found in functional performance.

5 | CONCLUSIONS

The *G. biloba* extract EGb 761 showed cognitive and behavioral benefits in patients with aMCI. These positive effects increased when EGb 761 and AChEIs were used in combined treatment, probably providing additional benefits by targeting different pathophysiological mechanisms. This study can serve as a model for the design of future long-term randomized controlled trials that help to support the combined use of EGb 761 and anti-dementia drugs in patients with aMCI. In addition, these findings provide clinicians new insight into the pharmacological management of MCI.

CONFLICT OF INTEREST

The authors report that they have no conflict of interest to disclose. [Author disclosures](#) are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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