Clinical Trials in Mild Cognitive Impairment: Lessons for the Future

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Abstract:
Mild cognitive impairment (MCI) is an operational definition for a cognitive decline in individuals that have a greater risk of developing dementia. With an increasing awareness of the heterogeneity of its clinical presentation, course and outcomes, diagnostic criteria have been further refined by addition of several MCI subtypes. The amnestic form of MCI is of particular interest because these individuals most likely progress to Alzheimer's disease (AD). Because of assumed pathophysiological relationship between MCI and AD, currently hypothesized therapeutical approaches in MCI are mainly based on treatment strategies for AD. Several long-term secondary prevention randomized clinical trials in, mainly, amnestic MCI population have been completed so far, encompassing agents with various mechanisms of action: all three on the market available acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine), antioxidants (vitamin E), antiinflammatories (rofecoxib), nootropics (piracetam). Design of clinical trials in MCI is influenced by study objectives and definition of primary end points: time to clinical diagnosis of dementia, and AD in particular, or symptom progression. The fact that none of the drugs previously shown to have clinical efficacy in AD trials as well as benefit in everyday practice have met the primary objectives of the respective trials, indicates that the clinical trial design in MCI have to be further developed with a special attention being paid to the selection of more homogeneous samples at entry, optimal treatment duration and multidimensional and reliable outcomes.
Aging brings physical and intellectual limitations and is a major risk factor for a number of chronic somatic and neurodegenerative diseases. It is well known that there is a wide variability among older individuals with respect to physical as well as cognitive aging. Scientific advances in our understanding of factors that contribute to optimal aging, characteristics of normal aging process as well as pathological conditions that occur more frequently with increasing age, such as dementia, have resulted in a broad social and medical initiative towards its prevention, early recognition and therapeutic interventions. In this context, one of the challenges for clinical investigators is to make with certainty distinction between a benign form of cognitive dysfunction associated with increasing age and cognitive decline that is most likely consistent with incipient dementing disease. The latter condition is known in the literature as mild cognitive impairment (MCI) and is hypothetically an important treatment target in order to stabilize the symptoms or delay the progression to dementia. This paper reviews the design and results of recently completed clinical trials in MCI. Information has been obtained from earlier reviews on ongoing trials in MCI from Schneider L (1) and Petersen RC (2), NIH website on drug trials (3), papers presented at the last Alzheimer’s Disease and Related disorders Conference in Philadelphia 2004 (4-8), as well as via correspondence with representatives of sponsors of respective trials. Standard search strategy for papers was employed via key-words in PubMed.

Refinement of clinical definition, neurobiological correlates and rationale for treatment

There have been various definitions of MCI in the literature with consequent variability in outcomes after follow-up of these subjects (9). In general, higher “conversion” rates in clinically selected samples, on average 15% per year as compared to 7.5% in the community samples were reported (10). So far the most popular and widely used clinical criteria are those developed by researchers at the Mayo Clinic (11). In the original version of the criteria there was an emphasis on a memory impairment without clinically manifest dementia and with preserved activities of daily living, which is designated as the amnestic form of MCI and suggested by the authors as the most common clinical presentation that most likely progresses to AD (11). With an increasing interest for the concept of MCI in the clinical practice and an increasing awareness of the heterogeneity of its clinical presentation, course and outcomes, the Mayo clinic criteria have been further refined by addition of several MCI subtypes based on different neuropsychological profiles and postulated different etiology (12-14). Although amnestic MCI showed in the American studies high “conversion” rates to AD retroactive application of MCI criteria to data from a prospective epidemiological study showed that isolated amnestic MCI is an unstable group in regard to its outcome after a longer follow-up period (15). In a recent clinical study where diagnosis of MCI was based on psychometric definitions without combination with a clinical judgement, Rasquin et al reported that multiple domain MCI had even higher sensitivity than amnestic MCI in identifying subjects at risk of developing AD in a 2-year follow-up study (16). Therefore, initial concept of amnestic MCI has undergone further revision by subclassification into “pure” isolated amnestic MCI with an emphasis on memory deficit only, and amnestic MCI which allows also presence of other non-memory deficits (12, 17). Additional difficulties in operationalization of MCI criteria in clinical settings are a requirement for a subjective report of memory problems and preserved activities of daily living. Recent efforts towards a consensus regarding these issues took place on an international expert meeting in Stockholm 2003. In this latest revision of general clinical criteria for MCI major requirements are that the individual is neither normal, neither demented according to current classification criteria for dementia, cognitive decline...
Clinically defined amnestic MCI has a neurobiological profile that supports the hypothesis of neurodegenerative aetiology and, therefore, potential treatment interventions. Several studies have reported that MCI subjects had intermediate values between normal aging and dementia, and AD in particular, on various psychometric measures, cerebrospinal fluid biomarkers and neuroimaging investigations showing atrophy in medial temporal lobe structures by means of MRI, reduced glucose metabolism or cerebral blood flow in temporoparietal cortex measured by means of PET and SPECT, respectively, or increased slowing in EEG. In addition, a higher prevalence of APOE e4 allele has been reported in this population and postmortem studies showed that subjects with MCI in close proximity to death have pathological changes characteristic for AD, such as severe neuron loss in the hippocampus and entorhinal cortex, \( \beta \)-amyloid load in the entorhinal cortex and a density of tau positive neurofibrillary tangles in the mesial temporal lobe intermediate between that found in healthy subjects and AD patients. Presence of typical AD pathology implies that pathological processes in the brain have already been set up in motion a long time ago and realistic expectations are that with currently available pharmacological interventions we most probably cannot reverse the disease process and already existing pathological changes but could eventually modify symptom progression and its clinical expression. However, it should be emphasized that we still cannot consider MCI as an exclusive predictor of AD in individual patients, since not all subjects with MCI have AD and subjects without MCI could have AD.

Due to this inherent heterogeneity of the MCI concept, we are still in a position with no definite and precise definition or clinical diagnosis but evolving working criteria. Criteria for amnestic MCI showed satisfactory reliability in a multicentre American clinical trial and were in general implemented in all clinical trials discussed in this review.

**Putative treatment strategies for MCI**

MCI treatment interventions have two aspects: improvement of memory loss and prevention of further cognitive decline to clinically manifest AD. Because of assumed pathophysiological relationship between MCI and AD, hypothesized therapeutical approaches in MCI are mainly based on current and hypothesized treatment strategies for AD: acetylcholinesterase inhibitors (AChEI), anti-oxidants, nootropics and antiinflammatories. The three acetylcholinesterase inhibitors (AChEI) (donepezil, rivastigmine, galantamine) are presently established treatment strategy in AD and are considered as the first choice candidates for the treatment of MCI. Randomized clinical trials up to 6 months duration have shown positive effects on cognitive measures and measures of global function and symptomatic improvements up to 1 year have been reported in patients with mild to moderate AD. Possible neuroprotective effects of AChEI have been suggested in the recent study, which showed that the mean annual rate of hippocampal volume loss among the patients treated with donepezil was significantly smaller than among the untreated controls. Open-label extension trials relying either on a historical placebo-treated cohort or a predicted rate of decline on some cognitive measures like ADAS-cog, have suggested that although most patients experience a cognitive decline after 1 year of treatment, benefits are maintained relative to placebo for 3 to 4 years.

Antioxidants in diet have been associated with a reduced risk of AD in observational studies. Furthermore, high plasma levels of antioxidant vitamins were related to better memory performance in elderly. In AD clinical trials antioxidants have shown modest but positive
effects on disease progression: selegiline or vitamin E in moderately severe AD in 2-years trial (35) and Gingko biloba in mild stages of the disease in 52-weeks trial (36).

Anti-inflammatory drugs have shown prophylactic and possible therapeutic neuroprotective properties in observational as well as in experimental studies: reduced risk of AD among users of non-steroidal anti-inflammatory drugs several years prior to dementia diagnosis and a role of inflammatory processes in pathogenetic cascade of AD (37). However, a one year randomized, double-blind clinical trial with a 3 group parallel design compared rofecoxib or low-dose naproxen with placebo and reported that there was no slowing of cognitive decline in patients with mild-to-moderate AD (38). Although this first large-scale trial does not support the hypothesis that NSAID therapy could slow the progression of AD, only primary prevention trial in elderly population without dementia could evaluate possible prophylactic neuroprotective properties of NSAID.

Nootropics have been present for more than three decades on the market and are probably first agents with indication for a treatment of dementia-related symptoms and age-related cognitive impairment. A recent meta-analysis re-examined 19 randomized clinical trials (RCT) of piracetam that included 1488 older subjects with diverse cognitive impairment ranging from Age Associated Memory Impairment (AAMI) (39) to dementia, and demonstrated improvements on Clinical Global Impression of Change (CGIC) (40) which was a common outcome measure in all studies (41). A one-year RCT with a high dose of 8 gram of piracetam per day in 33 patients with mild to moderate AD showed that drug was well tolerated and that the treatment group, although not improved in general, had significant positive differences with respect to four memory subtests (42). Possible modes of action of piracetam and similar drugs from the same class are non-specific. The agent influences neuronal and vascular function, has both central and peripheral effects probably mediated via influence on membrane fluidity that affects nonselectively neurotransmission, offers neuroprotective benefits, promotes neuroplasticity and has anticonvulsant and rheological properties (43). Therefore, it is biologically plausible to expect eventual symptomatic and not disease modifying effects.

Interestingly, results of a recent international survey on issues on diagnosis, therapeutic strategies and management of MCI showed that 93% of experts in the field from around the world shared the opinion that it will not be possible to develop a single treatment for patients with MCI due to the etiological heterogeneity (44).

**Clinical trials in MCI: Methodological issues**

During the meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration (FDA) held in March 2001, several issues have been raised in the context of the development of drugs intended for the treatment of MCI: a) valid, reliable and widely applicable criteria to define etiologically homogenous MCI (in terms of future transition to AD); b) appropriate instruments to measure the clinical effect of the drug; c) clinical trials designed to measure both, symptomatic and disease modifying effect; d) evidence of clinically meaningful effect and magnitude of benefits as compared to harms (45). Although current “diagnostic” criteria of MCI include neuropsychological assessment of cognitive loss, there is no suggested cut-off score for memory impairment and the clinician through the exam and interview determines the result and clinical significance of impairment (12). The second requirement for appropriate instruments to measure the clinical effect of the drug is equally demanding, since outcome measures were designed to assess symptomatic effects on various domains of impairment in AD. Judgment of treatment success is based on known deterioration rates during the natural history of untreated disease as measured by functional measures like Clinical Dementia Rating scale (CDR) (46), Global Deterioration
Scale (GDS) (47), Clinical Global Impression of Change (CGIC) (48) or psychometric measures like Alzheimer’s Disease Assessment Scale, Cognitive subscale (ADAS-Cog) (49). However, these efficacy measures were derived from AD trials and might be rather insensitive and non reliable in short-term MCI trials since the decline is slower in the early stages of the disease.

Design of clinical trials in MCI (study sample, duration, primary efficacy measures) is influenced by study objectives, symptomatic vs. disease modifying effect and consequent definition of primary end points: “conversion” to dementia or symptom progression (2), Figure. Symptomatic effect implies no effect on transition rate to dementia and positive change on one or both primary efficacy measures, such as the clinical rating scales measuring global change, function or cognition. Symptom progression as a primary end point based on a continuous measure requires a shorter duration of a trial and a smaller sample size, while a dichotomous outcome in studies with “conversion” as a primary outcome requires a large sample size for the power calculation. For example, in the piracetam trial with symptomatic effect as a primary objective it was calculated, based on the effect size from a previous trial with the same agent (42) that 140 subjects per treatment arm would allow detection with a 90% power of significant difference on a Cognitive Battery Composite Score (CBCS) between placebo and piracetam after 12 months of trial. On the other hand, disease modifying effect implies effect on transition rate to dementia and a positive change on one or both primary efficacy measures. A survival analysis, a larger sample size of at least 700 individuals and duration of trial of at least 3 years ensures adequate power to detect small and possible disease modifying effects, given the estimated annual “conversion” rate of 15%. Optimally, both end points, symptom progression and “conversion” are combined and symptom progression could be evaluated via annual interim analysis through change in surrogate markers. Assumption with surrogate markers is that they are biologically close to the disease process and correlate to symptom domains, clinical outcome and neuropathological features of the disease, as indirectly measured by cognitive and behavioural scales or neuroimaging and biochemical markers. A medial temporal lobe atrophy, and hippocampal volume in particular, as measured by MRI has been consistently reported as a predictor of future development of AD in MCI subjects (50, 51). Change in surrogate markers should not only be quantitative but also have clinical meaningfulness (52). In practice it means that treatment response on surrogate measure such as change in neuroimaging parameters or biochemical markers should be predictive of the treatment effect on the important clinical outcomes (53) Long-term trials increase a possibility of violation of the protocol as well as dropout rates for various reasons. Intention-to-treat principle should be applied to minimize bias in assessment of treatment efficacy in this case (54).

Finally, risk-benefit ratio in interpretation of the results is of utmost importance because eventual future treatment of MCI will also target a proportion of non-diseased elderly.

Review of clinical trials in MCI

Seven secondary prevention RCT in amnestic MCI have been performed so far, encompassing agents with various mechanisms of action: all three on the market available AChEIs (donepezil, rivastigmine, galantamine), antioxidants (vitamin E), antiinflammatories (rofecoxib), nootropics (piracetam). Study design and outcome measures of the respective trials, are summarized in the Table. A short 4-week trial with ampakine in MCI subjects is not reviewed in this paper due to its unusual design.
Donepezil and vitamin E

The MIS is the first reported large-scale trial in amnestic MCI (4, 57). Primary outcome measure was time to development of possible or probable AD as defined by NINCDS-ADRSA criteria (58). The combined group of subjects had mean age of 72 years and 55% were APOE e4 carriers (53% in the placebo, 58% in the donepezil and 55% in the vitamin E group, respectively). After 3 years 539 (70%) of participants completed the trial, 214 participants progressed to dementia (212 to probable or possible AD, 1 to mixed dementia and 1 to primary progressive aphasia, there was about 16% annual progression rate. Patients on donepezil were slightly better in terms of staying clinically stable during the first half of the trial and having more differences in the change from baseline scores on MMSE, CDR sum of Boxes, GDS, modified ADAS-Cog and cognitive scores as compared to placebo group. However during the second 18 months all three groups converged and after 36 months there were 73 transitions to AD in the placebo group, 63 in donepezil and 76 in vitamin E group in total. Since there is no information on eventual retrieved dropout analysis, proportions relative to the total number of “converters” per each arm were: 38% in the placebo group, 39% in the donepezil group and 41% in the vitamin E group. (4). Drop-out rate was about 12%/year and at 6, 12 and 18 months there was a higher drop-out rate in the donepezil group probably because they were slightly more impaired at the baseline. Ten deaths were reported in the donepezil group (3 cardiac arrests), 7 in the placebo and 6 in the vitamin E group (4). APOE e4 allele showed a modifying effect on the rate of progression and the overall result is driven by e4 positive group, 76% of cases who progressed to AD was APOE e4 carriers. After adjustment for multiple comparisons hazards ratio (HR) for progression to AD in the total sample on donepezil vs. placebo were only significant during the first 12 months, while in APOE e4 carriers HR was significant during the first 24 months and trends were observed throughout the 36 months of trial. In summary, amnestic MCI and presence of APOE e4 allele were predictive of progression to AD in this study.

Donepezil

Efficacy and tolerability of donepezil in patients with MCI was evaluated in a 24-weeks multicenter, randomized, double blind placebo-controlled parallel group trial (59). Enrolled subjects had a CDR of 0.5 (memory box score 0.5 to 1.0) and MMSE score ≥24. At the end of the trial at week 24 significant improvement was observed in the donepezil group in ADAS-Cog total score, ADAS-Cog Immediate Word Recall test. In fully evaluable (study medication compliance at least 80%, and no significant protocol violations at week 24) study population scores on NYU Paragraph Immediate and Delayed Recall tests as well as Digit Span Backwards were also significantly different in favour of donepezil. The CGIC-MCI improved in both treatment and the placebo group with no difference between the groups at the end of the trial and self-rated Patient Impression of Change was significantly different in favour of the donepezil group. Adverse events, predominantly gastrointestinal, were reported in 88% of the donepezil group and 73% of the placebo group, occurring at the higher frequency than in AD trials (60).

Rivastigmine

The Investigation into the Delay to Diagnosis of AD with Exelon (InDDeX) study is a multicentre trial on Rivastigmine, a large double-blind placebo-controlled parallel group trial of Rivastigmine 3-12 mg/day. Similarly to the MIS the entry criteria correspond to that of amnestic MCI (61). Primary outcomes were time to clinical diagnosis of AD (NINCDS-
ADRA criteria) and change from baseline on cognitive function as measured by change on overall summary score on neurocognitive test battery (series of individual tests measuring working memory, immediate and delayed recall, cued recall, attention/concentration, language, executive functioning and praxis). Forty-nine percent of the total study sample consented to pharmacogenetic assessment. 41% of them were e4 allele carriers. There was a high prevalence of concurrent medical illness, over 97%, and more than 90% of patients were receiving medication for concomitant illness. Adverse events occurred more frequently in the rivastigmine group, 80.2 %, as compared to the placebo group 41.7%. Preliminary results of the per protocol analysis show that study objectives were not satisfied. During the trial there was a high percentage of dropouts, 51% of rivastigmine treated patients and 63% of placebo treated patients completed the trial. Preliminary reported conversion rate was lower than expected, 19.4% during the 3-4 years of trial, 17.3% of patients in the rivastigmine group and 21.4% in the placebo group progressed to probable or possible AD. It has been observed that patients who converted to AD tended to be older, less educated, with a lower body mass index, higher baseline scores on GDS and CDR, more pronounced cognitive impairment as measured by the MMSE and NYU delayed paragraph recall and smaller brain volumes as measured by MRI.

**Galantamine**

Efficacy and safety of a flexible dose of galantamine in patients with MCI was evaluated in two 24 months duration multicenter, randomized, double blind, parallel-group placebo-controlled studies (62, 63). The process of data evaluation is still ongoing but some preliminary results have been reported (5-8). According to baseline demographics patients had a mean age of about 70 years, the duration of cognitive problems showed high variability among individuals, there was a greater impairment in immediate than in delayed recall. Conversion to dementia (CDR≥1.0) at month 24 was similar in two studies: 13% in the galantamine, 18% in the placebo group in study 1, and in study 2 17% in the galantamine, 21% in the placebo group. In either studies no statistically significant treatment effect was observed on cognition as assessed by ADAS-Cog or ADL measures at 24 months. Treatment effect on global functioning was demonstrated in study 1 by significant difference in CDR-SB scores in favour of galantamine at 12 and 24 months and no difference in study 2 on neither of two occasions. Attention assessed by DSST was significantly improved at 12 months in galantamine group in study 1 and at 24 months in study 2. Although no detailed results are available, it has been reported that a reduced rate of whole brain atrophy, but not hippocampal atrophy, has been found in patients on galantamine treatment at month 24 (8). Pharmacogenomic analyses are still ongoing and reported preliminary frequencies of the e4 allele for the study 1 are 29.5% and 26.4% in the placebo and galantamine group, respectively and in the study 2 in the placebo group 23.5% and in the galantamine group 24.4%. An effect of duration of symptoms and baseline severity of cognitive impairment was observed in both studies. In study 2 in the subgroup of patients with NYU Delayed Recall score of 4-5, 9% in the galantamine, and 26% in the placebo group “converted” to dementia. In the same study in the subgroup with NYU Immediate recall score ≤1, there was a significant positive effect in the galantamine group on CDR-SB scores at month 24. In the study 1 superiority of galantamine over placebo in change on ADAS-Cog/MCI score at 24 months was shown in the subgroup of patients with duration of symptoms 2-3 years and worse baseline performance on NYU Delayed Recall (score 2-3) and NYU Immediate recall (score 2-3).

Adverse events judged to be treatment relevant were >10% and were similar between two groups. A greater mortality was observed in galantamine group in both studies, 5 patients on placebo died, and 15 patients on galantamine died. Investigators did not consider causes of
death to be related to treatment, however the imbalance in the number of deaths between the
treatment and placebo group remains a concern. Further evaluation of a mortality rate in this
study will be conducted in a retrieved dropout study, GAL-COG-3002.

**Rofecoxib**

Recently completed randomized double-blind placebo-controlled multicenter trial evaluated
whether a fixed dose of a COX-2 inhibitor rofecoxib 25 mg/day could delay an AD diagnosis
in elderly MCI patients and investigated a long-term tolerability of this agent (64). The
primary outcome was a number of patients with CDR $\geq$ 1.0 and incident AD according to
NINCDS-ADRDA criteria. The two randomized groups were balanced with respect to gender,
family history of AD, years of education, age (mean 75 years) and APOE e4 allele (36%
carriers in the placebo, 35% in the rofecoxib group). The study was terminated after 189
clinically diagnosed cases of AD were reached, because of lower than expected conversion
rates and high drop-out rate that compromised the power of the study. The estimated
incidence of AD was lower than expected 10-15%, 6.4% in the rofecoxib group and 4.5% in
the placebo group giving a rofecoxib: placebo hazard ratio of 1.46 (CI 1.09 to 1.94).
However, this treatment difference in favour of placebo was not consistent with results from
secondary measures of cognition and function, which did not demonstrate any significant
differences between the treatment groups.

In the placebo group 45% of patients discontinued the study, 10% due to the adverse events.
Same rate of 45 % of discontinuation occurred in the rofecoxib group, 11% due to the adverse
events, but relatively few subjects discontinued the study due to drug-related adverse events,
8% in the rofecoxib group and 5.6% in the placebo group.

**Piracetam**

Efficacy and tolerability of piracetam in MCI patients was evaluated in a multicenter trial of
12 months duration sponsored by UCB Pharma. Trial objective was symptom progression and
primary efficacy measure was Composite Score that contained key outcomes from 8 tests: the
NYU Paragraph Recall Test (Delayed Recall), ADCS Cancellation Test, Symbol-Digit
Modalities Test, Colour Trails Test (form A), Letter Number Sequence Test from the WMS
III, Free and Cued Selective Reminding Task, Block Design from the WAIS-R and Semantic
Category Fluency. All tests were applied at both the selection and the baseline visit to
document any learning effect. A ceiling effect was observed on the Free and Cued Selective
Reminding task. The sum over the 8 standardized variables (the mean of each test score
subtracted from the individual score and divided by the pooled standard deviation) was
declared as the Cognitive Battery Composite Score (CBCS). All primary and secondary
efficacy parameters were assessed at the selection, baseline, interim evaluation visit and the
final evaluation visit. In addition, the study had exploratory objectives with an aim to describe
the relationship between cognitive decline and APOE e4 allele and (in a subpopulation)
neuroimaging, CSF and neurophysiological markers.

All treatment groups were similar in demographic variables with a mean age of 68 years.
Overall 405 (60%) patients out of 675 total patients had a determination of APOE genotype.
173 (43%) out of these 405 were carriers of APOE e4 allele, 141 (35%) out of 405 were
heterozygotes and 32 (8% out of 405) were homozygotes.

All analyses were performed on both the ITT and the per protocol (PP) population.
Discontinuation from the study was similar in all treatment groups: 24 % in the placebo, 27%
in the piracetam 4800 mg and 21% in the piracetam 9600 mg group. The most frequent reason
for discontinuation was due to an adverse event: 12% in the placebo, 13 % in the piracetam
4800 mg and 8% in the piracetam 9600 mg group. Overall 72% of subjects reported 1755 adverse events: 76% in the placebo group, 72% in the piracetam 4800 mg group and 68% in the piracetam 9600 mg group. All these data confirm the good safety profile of piracetam given a relatively high dose during a long time period (1 year). No statistically significant difference on any of primary or secondary outcomes at month 12 was observed for either of two piracetam doses or placebo. The results were consistent for both per protocol (PP) and ITT population and results of analysis of primary and secondary outcomes were consistent with each other.

Summary and concluding remarks

This review shows that none of the listed clinical trials in MCI met their primary objectives. A short 6 months donepezil trial and 3-years secondary prevention study confirmed previous observations from AD trials on symptomatic effects of AChEI. Nevertheless, the scientific community has got valuable information on natural course of MCI as defined by currently accepted clinical criteria as well as lessons for the future with regard to design and methodology of MCI trials.

The questions arise whether the study objectives were justified by scientific proofs or also based on a lot of assumptions. The strongest assumptions are that we know what the treatment will do in this still controversial early stage of the disease and that effects would be clearly demonstrated on cognitive and functional measures used earlier in AD trials. Despite the consensus on a generally accepted clinical definition of amnestic MCI that isolates individuals at high risk to develop AD within several years, “conversion” rate varied considerably among the trials from 4.5% and 6.4%/year in the rofecoxib trial to 16%/year in the MIS (donepezil and vitamin E study). Obviously, very similar entry criteria choose different populations of patients, in some centres some of them probably being early AD cases. In their most recent article Visser et al (65) investigated retrospectively the diagnostic accuracy of MCI criteria used in different MCI trials for predementia Alzheimer’s disease in a cohort of non-demented patients from their clinic. The authors pointed out that there were marked differences in the definition of cognitive impairment. The MIS study had a strict cut-off score for memory impairment and higher positive predictive value as well as a “conversion rate” in contrast to the Gal-Int-11 and rofecoxib study, which used a more lenient cut-off score. In the MIS a considerably higher percentage of patients (55%) are carriers of APOE e4 allele as compared to those published in a metaanalysis of 42 case-control series where reported frequencies of e4 allele were 32% in sporadic AD cases over 65 years of age and 41% in sporadic AD cases under 65 years of age (66). One possible explanation is that the variation in the APOE e4 prevalence across the studies results from variation in definition of memory impairment, meaning that more severe impairment in the MIS study is clearly associated with higher APOE e4 allele frequency.

Another important methodological concern is the choice of primary and secondary outcome measures. In the current trials they were chosen according to previous FDA guidelines for AD trials and should include assessments of global function and cognition with scales well validated in AD patients, such as CGIC and its more popular formats Clinician’s Interview-Based Impression of Change (CIBIC) and Clinician’s Interview-Based Impression of Change with caregiver input (CIBIC-plus), and ADAS-Cog. Although there have been adaptations of these scales to MCI population of patients, there is still uncertainty about the expected range of change during the time period of trial, which does not equal that of AD population of patients where it has been shown that rate of cognitive deterioration was strongly related to baseline severity (67). Very few studies have investigated performance of normal subjects on ADAS-Cog and effect of age, gender and level of education (68). Such normative studies
provide a reference for the clinician to distinguish variations in normal cognitive aging from those accelerated by subclinical neurodegenerative disorder probably occurring in a majority of individuals with MCI. With respect to MCI version of ADL scale, there is a concern that it does not cover high-order instrumental tasks previously shown to have high predictive validity of future conversion to AD. Low “conversion” rates are also influenced by strict entry criteria in some studies, which exclude significant co-morbidity that probably determines faster progression and “conversion” rates. These limitations might considerably reduce a therapeutical potential of agents with effects on microcirculation such as piracetam, which have documented efficacy in elderly patients with etiologically broad range of cognitive disorders (43). Exclusion of patients with depressive symptoms and silent cerebrovascular pathology on CT or MRI probably selects a very exclusive group not representative of MCI in general or overall clinical population. It has been observed that placebo treated AD patients in clinical trials declined 0.55 MMSE points per year as compared with 2.5 to 3 points per year in natural cohorts (69, 70).

Differences in study populations raise the question if current generally accepted clinical criteria are also generally applicable across different clinical centres in a multicenter international trial. It could be of importance that multicenter cross-cultural studies report the intersite variability of baseline measures as well as the outcomes. Furthermore, there is evidence that there is ca 20% discordance between clinical diagnosis of probable AD and definite pathological diagnosis (71). Therefore, if a clinical diagnosis of AD could be questioned from a neuropathological perspective, etiological diagnosis of MCI based exclusively on clinical grounds should be a matter of even greater concern. Would it help increase the sensitivity and specificity and ensure the outcome if the inclusion criteria were to be further enriched by the addition of biological markers, such as genetic and CSF markers or atrophy measures on MRI? In most of the listed trials instrumental investigations and biochemical and genetic markers were included as exploratory objectives, and none of these trials included them as enrichment criteria.

An useful approach has been suggested recently which combines a number of predictor variables for AD, such as age, MMSE score, degree of functional impairment, neuropsychological test impairment, medial temporal lobe atrophy and APOE genotype in the Preclinical Alzheimer’s Disease scale (PAS) (72). Study sample enriched in this way could have a higher diagnostic sensitivity and specificity for a prodromal AD (73), which is of great importance for a clinician who needs a higher level of certainty in possible clinical outcome in order to initiate treatment in MCI subjects. Indeed, predementia or prodromal AD could be a better designation for a selection of non-demented subjects for secondary prevention trials in AD.

While sub analysis of predictors of progression to AD is still ongoing in most of the trials, in particular in APOE e4 allele carriers, it has been reported that the APOE e4 carriers in the MIS progressed faster and showed more sustained response on the donepezil treatment (57). Epidemiological, clinical and basic science evidence supports relationship between APOE genotype and risk for AD (75-77). Furthermore, it has been reported that APOE e4 carriers over the age of 50 demonstrated a modest decline in memory skills over a median period of 33 months prior to the symptomatic onset of MCI (77). In a subpopulation of 494 subjects participating in the InDDEex study and consenting to the pharmacogenetic assessment, APOE e4 genotype was associated with greater memory and functional impairment and hippocampal atrophy (61). It is plausible to believe that in such a heterogeneous condition as MCI, subjects with APOE e4 more likely have AD as underlying pathology, which might also explain a better treatment response. While post-mortem study on MCI subjects of DeKosky et al (78) showed that there was an up-regulation of choline acetyltransferase activity in the frontal cortex and hippocampus, this compensatory mechanism might be compromised in
MCI patients who are also APOE e4 carriers and, therefore, could be better responders to the therapy with AChEI. However, observed treatment difference according to the APOE e4 status in the MIS was not statistically impressive and taken together with the results from the entire study cohort could suggest alternative explanation that of “wearing-off” of the beneficial effects of the treatment, as noted in the accompanying editorial to the article (80). It should be noted that in AD trials with tacrine, galantamine and donepezil APOE e4 allele was not found as a predictor of more favourable outcome (80-82).

Evaluation of treatment effects in long-term trials is also compromised by the effect of missing data due to large drop-out rates, which varied between 40-45% in the case of MCI trials lasting more than 24 months; donepezil+vitamine E, rivastigmine and rofecoxib, respectively. Although reported adverse events were equally balanced between the active treatment and placebo groups in most of the studies, in the MIS study a higher withdrawal was observed in the donepezil group due to the more severely impaired cognitive status at the baseline. Analysing a random sample from discontinued patients is not optimally solving a problem of the dropout bias, which compromises understanding of group differences in the clinical trials. A retrieved dropout analysis should be established as a standard method since it minimizes a dropout bias by assessment of as many as possible patients who did not completed a trial for various reasons (83).

Secondary objective in most of the secondary prevention trials is improvement on the specific tests in neuropsychological battery covering major cognitive domains. What do small statistical improvements on test scores on individual neuropsychological test mean for the patients overall functioning? Clinical relevance of improvements on cognitive tests and global measures of change has been questioned from the perspective of caregivers of AD patients (84). A cognitive battery composite score (CBCS) used in the piracetam trial as a primary outcome, in general enhances effects of standardized change in any of 8 tests that compose this battery, however it would be difficult to interpret, either positive or negative effects, in terms of clinically meaningful effects. In addition, a few outliers could influence the magnitude of standardized change on CBCS. Correspondence with secondary outcomes encompassing global cognitive and functional measures could support finding in primary efficacy parameters. Still, there remains a concern that a one-year duration trial in a population who shows ceiling effects on some of the tests at baseline and does not deteriorate quickly, could not detect any significant changes. Indeed, in the piracetam trial there was a ceiling effect on the Free and Cued Selective Reminding task at the baseline and neither placebo nor the treatment groups deteriorated during the course of the trial.

In summary, experience with the clinical trials in MCI performed so far has shown that even with the criteria for amnestic MCI, that were created to increase the specificity and reduce the heterogeneity of MCI, various studies were recruiting different samples with respect to the “conversion” rates to dementia and other biological characteristics like APOE genotype. Lack of effects on symptom progression are not only questioning the clinical efficacy of the evaluated agents in MCI but also the sensitivity of outcome measures used in the trials and calling for more effective and reliable markers of disease progression. The fact that none of the drugs previously shown to have clinical efficacy in AD trials as well as benefit in everyday practice have met the primary objectives of the respective trials, indicates that the clinical trial design in MCI has to be further developed with a special attention being paid to the selection of more homogeneous samples at entry, optimal treatment duration and multidimensional and reliable outcomes. Both, validation of natural cohorts of MCI subjects followed for a longer time period in clinical settings and biological markers are needed. Because of these unresolved issues it is still premature to conclude that lack of proof of efficacy in MCI trials performed so far is a definite lack of efficacy of the therapeutical agents being evaluated.
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Figure legend:

**Figure.** Primary objectives, theoretical designs and optimal duration of clinical trials in MCI. Solid lines indicate minimum trial duration, dashed lines optimal trial duration. Probable disease modifying effect requires a randomized start or randomized withdrawal design (56, 57), where after delayed start or withdrawal of active treatment the placebo group does not catch the treatment group effect. The last design is a theoretical one and has not been applied neither in AD or MCI trials.

Competing interest statement:

The authors have no research grants from any of the pharmaceutical companies marketing antidementia drugs, neither they have stocks in any of these companies. Dr Bengt Winblad has been receiving consultancy fees for advisory board meetings from all companies marketing anti dementia drugs. Dr Miia Kivipelto received consulting fees for advisory board meeting from Pfizer. All authors received fees for lecturing or organizing education sponsored by Novartis.

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<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Donepezil + vitamin E*</th>
<th>Donepezil</th>
<th>Rivastigmine**</th>
<th>Galantamine Study 1 (GAL-INT-11)</th>
<th>Galantamine Study 2 (GAL-INT-18)</th>
<th>Rofecoxib</th>
<th>Piracetam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>RCT, placebo-controlled, double-blind, three-arms</td>
<td>RCT, placebo-controlled, double-blind, parallel group</td>
<td>RCT, placebo-controlled, double-blind, parallel group</td>
<td>RCT, placebo-controlled, double-blind, parallel group</td>
<td>RCT, placebo-controlled, double-blind, parallel group</td>
<td>RCT, placebo-controlled, double-blind, three-arms</td>
<td></td>
</tr>
<tr>
<td>Daily dose</td>
<td>Vitamin E (1000 IU/bid) donepezil (10 mg/d)</td>
<td>5 mg/d first 42 days, thereafter 10 mg/d</td>
<td>3-12 mg/d</td>
<td>16 or 24 mg/d flexible dose</td>
<td>16 or 24 mg/d flexible dose</td>
<td>25 mg/d</td>
<td></td>
</tr>
<tr>
<td>Trial duration</td>
<td>3 years</td>
<td>24 weeks</td>
<td>planned 73 days, extended to 4 years</td>
<td>24 months</td>
<td>24 months</td>
<td>planned 2-3 yrs, extended to 4 yrs</td>
<td>12 months</td>
</tr>
<tr>
<td>Enrollment criteria</td>
<td>Amnestic MCI, not published, CDR 0.5 (0.5-1.0 memory domain), MMSE &gt; 24</td>
<td>Amnestic MCI, (NYU Pg Rec Delayed Recall &lt;9), CDR 0.5 (&gt;0.5 memory domain), HDRS &lt;13, HDRS item 1 ≤1</td>
<td>Amnestic MCI, (NYU Pg Rec Delayed Recall &lt;10), CDR 0.5 (&gt;0.5 memory domain)</td>
<td>Amnestic MCI, (NYU Pg Rec Delayed Recall &lt;10), CDR 0.5 (&gt;0.5 memory domain)</td>
<td>Amnestic MCI, (NYU Pg Rec Delayed Recall &lt;10), CDR 0.5 (&gt;0.5 memory domain)</td>
<td>Amnestic MCI, CDR 0.5, (&gt;0.5 memory domain), WMS-R Logical Memory Immediate Recall &lt;10 or difference between immediate and delayed recall &gt; 5; HDRS&lt;18.</td>
<td></td>
</tr>
<tr>
<td>No of subjects</td>
<td>769</td>
<td>269</td>
<td>1018</td>
<td>995</td>
<td>1062</td>
<td>1457</td>
<td>675</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 – 90 (mean 72.9)</td>
<td>mean 73</td>
<td>mean 70.5</td>
<td>&gt; 50</td>
<td>&gt; 50</td>
<td>&lt; 65</td>
<td>50 – 89 (mean 68)</td>
</tr>
<tr>
<td>APOe e4</td>
<td>58% donepezil</td>
<td>55% vitamin E</td>
<td>53% placebo</td>
<td>not available</td>
<td>41% (determined in the 49% of sample)</td>
<td>26% galantamine 25.5% placebo</td>
<td>24% galantamine 23.5% placebo</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Time to clinical diagnosis of AD (NINCDS-ADRDA criteria)</td>
<td>Symptom change: CGIC-MCI, ADAS-Cog</td>
<td>(i) Time to clinical diagnosis of AD (NINCDS-ADRDA criteria) (ii) change from baseline on cognitive function as measured by a single score summed from weighted scores on a series of individual cognitive tests</td>
<td>Incident dementia (CDR &gt; 1.0) at 24, ADAS-Cog/MCI, CDR-SB at 12 months</td>
<td>Incident dementia (CDR &gt; 1.0) at 24, ADAS-Cog/MCI, CDR-SB at 12 months</td>
<td>CDR &gt; 1.0 &amp; incident AD (NINCDS-ADRDA criteria)</td>
<td>Symptom change: Cognitive battery composite score (CBICS)</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>MMSE, ADAS-Cog, NP tests, CGIC, CDR, GDS, QL, ADL, outcome by APOE e4 status.</td>
<td>CGIC-MCI, ADAS-Cog, ADAS-Cog, NYU Pg Rec, DS-backw, Symb. Dig. Modalities, PGA</td>
<td>CGIC-MCI, MMSE, CDR, GDS, ADAS-Cog, NPL, QOL-AD, healthcare utilization, outcome by APOE e4 status, volumetric MRI, and biomarkers (e.g., CSF and blood levels of tau, amyloid-beta peptide)</td>
<td>ADAS-Cog/MCI, CDR-SB, ADACS-ADL/MCI, DSST, ADAS-Cog/11 &amp; ADAS-Cog/13, MRI brain &amp; hippocampal atrophy</td>
<td>ADAS-Cog/MCI, CDR-SB, ADACS-ADL/MCI, DSST, ADAS-Cog/11 &amp; ADAS-Cog/13,</td>
<td>ADAS-Cog, MMSE, Selective Reminding Test, CDR, BDRS</td>
<td>CBIC, plus change in separate tests of CBICS, ADL, MMSE, BSI, GDS.</td>
</tr>
<tr>
<td>&quot;Conversion&quot; rate</td>
<td>16% / y</td>
<td>19.4% / 5 - 4 yrs</td>
<td>13% (galant.) 18% (placebo)</td>
<td>17% (galant.) 21% (placebo)</td>
<td>6.4% (rofecoxib) 4.5% (placebo) / y</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Drop-out rate</td>
<td>12%/year</td>
<td>20%</td>
<td>43%</td>
<td>Not available</td>
<td>Not available</td>
<td>45% (rofecoxib) 45% (placebo)</td>
<td>27% (4800 mg) 21% (9600 mg) 24% (placebo)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>88% (donep.) 73% (plac.)</td>
<td>96% (rivastig.) 93% (plac.)</td>
<td>90% (galantam.) 86% (placebo)</td>
<td>90% (galantam.) 86% (placebo)</td>
<td>90% (galantam.) 92% (placebo)</td>
<td>72% (4800 mg) 68% (9600 mg) 76% (placebo)</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>Significant positive effect on &quot;conversion&quot; time and cognitive tests during first 18 months. In e4 carriers positive treatment effect during 36 months. No effect in the vitamin E group.</td>
<td>Significant positive effect on ADAS-Cog in donep. group FE population. Immediate and delayed recall tests and DS backw, PGA. Both groups: improvements in CGIC-MCI</td>
<td>The study did not achieve its primary objectives.</td>
<td>No effect on &quot;conversion&quot; rate and ADAS-Cog, positive effect on CDR-CB, attention (DSST) at month 12, rate of atrophy of whole brain volume (not hippocampal), effect of symptom duration and baseline severity (NYU Pg Rec).</td>
<td>No effect on &quot;conversion&quot; rate, ADAS-Cog, or CDR-CB. Positive effect on attention (DSST) at month 24. Effect of baseline severity (NYU Pg Rec) on &quot;conversion&quot; at month 24 (9% galantamine, 26% placebo).</td>
<td>No change in primary or secondary efficacy parameters</td>
<td>No change in primary or secondary efficacy parameters</td>
</tr>
</tbody>
</table>
Table. Selected review of short- and long-term completed clinical trials in MCI.

*Memory Impairment Study (MIS); ** The Investigation into the Delay to Diagnosis of AD with Exelon (InDDEEx); NIH – The National Institute of Aging; ADCS - Alzheimer Disease Cooperative Study; RCT – randomized clinical trial; Amnestic MCI: defined according to generally accepted criteria, Petersen et al, 1999 (reference 1) by memory complaint, corroborated by an informant, abnormal memory function documented by a variant of a delayed recall test, normal general cognitive function as determined by CDR and MMSE, no or minimal impairment in ADL, not clinically demented; ADAS-Cog – Alzheimer’s Disease Assessment Scale, Cognitive subscale; NINCDS-ADRDA criteria – National Institute of Neurological Disorders and Communicative Disorders-Alzheimer’s Disease and Related Disorders criteria; Del Pg Rec: delayed paragraph recall; WMS-R: Wechsler Memory Scale-Revised; HDRS – Hamilton Depression Rating Scale; CDR – Clinical Dementia Rating scale; MMSE – Mini Mental State Exam; NYU Pg Rec – New York University Paragraph Recall; AVLT – Auditory Verbal Learning Test; BDRS – Blessed Dementia Rating Scale; CGIC – Clinical Global Impression of Change scale; NP tests – neuropsychological tests; GDS – Global Deterioration Scale; QL – quality of life; ADL – Activities of Daily Living scale; DS backw. – Digit Symbol backwards; PGA – Patient Global Assessment; CSF – cerebrospinal fluid; MRI – Magnetic Resonance Imaging; PET – positron Emission Tomography; DSST – Digit Symbol Substitution Test; FE – fully available population.
**Trial objectives**

- Disease modifying effect
- Delay to dementia/AD diagnosis
- Symptom progression

**Trial design**

- Randomized start / withdrawal
- Survival analysis
- Parallel group comparison

**Duration of the trial**

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References


CORRECTION

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In table 1 the column with heading Galantamine study 1 (GAL-INT-11) and row with heading ApoE e4, 26.4% galantamine, 29.5% placebo should be 45% galantamine, 47% placebo.

In table 1 the column with heading Galantamine study 2 (GAL-INT-18) and row with heading ApoE e4, 24.4% galantamine, 23.5% placebo should be 42% galantamine, 41% placebo.