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# A COMBINATION OF GALANTAMINE AND MEMANTINE MODIFIES COGNITIVE FUNCTION IN SUBJECTS WITH AMNESTIC MCI

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**Abstract:** *Objectives:* Mild cognitive impairment (MCI) is etiologically heterogeneous, and a substantial proportion of MCI subjects will develop different dementia disorders. One subtype of this syndrome, amnestic MCI, occurs preferentially but not exclusively in prodromal AD and is characterized by defined deficits of episodic memory. *Design, setting and participants:* For a 2-year, double-blinded, placebo-controlled study MCI patients, presenting with an amnestic syndrome but not necessarily based on presumed prodromal AD were randomized. *Intervention:* Patients received (a) a combination of 16 mg galantamine plus 20 mg memantine, or (b) 16 mg galantamine alone or (c) placebo. *Measurements:* The primary objective was to explore the differential impact of these interventions on the progression to dementia and on cognitive changes as measured by the ADAScog. *Results:* After recruitment of 232 subjects, the trial was halted before reaching the planned sample size, because safety concerns arose in other studies with galantamine in MCI. This resulted in a variable treatment duration of 2-52 weeks. The statistical analysis plan was amended for studying cognitive effects of discontinuing the study medication, which was done separately for galantamine and memantine, and under double-blind conditions. There was one death, no unexpected severe adverse events, and no differences of severe adverse events between the treatment arms. The cognitive changes on the ADAScog were not different among the groups. Only for the subgroup of amnestic MCI with presumed AD etiology, a significant improvement of ADAScog score over placebo before the discontinuation of medication was observed, while amnestic MCI presumably due to other etiologies showed no cognitive changes with broad variation. Cognitive improvement was numerically larger in the combination treatment group than under galantamine alone. Patients who received placebo declined as expected. Discontinuation of galantamine, either as part of the combination regimen or as mono treatment, resulted in a transient decline of the ADAScog score in amnestic MCI of presumed AD etiology, while discontinuation of Memantine did not change the cognitive status. *Conclusion:* In an interrupted trial with amnestic MCI subjects the combination of galantamine plus memantine were generally well tolerated. In the subgroup of MCI subjects with presumed AD etiology, a cognitive benefit of a short-term combination treatment of galantamine plus memantine was observed, and cognitive decline occurred after discontinuation of galantamine.

**Key words:** Mild cognitive impairment, dementia, cognitive function, antidementiva.

## Introduction

To prevent dementia by treating neurodegenerative diseases as early as possible is a major goal for health systems in many industrial countries. The concept of mild cognitive impairment (MCI) has been developed to identify a phenotype in the transitional stage between normal cognitive function and dementia with heterogeneous etiology. The term MCI refers to a significant lowering of memory function with or without other cognitive deficits and without major functional impairment (1, 2). In a substantial proportion of subjects, MCI may represent an early stage of Alzheimer's disease (AD) where treatment may be most effective. However, mild impairment of episodic memory is not exclusive for patients with early AD, but may also occur in other forms of dementias, like vascular and mixed dementia or more rare forms like Pick - and diffuse Lewy-body-disease.

Depending on the neuropsychological profile, different MCI subtypes can be distinguished by neuropsychometric tests, including the single domain amnestic subtype, the single domain non-amnestic subtype and the multidomain MCI (3). The single domain amnestic subtype and the multidomain MCI with amnestic deficits are most likely to represent early AD (4, 5, 6). According to this rationale the German dementia competence network (DCN) designed a randomized, controlled clinical trial for subjects meeting the single domain or multidomain amnestic MCI criteria with two objectives: to study effects of combination treatment with galantamine plus memantine in comparison to placebo and/or a mono treatment with galantamine (A) on cognitive function; (B) on delaying

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clinical progression to AD-dementia. During recruitment, the trial continuation had to be stopped for safety reasons (for details see methods), thus the effects of a controlled discontinuation of the two study drugs on cognitive function were tested.

## Materials and Methods

### *Study population: Definition of amnestic MCI and presumed etiological diagnosis*

We identified amnestic MCI by a standardized screening assessment comprising the test battery of the Consortium to Establish a Registry for Alzheimer´s Disease (CERAD), the Wechsler Memory Scale Revised (WMS-R), the Clock Drawing Test (CDT) and the Trail Making Test A and B (TMT A/B). The syndrome of mild cognitive impairment (MCI) was diagnosed when the subject (A) complaint about decline in cognitive ability, (B) showed deficits in at least one of the domains learning/memory, language, attention and visuoconstructional ability of the CERAD battery, (C) general intellectual functioning was unimpaired, (D) the activities of daily living were normal as demonstrated by a BAYER-ADL score <4 (E) the Clinical dementia rating (CDR) was rated 0.5 (not demented). Patients with the amnestic MCI subtype were eligible for inclusion by applying neuropsychological cut-off values: (A) performance below norm for the Wechsler memory scale revised (WMS-R) delayed recall or (B) at least one standard deviation below the norm of the appropriate age group of the delayed recall of the CERAD test battery word list, and (C) a New York university paragraph recall test paragraph test (NYU) with a delayed recall score less than or equal to 10.

After identification of eligible amnestic MCI patients, a presumed etiological diagnosis was given by the treating physician integrating the clinical picture, the medical history of the patient, a comprehensive physical and neuropsychiatric examination, neuropsychological test results and findings in the magnet resonance tomography or cranial computer tomography. However, inclusion into the trial was not based on this additional label. They were classified as MCI presumably "AD-type" (pre-AD), "mixed type" (pre-MD), "FTD-type" (pre-FTD), "vascular type" (pre-VD), following the published research criteria for the respective dementia diagnoses (without requiring the dementia criterion) or remained “not classified” because clinical diagnosis remained doubtful at study entry (7). All clinical diagnoses and assignments of MCI subtypes were routinely made by team conferences at the local study centers.

Further inclusion criteria were the availability of a consistent informant, and sufficient visual, hearing and communication capabilities; major exclusion criteria were the presence of other clinically significant medical, psychiatric, neurodegenerative or intracerebral diseases.

### *Study design*

Twelve centers in Germany enrolled subjects into the study. After a 1-month screening period, subjects were randomly assigned (1:1:1 ratio) to receive galantamine plus memantine, galantamine alone or placebo. Provided all entry criteria were met, randomization occurred immediately before administration of study medication. All subjects were randomized to one of three arms using a double-dummy technique: (A) Placebo (placebo/placebo; PLAC) or (B) galantamine 8 mg b.i.d. (galantamine/placebo; MONO) with dose-titration over eight weeks, or (C) a combination of galantamine 8 mg b.i.d. plus memantine 10 mg b.i.d. (COMBI) with a dose titration of twelve weeks (8 weeks for galantamine, additional 4 weeks for memantine). Regardless of treatment assignment, subjects who progressed from MCI to dementia (i.e., CDR 1.0) were terminated from the double-blind phase of the study and were eligible for open-label antidementive treatment as standard care.Within the initial statistical plan a conversion rate of 15% per year was calculated for the placebo group. The total number of MCI patients for this trial was fixed at 600, assumming a drop-out rate of 40%, to ensure a power of at least 80% even in a worst case scenario.

Nine month after recruitment start, further continuation of the trial was stopped by the steering committee and the data safety and monitoring board because the results of an intermediate analysis of safety data of two industry-sponsored trials on galantamine in MCI (Gal-Int-11 and Gal-Int-18) became available, which showed significant more serious adverse events (SAE) includings deaths in the group receiving galantamine (11). Thus, it was decided to discontinue all study medication by a defined scheme while drug allocation remained double-blinded and repetitive cognitive tests were performed.

### *Statistical analysis*

Baseline demographic characteristics and neuropsychological test scores were compared using analysis of variance models (ANOVA) or Chi-Square-Tests. For small samples ($n \leq 15$), it was assumed that scores are not normally distributed and the variances are heterogeneous. In these cases the nonparametric equivalent of analysing variances between more than two independent groups were used (Kruskal-Wallis-analysis of ranks) to check for differences in group changes. Within the three treatment groups the changes from baseline scores in ADAS-cog were also analysed using the nonparametric Kruskal-Wallis-analysis of ranks. For posthoc analysis alpha-level-corrected single U-tests were used. Statistical tests were two-tailed, and a $\alpha$-level below to 0.05 (*) was used as an indicator of significance. A $\alpha$-level below 0.1 (+) was regarded as an indicator for a tendentious significant effect.

Safety analyses included all patients who were randomly assigned to treatment and received at least one dose of study medication. Safety analyses consisted of descriptive statistics and tabulations of AEs, serious AEs, and deaths.

## Results

All MCI patients from the DCN cohort (n=1080) had been screened and 243 MCI patients were eligible for inclusion before recruitment was halted. At this timepoint 232 patients formed the ITT population: Placebo (placebo/placebo; PLAC) n=79, galantamine only (galantamine/placebo; MONO) n=75 or galantamine plus memantine (COMBI) n=78. They had received study medication for a minimum of two weeks and a maximum of one year before discontinuation. The groups did not differ with respect to sex, age, word fluency, BNT (Boston naming test), MMSE (Mini mental state examination), ADAS-cog (Alzheimer´s disease assessment scale – cognitive subscale), NYU (New York University Paragraph recall test – delayed recall), TMT A/B (Trail making test) and duration of symptoms. The scores in the Montgomery-Asberg Depression Rating Scale (MADRS) were below cutoff values indicating a depressive disorder. For details of baseline demographic characteristics and neuropsychological test scores see Table 1.

**Table 1**
MCI baseline demographic characteristics and neuropsychologic test scores

| | PLAC (n= 79) | | MONO (n= 75) | | COMBI (n= 78) | | |
|---|---|---|---|---|---|---|---|
| | Mean/SD | Med | Mean/SD | Med | Mean/SD | Med | p-value |
| Age | 67.2 ± 7.6 | 66 | 67.9 ± 8.3 | 68 | 67.3 ± 7.7 | 67 | 0.85 |
| Word fluency | 18.0 ± 5.4 | 19 | 19.1 ± 5.6 | 19 | 17.0 ± 5.1 | 18 | 0.08 |
| BNT | 13.5 ± 2.3 | 14 | 13.9 ± 1.4 | 14 | 13.4 ± 1.9 | 14 | 0.44 |
| MMSE | 26.9 ± 2.1 | 27 | 27.4 ± 2.2 | 28 | 27 ± 2.6 | 27 | 0.19 |
| ADAS-cog | 11.2 ± 4.9 | 10 | 11.5 ± 4.4 | 11 | 11.4 ± 5.5 | 10 | 0.77 |
| NYU | 4.9 ± 2.5 | 4.5 | 4.6 ± 2.6 | 5 | 5 ± 2.9 | 5 | 0.71 |
| MADRS | 6.4 ± 5.7 | 6 | 6.5 ± 5 | 6 | 7.4 ± 6.3 | 6 | 0.73 |
| TMT A | 63.9 ± 47 | 46 | 58 ± 28 | 51 | 59 ± 40 | 49 | 0.78 |
| TMT B | 144 ± 62 | 122 | 139 ± 57 | 130 | 142 ± 65 | 119 | 0.97 |
| Duration of symptoms (months) | 29.3 ± 29.5 | 24 | 34 ± 27.9 | 24 | 27.4 ± 24.3 | 24 | 0.15 |

MCI baseline demographic characteristics and neuropsychologic test scores. Treatment groups: Mono = galantamine, Combi = galantamine plus memantine. Neuropsychological tests: Word fluency (subscale from the Consortium to establish a Registry for Alzheimer´s Disease: CERAD); BNT: Boston Naming Test (short version, subscale from CERAD); MMSE: Mini-Mental State Examination; ADAS-cog: Alzheimer Disease Assessment Scale – cognitive subscale; NYU : New York University Paragraph Recall Test (version 1) delayed recall; MADRS: Montgomery-Asberg Depression Rating Scale; TMT A/B: Trail Making Test version A/B; Med: Median.

### *Presumed etiological diagnoses of patients with amnestic MCI*

In 172 patients (approx. 74%) presenting with an amnestic MCI syndrome the clinical diagnosis of early Alzheimers disease (pre-AD) was presumed. 12 of MCI patients received the diagnosis of mixed dementia (pre-MD), 3 vascular dementia (pre-VD), 5 fronto-temporal dementia (pre-FTD) and 40 MCI patients remained not classified (Figure 1). In the subpopulation of MCI with presumed AD etiology, which were analyzed separately, the treatment arms are equally distributed in terms of all criteria tested (data not shown).

### *Efficacy of combined antidementive therapy in amnestic MCI and in the subgroup of MCI with presumed AD etiology*

Only individuals that completed titration procedure and performed complete neuropsychological assessments at follow up were used for further data analysis. Measures of ADAS-cog sixteen weeks after the treatment was initiated (n=79) showed slight differences in favor to the verum groups. At the consecutive follow up examination, six month after treatment was started, the trend in favor of the verum groups in the ADAS-cog had increased, but remained not significant altered when cognitive changes of all amnestic MCI were analyzed (n=48): PLAC -4/-1/1, MONO -1/1/1.75 and COMBI -1/1/3.75 (data are given as P25/Median/P75). Interestingly at six month of treatment only the subgroup of presumed pre-AD (n = 39, Figure 2) treated with the verum medication showed a significant benefit from antidementive treatment: PLAC -4.5/-1/0.5, MONO -1.25/1/1.25 and COMBI -0.75/2.5/4.75; $p<0.05$. Posthoc analysis using alpha-level-corrected single U-tests showed significant differences between the PLAC and COMBI group ($\Delta$ COMBI > $\Delta$ PLAC; U= 38; p=0.01).

**Figure 1**
Distribution of presumed etiological diagnoses of the study population. Prodromal Alzheimer disease: pre-AD; prodromal mixed dementia: pre-MD; prodromal vascular dementia: pre-VD; prodromal fronto-temporal dementia: pre-FTD

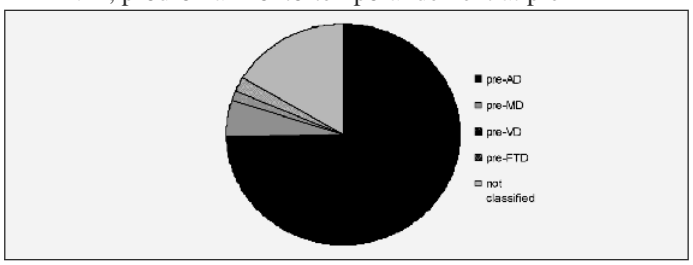
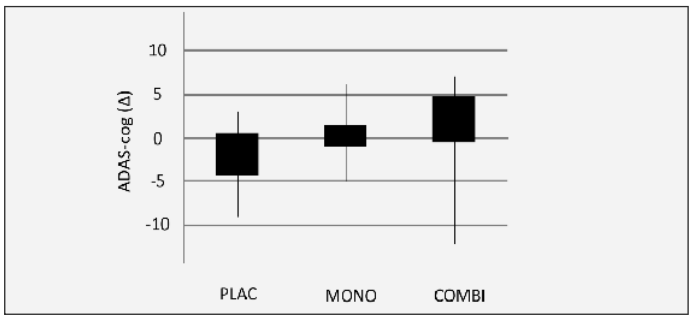



**Figure 2**
Cognitive changes in MCI patients with presumed prodromal AD as measured by the ADAS-cog at six month of treatment



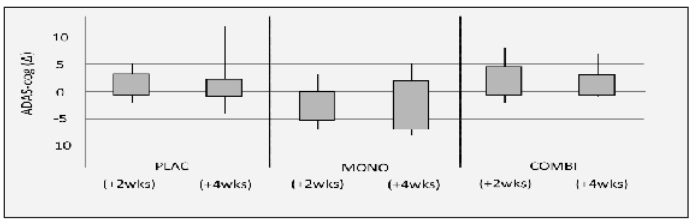

### *Effect of discontinuation of antidementive treatment on cognitive function in amnestic MCI*

About one half of all randomized amnestic MCI patients who had reached the maximum dose of study medication (twelve weeks of treatment, n=39) agreed to repeat the cognitive testing during controlled discontinuation of

antidementive treatment and signed an additional form of consent for a separate add-on study. First, a new baseline visit including ADAS-cog was performed (Visit A). Afterwards galantamine in the MONO and COMBI group was tapered within one week, while memantine (COMBI only) was for now continued as before. Two weeks after baseline the second visit of the add-on study was scheduled and patients were reassessed (Visit B). Finally the trial medication consisting meanwhile only of memantine for those amnestic MCI in the COMBI group was stepwise discontinued and a final testing was done two weeks later (Visit C). The discontinuation of galantamine led to a marked decrease of cognitive performance measured by ADAS-cog only in patients receiving galantamine only (MONO), but interestingly not in those who were still on memantine (COMBI). Two weeks after galantamine was stepwise reduced the performance was found to be significantly worsened (PLAC -1/0.5/3.25, MONO -5.5/-3/0, COMBI -1/1/4.5, $p<0.05$; Figure 3). Post hoc analysis using alpha-level-corrected single U-tests showed significant differences between MONO and both other groups ($\Delta$ MONO < $\Delta$ COMBI and $\Delta$ MONO < $\Delta$ PLAC, $p=0.01$).

**Figure 3**

Cognitive changes as measured by the ADAS-cog after discontinuation of galantamine (+2wks) and memantine (+4wks)




At Visit C, four weeks after baseline when discontinuation of trial medication had started, none of the participants still received medication. Notably patients in the COMBI group performed better at that time compared to subjects in the MONO group. The worsening of cognitive impairment measured by ADAS-cog was still present in the MONO therapy group and more pronounced in the presumed pre-AD subgroup compared to all aMCI (all aMCI: -5/0/1; presumed pre-AD: -7.25/1.5/2). Surprisingly the COMBI group did not show a cognitive decline after medication was tapered. The PLAC group showed a slight improvement at Visit B and C most likely due to a learning effect caused by repetition of tests in short intervals.

***Safety analyzes***

MCI patients received study medication for a time period of 2 weeks minimum and 52 weeks maximum. In total 17 serious adverse events (SAE) were reported. None of the SAE fulfilled the criteria for a suspected unexpected serious adverse reaction (SUSAR). 11 SAE were reported to be unrelated (n =9) or unlikely to be related to study medication (n=2). 6 SAE were possibly related (n=2) or were described as probable related (n=4) with the following symptoms described: tachycardia, tremor, vertigo, queasiness, headache, weakness and abdominal pain. There was one death noted of a MCI patient who died four month after discontinuation of treatment due to a cardiac arrest.

## Discussion

This is the first prospective, double-blind, placebo-controlled study examining the benefits of combining an NMDA receptor antagonist with a ChE-I in community-dwelling patients with amnestic MCI. A combination of memantine at 20 mg/day with galantamine 16 mg/day did not show statistically significant benefit over placebo in amnestic MCI on the protocol-specified primary or secondary efficacy measures.

However, there is indication that in a subgroup of MCI patients with presumed AD etiology, the initiation of a ChE-I treatment as well as the discontinuation of ChE-I may exert some cognitive effects. All information provided by the trial is clearly limited by its premature termination at a maximum treatment duration of 12 months. Several MCI trials have shown that the use of ChEIs alone in MCI was not associated with any delay in the onset of AD or dementia (8, 9, 10, 11). The NMDA receptor antagonist memantine (12) has been shown to be effective in moderate to severe AD and the efficacy has also been tested in MCI patients in a small open trial recently (13).

Here, no indication for a cognitive benefit of a combination of two antidementive drugs with different mechanism of action, i.e. galantamine plus memantine, in a placebo-controlled double blind setting could be found. Initially, the study intended to assess the effects of the combined treatment on a delay of clinical progression to dementia. But the trial had to be terminated prematurely after one year, because in two earlier trials (Gal Int-11, Gal Int-18) in MCI, intermediate analyses showed an increase of serious adverse events in patients receiving galantamine (11). Because similar effects in the MCI-COMBI study could not be excluded at that time the recruitment was stopped for safety reasons. In our study severe unexpected adverse events were not noted and the combination therapy of galantamine and memantine in MCI was safe and well tolerated, in line with earlier studies in demented patients (14, 15).

The major results of our trial concern the effect of discontinuation of a combination of antidementive treatment in amnestic MCI. Interestingly we found significant changes in memory performance as measured by the ADAS-cog after six month of treatment exclusively in those amnestic MCI which who were diagnosed as pre-AD, while the effect in amnestic MCI due to presumed other clinical etiology was smaller. Due to premature discontinuation, the resulting low follow up rate and the limited number of observed cases, all conclusions on the results of the treatment phase are exploratory and obviously limited.

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