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Research Article

The Effect of Memantine on Cognitive Performance with Amnestic Mild Cognitive Impairment

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Summary

Objective: Amnestic mild cognitive impairment (aMCI) refers to cognitive changes that occur during the period of normal cognitive decline and very early dementia. We aimed to assess the efficacy of memantine used for the treatment of patients with aMCI.
Methods: All patients were diagnosed as having aMCI according to the Petersen criteria and were assigned to one of three groups. Group 1 comprised patients who received memantine following examination (n=23), group 2 included patients who did not receive memantine treatment following examination (n=22), and group 3 was constituted by healthy age-matched volunteers (n=20). Following the examinations, neuropsychiatric tests from the Turquoise Alzheimer"s Study Group database used in dementia polyclinics were performed.
Results: The mean age of patients was 66±7.04 years in group 1, 65.3±6.20 years in group 2, and 57.6±5.40 years in group 3. The most noticeable improvements in group 1 were seen in the Mini-Mental State Exam, Wechsler memory scale subtests, Blessed Dementia Rating Scale, and the Boston Naming Test ($p<0.05$). Treatment with memantine was associated with an improvement in Geriatric Dementia Scale scores over the 24- week study period.
Conclusion: These results suggest that memantine treatment in patients with aMCI acts to enhance cognitive functioning compared with no treatment. These findings suggest the need for a larger randomized placebo-controlled trial.

Key words: Memantine, dementia, amnestic mild cognitive impairment

Memantin'in Amnestik Hafif Kognitif Bozuklukta Kognitif Performans Üzerine Etkisi

Özet

Amaç: Amnestik hafif kognitif bozukluk (aMCI) normal bilişsel gerileme ve çok erken demans döneminde ortaya çıkan bilişsel değişimleri ifade eder. Biz aMCI hastalarında tedavide kullanılan memantin etkinliğini değerlendirmeyi amaçladık.
Metod: Tüm hastalara Petersen kriterlerine göre aMCI tanısı kondu ve üç gruba ayrıldı. Grup 1, muayene sonrası memantin başlanan hastalardan oluştu (n=23), Grup 2'de muayene sonrası memantin tedavisi almayan hastalar (n=22), Grup 3 sağlıklı yaşa uygun gönüllülerden (n=20) oluşuyordu. Muayeneleri takiben demans polikliniğimizde kullanılan Turkuaz Alzheimer Çalışma Grubu veri tabanından nöropsikiyatrik testler yapıldı.
Sonuçlar: Hastaların yaş ortalaması Grup 1'de 66±7.04, Grup 2'de 65.3±6.20 ve Grup 3'te 57.6±5.40 idi. Grup 1'deki en belirgin iyileşme Mini Mental Durum Muayenesinde (MMSE), Wechsler bellek ölçeği alt grup testleri, Blessed Demans Derecelendirme Ölçeği (BDRS),

Boston adlandırma testinde (BNT) görüldü ($p<0.05$). Memantinin tedavisi, 24 haftalık çalışma süresi boyunca Geriatrik Demans Ölçeği skorlarında düzelme ile ilişkiliydi.
Tartışma: Bu sonuçlar memantinin aMCI hastalarında tedavi almayan grupla karşılaştırıldığında bilişsel işlevsellik düzeyini artırdığını göstermektedir. Bu bulgular, plasebo kontrollü daha geniş randomize bir çalışmaya ihtiyaç olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Memantin, demans, amnestik hafif kognitif bozukluk

INTRODUCTION

Mild cognitive impairment (MCI) is the intermediate stage between cognitive and neuropathology changes of normal aging and dementia. MCI is very common and affects approximately 19% of older people aged over 65 years. Compared with older people with normal cognition, patients with MCI are at 3-5 times increased risk of developing Alzheimer's disease (AD). Petersen`s criteria are frequently used to define MCI. Patients with MCI can be categorized further as amnestic (aMCI) and non-amnestic MCI (naMCI). In aMCI, memory loss is predominant, and it is associated with a high risk of further conversion to AD (1-3). Individuals with naMCI have impairments in domains other than memory and have a higher risk of conversion to other dementia forms such as diffuse Lewy body dementia. Both types can be categorized further into single domain and multi-domain subtypes; however, in the present investigation, no further categorization was made due to the limited sample size (4,5). Although there are several Food and Drug Adminsitration (FDA)-approved medications for AD, there are no approved medications for patients with MCI. For AD treatment, clinical practice guidelines suggest trialling a cholinesterase inhibitor (ChI) for mild to moderate severity and memantine for moderate to severe disease (6).

The memantine mechanism involved in learning and memory entails long-term potentiating, mediated by the neurotransmitter glutamate via the NMDA receptor. Recent studies showed that memantine also reduced levels of amyloid β (A β) peptides, which inhibited A β oligomers, and provided an improvement in cognitive performance (7,8). These effects result from neuroprotection induced through the blockade of glutamatergic NMDA receptors (NMDARs). In clinical trials, memantine led to a small but significant beneficial effect on cognition, daily activity living, and behavior when compared with placebo. Randomized controlled trials and their meta-analysis confirmed its beneficial effects in slowing the long-term progression of the disease. Memantine can usually be used in addition to acetylcholinesterase inhibitors (ChEI) in AD (9,10).

We conducted a prospective open-label study to test the hypothesis that memantine`s anti-glutamatergic activity could improve cognitive functioning. For this, patients with aMCI who did and did not receive memantine were compared using neuropsychiatric tests.

MATERIAL AND METHODS

This was a 48-week, open-label extension study that included a total of 45 patients with aMCI and 20 healthy controls who were consecutively examined at the Memory and Dementia Outpatient Clinic of Eskişehir Osmangazi University Neurology Department. All patients were randomly selected from our outpatient clinic. Patients with MCI expressed a memory problem representing a change from previous functioning and met Petersen criteria and fulfilled criteria for the diagnosis of MCI according to the American Academy of Neurology for MCI at screening. Subjects with depressive mood as evaluated using the Geriatric Depression Scale (GDS short version-15 item; a total score greater than 5 indicating depression) were excluded from the study. Neuropsychologic testing was performed

at baseline (week 0) and at the 12, 24, and 48-week time points. All data were recorded in the database program of the Turquoise Alzheimer's Study Group as used in dementia clinics. This was an open-label study, with a follow-up plan prepared for the patient and control group.

A total of 65 participants (group 1, n=23; group 2, n=22; group 3, n=20) were included the study. Patients in group 1 included patients with aMCI who received memantine. Subjects initially received memantine at 5 mg once daily, which was increased weekly by 5 mg/day in divided doses to a dosage of 20 mg/day. Patients in group 2 included the patients with aMCI, but these received no treatment.

Exclusion criteria were as follows: probable or possible AD, the presence of other neurodegenerative conditions such as parkinsonian, frontal, vascular, or metabolic dementias; a history or diagnosis of other neurologic diseases such as stroke or hydrocephalus; a primary psychiatric diagnosis such as depression or schizophrenia; the presence of sedating medications at the time of testing; or a metabolic or systemic disorder that might influence cognitive performance.

All subjects received the same research magnetic resonance imaging (MRI) or brain computerized tomography examinations, medical and neurologic examinations, and neuropsychologic testing. Laboratory tests for dementia including complete blood counts, blood chemistry, serum vitamin B12 and folic acid levels, thyroid function tests, and syphilis serology were requested.

Trained neuropsychologists administered neuropsychologic assessments to all study participants. The Mini-Mental State Exam (MMSE) was applied to all patients and controls by an experienced neurologist to evaluate the status of cognitive decline (11).

The neuropsychologic battery included tests for memory: Wechsler memory scale subtests (immediate word recall list, delayed word recall, delayed word recognition, visual copy, visual memory); for language: verbal fluency (category: fruit) and Boston Naming Test (BNT); and for executive function: the clock- drawing test and Calculation and Constriction Ability. Additionally, the following scales were allowed; Blessed Dementia Rating Scale (BDRS), Instrumental Activities of Daily Living Assessment (IADL), Clinical dementia rating (CDR), and Geriatric Dementia Scale (GDS) (12-19).

All neuropsychologic assessments were implemented by the same person for each patient. Sessions were conducted in the morning in a quiet room and lasted for 45-60 minutes.

Ethics Statement

The experiments were conducted in full compliance with the Helsinki Declaration and all relevant national and international ethical guidelines. The research was approved by the local Ethics Committee. All procedures were performed only after written informed consent was obtained from the participants.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows 13.0 and Sigma Stat 3.1. For each variable, the differences between the control and patient groups were analyzed using Student"s t-test, and the differences between and within the groups were analyzed using repeated measures ANOVA. P values less than 0.05 were considered statistically significant. In multiple comparisons, Dunn`s method and Tukey`s test were used.

In a one-way ANOVA study, sample sizes of 25, 20, and 20 are obtained from 3 groups whose means are to be compared. The total sample of 65 subjects achieves 80% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05000

significance level. The size of the variation in the means is represented by their standard deviation, which is 70. The common standard deviation within a group is assumed to be 1.90.

RESULTS

The study included sixty-five participants who were admitted to our neurology clinics. The mean age was 66±7.04 years for the memantine group (group 1), 65.3±6.20 years for the non-memantine group (group 2), and 57.6±5.40 years for the control group (group 3).

Demographic data including age, sex, educational status, and hand dominance of the participants are summarised in Table 1. There was no difference between the groups.

Complete blood counts, blood chemistry, serum vitamin B12, folic acid, and thyroid function tests were performed in the patient and control groups. There was no significant difference between the groups in the blood tests ($p>0.05$).

At the beginning of the study, there was no significant difference in all scores between groups 1 and 2. There were significant differences in neuropsychiatric tests between the patient and control groups. At baseline, there were differences in calculation, word list memory, word list recall, word list recognition, BDRS, and CDR scores between the patient and control groups ($p<0.05$) (Table 2).

At week 12, group 1 had significantly improved scores on MMSE, word list memory-2, word list recall, BNT and CDR scores compared with group 3. For group 2, only GDS scores were significantly higher than those of group 1 ($p<0.05$). A statistically significant improvement in the MMSE score was observed in group 1. There was no significant improvement in the MMSE score in group 2 and 3 compared with baseline. Word list recall scores were increased in all groups, especially in group 1. There was a statistically significant improvement in calculation scores in groups 1 and 2. BNT and BDRS scores significantly improved in group 1 only ($p<0.05$) (Table 3).

At week 24, MMSE scores increased compared with scores at week 12 in groups 1 and 2. Compared with baseline scores (week 0), word list memory-2, word list recall, BDRS, and GDS scores significantly improved in group 1 ($p<0.05$). Differences in GDS scores were still statistically significant. GDS scores increased at week 24 compared with baseline in group 2. Although not statistically significant, improvement was observed in test scores at week 48 in group 1. No statistically significant difference was found in the other test scores between groups ($p>0.05$) (Table 3).

Table 1: Demographic characteristics of groups.

	Group 1 (n=23)	**Group 2 (n=22)**	**Group 3 (n=20)**	**P value**
Age	66 ± 7.04	65.3 ± 6.20	57.6 ± 5.40	>0.05
Hand dominance(right/left)	22/1	20/2	18/2	>0.05
Educational Status (Educated/Uneducated)	20/3	18/4	17/3	>0.05
Sex (F/M)	13/10	13/9	12/8	>0.05

Table 2: aMCI baseline neuropsychologic test scores.

	Group 1 (n=23)		Group 2 (n=22)		Group 3 (n=20)		P
Baseline	Mean/SD	Med	Mean/SD	Med	Mean/SD	Med	**value**
MMSE	27.0±1.8	27	27.2±2.1	27	28,4±2.3	28	0.31
Word List Memory 1	5.4±1.3	5	5.3±1.8	5	5.7±1.2	6	0.07
Word List Memory 2	5.4±1.2	5	5.6±1.8	5	5.9±1.2	6	0.06
Word List Memory 3	6.2±1.5	6	6.1±1.9	6	7.6±1.2	7.5	0.03
Word List Recall	4.2±1.9	4	4.7±1.8	4.5	5.9±1.6	5.5	0.04
Word List Recognition	18.1±1.7	18	19.6±1.2	19	19.8±1.4	19.50	0.04
Constriction Ability	10.2±2.1	10.5	11.0±0.0	11	11.0±0.0	11	0.04
Calculation	3.5±2.7	3.5	4.6±1.3	4	5.0±0.0	5	0.03
Verbal fluency	18.3±1.5	18	18.7±2.1	18	20.4±3.1	20	0.08
Backward Digit Span	3.6±1.5	3.5	4.1±0.9	4	4.3±1.5	4	0.06
BNT	11.7±1.2	14	13,6±1.3	14	13.9±1.4	14	0.42
BDRS	1.16±1.3	1	1.14±1.9	1	017.9 ±2.0	0.5	0.004
IADL	15.6±1.8	15.5	15.8±1.4	15.5	16.4 ±1.9	16	0.08
CDR	0.5±0.0	0.5	0.5±0.0	0.5	0.0 ±0.0	0.0	0.001
GDS	7.3± 1.4	7.5	6.8±1.2	7	6.2±1.1	6.5	0.06

Mini-Mental State Exam (MMS), Boston naming test (BNT), Blessed Dementia Rating Scale (BDRS), Instrumental Activities of Daily Living Assessment (IADL), Clinical Dementia rating (CDR), Geriatric Dementia Scale (GDS).

Table 3: Weekly differences on neurophysiologic tests between the groups.

Scale	**Baseline**	**12th Week**	**24th Week**	**48th Week**	**P value**
MMSE					
Group 1	27.0±1.8	29.1±0.01	29.1±0.09	29.2±1.3	0.033
Group 2	27.2±2.1	28.7±1.9	28.7±1.5	29.4±2.6	0.064
Group 3	28.4±2.3	29.5±1.1	29.3±1.2	29.5±1.3	0.072

Word List Memory 1					
Group 1	5.4±1.3	5.4±1.5	5.4±1.2	5.5±1.1	0.065
Group 2	5.3±1.8	5.2±1.6	5.2±1.7	5.4±1.9	0.080
Group 3	5.7±1.3	5.8±1.2	5.8±1.6	5.9±1.6	0.075
Word List Memory 2					
Group 1	5.4±1.2	6.7±2.2	6.3±1.9	6.3±1.5	0.042
Group 2	5.6±1.8	5.9±1.1	6.2±1.0	6.1±1.6	0.065
Group 3	6.3±1.8	6.3±2.1	7.2±1.5	7.2±1.5	0.062
Word List Memory 3					
Group 1	6.2±1.5	6.7±1.1	6.6±1.2	6.4±1.5	0.035
Group 2	6.1±1.9	6.7±1.1	6.4±1.0	6.3±1.6	0.042
Group 3	7.6±1.2	7.9±2.2	8.1±1.2	8.1±1.3	0.037
Word List Memory Total					
Group 1	**16.9±4**	**17.8±4.5**	**18.3±4.5**	**18.2±4.2**	**0.031**
Group 2	**16.9±5.8**	**17.8±3.6**	**17.8±2.8**	**17.8±4.8**	**0.054**
Group 3	**19.7±4.2**	**21±5.9**	**21.2±4.1**	**21.2±4.6**	**0.064**
Word List Recall					
Group 1	4.2±1.9	6.2±1.4	6.5±1.3	6.6±1.6	0.045
Group 2	4.7±1.8	6.3±1.2	6.4±1.5	6.5±1.1	0.004
Group 3	5.9±1.6	6.6±1.4	7.7±1.5	7.3±1.4	0.008
Word List Recognition					
Group 1	18.1±1.7	20.2±1.6	19.4±1.6	19.7±1.2	0.003
Group 2	19.6±1.2	19.8±1.3	20.1±1.1	21.1±1.3	0.037
Group 3	19.8±1.1	19.8±1.2	20.0±0.0	20.0±0.0	0.015
Calculation					
Group 1	3.5±2.7	4.6±1.3	5.1±1.5	5.0±1.0	0.025
Group 2	4.6±1.8	4.9±1.2	5.0±0.0	5.0±1.0	0.045
Group 3	5.0±0.0	5.0±0.0	5.0±0.0	5.0±0.0	0.070
Werbal Fluency					

Group 1	18.3±1.5	17.4±2.2	18.4±3.1	18.0±5.0	0.058
Group 2	18.7±2.1	17.6±3.1	15.3±3.4	15.0±4.0	0.035
Group 3	20.4±3.1	22.7±3.4	21.7±5.6	23.1±6.2	0.040
BNT					
Group 1	11.7±1.2	13.6±1.4	13.6±1.5	14.5±1.0	0.002
Group 2	13.6±1.3	13.5±1.2	13.6±1.1	13.8±1.0	0.075
Group 3	13.9±1.4	14.1±0.8	14.3±1.0	14.4±0.8	0.062
BDRS					
Group 1	1.16±1.3	1.12±0.9	0.94±1.4	08.5±0.6	0.020
Group 2	1.14±1.9	1.14±1.2	1.11±1.3	1.11 ±1.0	0.065
Group 3	017.9±2.0	017.8±0.8	016.3±1.2	016.2±0.6	0.085
GDS					
Group 1	7.3±1.4	6.4±0.9	5.3±1.4	5.2±1.0	0.030
Gorup 2	6.8±1.2	5.6±1.3	5.7±1.6	5.6±1.3	0.045
Group 3	6.2±1.1	5.5±0.8	5.1±1.2	5.4±0.7	0.082

Mini-Mental State Exam (MMS), Boston naming test (BNT), Blessed Dementia Rating Scale (BDRS), Geriatric Dementia Scale (GDS).

DISCUSSION

The risk of development of dementia is as high as 10-15% a year in patients with MCI as compared with 1-2% in the normal population. Clinical follow-up and treatment of these patients are thus critical (20). However, the efficacy of pharmacologic treatment of MCI is still a matter of debate. To date, acetylcholinesterase inhibitors have accounted for the majority of treatments administered for MCI, a trend that follows the cholinergic hypotheses (21-23). Another approach that is accepted at least as widely in the histopathogenesis of AD is the glutaminergic hypothesis, which is related to the hyper effects of glutamate, the brain´s main stimulating neurotransmitter (24). The discovery that the toxic effect of glutamatergic neurotransmission is present in the very early phases of the disease brought modulatory treatments up to date. Memantine acts as a partial antagonist for NMDA receptors. Animal studies have shown that partially effective antagonists on NMDA receptors may protect neurones against the harmful effect of glutamate. However, studies have yet to be performed on humans to confirm this hypothesis (25).

The current use of memantine is aimed at cognitive and behavioral disorders in patients with mild-moderate-severe AD and mild-moderate vascular dementia (26). It is believed that neuron-protective treatments should be started at very early stages beacuse neuronal damage begins in the pre-clinical phase of the disease. With this in mind, and considering the lack of data, the aim of this study was to

investigate the effects of memantine on neuropsychologic measures at the very earliest stages of AD, improvements of which could be mediated by a neuron-protective effect of memantine.

Currently, no mild cognitive impairment (MCI) drugs are specifically approved by the FDA for this clinical picture (27). It is logical to investigate whether drug treatment strategies for AD might be effective in the treatment of MCI (e.g., treatment with acetylcholinesterase inhibitors or memantine, nonsteroidal anti-inflammatory drugs, estrogen, Ginkgo biloba drugs, vitamin E) because patients with aMCI have an underlying pathology of AD (28,29). Rivastigmine failed to stop or slow progression to AD or effects on cognitive function in individuals with mild cognitive impairment, and donepezil showed only minor, short-term benefits and was associated with significant adverse effects (30). The combination treatment of galantamine plus memantine provided a short-term cognitive benefit, and a cognitive decline occurred after discontinuation of galantamine (31,32). Despite the fact that studies of donepezil, rivastigmine, and galantamine alone or in combination with memantine have been done, reliable data on the influence of memantine alone is not yet available in the treatment of aMCI.

Episodic memory, as defined as recollection of specific past events or information, is the first and most severely affected cognitive domain in AD. Episodic memory deficits are a key indicator of prodromal dementia stages, specifically for aMCI (33,34). In our study, the most prominent difference was seen in Wechsler memory scale subtests (word list-2, word list-3, word list total, word list recall, and word list recognition), BDRS, and BNT among the patients with aMCI. The usefulness of word list memory tests for detecting early episodic memory change is well established with some studies reporting accuracy rates of 85-90% for correct identification of patients with MCI who will progress to AD (33). In our study, the difference in word memory tests was significant in patients with aMCI compared with the control group. The word list may have an effect on learning to repeat the same words on the 12th, 24th and 48th week of the test.

It was thought that the learning effect could be present for all groups, because the same 10 words in the word list memory were applied all groups. We concluded that learning effect did not affect the results. We also think that the learning effect can be reduced by changing the order of the words during repetitions.

In the group that received and did not receive memantine treatment, the same 10 words in the word memory list were repeated.

In one related study with 270 patients with amnesia and MCI, Salloway et al. investigated the efficacy of donepezil in cognitive impairment by comparing the patient group with a placebo group. Even though the donepezil treatment was not strong enough to affect pure memory test scores (a primary scale of efficacy), it had positive effects on attention, concentration, and psychomotor speed (35,36). Other similar studies have suggested that donepezil improves logical memory at week 24. In a study that investigated the effects of galantamine treatment in patients with MCI, the improvement was seen in global rating scales and resulted in a decrease in ADAS-cog scores after 6 weeks, and at all dose levels (37,38). In another study by Gregory H and Pelton et al. with 35 patients, antidepressant and memantine treatment were found effective on cognition and had a low rate of conversion dementia when compared with the control group; the comparison was statistically significant (39).

In our study, the differences between the group receiving memantine and the control group in word list memory, word list recall, recognition, BDRS, and GDS

became less, until it disappeared at week 48. Similar results were observed for STMS scores and the global assessment scale, where scores of the group receiving memantine increased at week 48, and the significant differences in scores from the control group were no longer present. These results suggest that 48 weeks of memantine treatment improved patient functioning to the point that scores were comparable with the healthy controls; this was not the case for patients with aMCI who received no memantine. No change was observed in global cognitive and functional scales of the patients with aMCI who received no memantine. However, memory tests progressed with improvement. The fact that fewer significant between-group differences were apparent between the patients who received no memantine and the control group over time suggests that memory functions improved over time in group 2. We found that patients who did not receive memantine treatment showed a deterioration of GDS; thus, memantine may reduce the risk of development of depression.

Ramaswamy et al. observed improvement in memory, core symptoms of posttraumatic stress disorder (PTSD), and depression in combat veterans with PTSD following open-label treatment with memantine (40).

One limitation of the present study was the relatively small number of participants. The low prevalence of aMCI restricted our ability to conduct the study on a greater number of cases. Another limitation is the duration of the study. As noted, a longer-term study would have allowed us to observe the efficacy of memantine better, and to measure which patients did/did not progress to AD or dementia.

In conclusion, we investigated the effect of memantine treatment in patients with aMCI. Our results suggest that memantine significantly impairs the cognitive function and GDS. The initiation of a specific treatment in these patients is still a matter of debate because aMCI is not a clinical syndrome. We argue that memantine could be an effective first-line treatment for MCI, and future studies should investigate this by including greater sample sizes and performing long-term follow-ups.

Ethics approval and consent to participate

All participants received complete information about the project and written informed consent was provided. The study was approved by the Clinical Research Ethics Committee of the Eskisehir Osmangazi University (13 February 201-90).

Consent for publication

Consent was obtained from all authors.

Availability of data and materials

The database set was available for all authors of the study.

Abbreviations

MCI: mild cognitive impairment; aMCI: amnestic mild cognitive impairment; AD: alzheimer's disease; naMCI: non-amnestic MCI; ChEI: acetyl cholinesterase inhibitors; MMSE: mini-mental state exam; BNT: Boston naming test; BDRS: Blessed Dementia Rating Scale; IADL: Instrumental Activities of Daily Living Assessment; CDR: clinical dementia rating; GDS: geriatric dementia scale; SD: standard deviations.

Competing interests

The authors declare that they have no competing interests.

Authors" contributions

DIA, SD, SO, DOA have made substantial contributions to conception and design of the study; SD, performed the analysis and DIA, SO,DOA interpreted the data; DIA, SD, SO, DOA have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the

accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1. *Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA 2014;312:2551-2561.*
2. *Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183-194.*
3. *Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. Arch Neurol 2005; 62:1160-1163.*
4. *Edmonds EC, Delano-Wood L, Clark LR, et al. Susceptibility of the conventional criteria for mild cognitive impairment to false positive diagnostic errors. Alzheimers Dement 2015; 11:415-424.*
5. *Eshkoor SA, Hamid TA, Mun CY, Ng CK. Mild cognitive impairment and its management in older people. Clin Interv Aging 2015;10:687-693.*
6. *Jak AJ, Preis SR, Beiser AS, et al. Neuropsychological Criteria for Mild Cognitive Impairment and Dementia Risk in the Framingham Heart Study. J Int Neuropsychol Soc 2016;9:937-943.*
7. *Buse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC. Subclassifications for mild cognitive impairment : Prevalence and predictive validity. Psychol Med 2003;33: 1029-1038.*
8. *Peskind ER, Potkin SG, Pomara N, et al.Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. Am J Geriatr Psychiatry 2006;14:704-715.*
9. *Fitzpatrick-Lewis D, Warren R, Ali MU, Sherifali D, Raina P. Treatment for mild cognitive impairment: a systematic review and meta-analysis. CMAJ Open 2015;3:19-27.*
10. *Fellgiebel A. Alzheimer drugs for mild cognitive impairment. Neuropsychiatry 2007;21:230-233.*
11. *Folstein M, Folstein S, McHugh P. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.*
12. *Wechsler D. Wechsler Memory Scale-Revised manual. New York: Psychological Corporation, 1987.*
13. *LaBarge E, Edwards D, Knesevich JW.Performance of normal elderly on the Boston Naming Test. Brain Lang 1986;273:80-84.*
14. *Sunderland T, Hill JL, Mellow AM, Lawlor BA, Gundersheimer J, Newhouse PA. Clock drawing in Alzheimer`s disease. A novel measure of dementia severity. Journal Am Geriatr Soc 1989;37:725-729.*
15. *Blessed G, Tomlinsin B, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral gray matter of elderly subjects. Brit J Psychiatry 1968;114:797-811.*
16. *Thal LJ, Grundman M, Golden R.Alzheimer´s disease:a correlational analysis of the Blessed Information-Memory-Concentration Test and the Mini-Mental State Exam.Neurology 1986;36:262-264.*
17. *Lawton MP, Brody EM. Assessment of older people: self maintainning and instrumental activities of daily living. Gerontologist 1969;9:179-186.*
18. *Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566-572.*
19. *Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS):Recent evidence and development of a shorter version. 1986. Clinical Gerontology: A Guide to Assessment and Intervention.The Haworth Press: New York; 165-173.*

20. *Petersen RC. Mild cognitive impairment. Continuum. Dementia 2004;10:9-28.*
21. *Morris JC. Challenging assumptions about Alzheimer`s Disease: mild cognitive impirment and the cholinergic hypothesis. Ann Neurology 2002;51:143-144.*
22. *Ashford JW. Treatment of Alzheimer's Disease: The Legacy of the Cholinergic Hypothesis, Neuroplasticity, and Future Directions.J Alzheimers Dis 2015;47:149-156.*
23. *Palmer A, Gershon S.Is the neuronal basis of Alzheimer"s disease cholinergic or glutamatergic ? FASEB Journal 1990;4:2745-2752.*
24. *Muller W,Mutschler E, Riederer P. Noncompetitive NMDA reseptor antagonists with fast open-channel blocking kinetics and strong voltage-dependency as potential therapeutic agents for Alzheimer"s dementia. Pharmacopsychiatry 1995;28:113-124.*
25. *Winblad B,Jones RW,Wirth Y, Stoffler A, Mobius HJ. Memantine in moderate to severe Alzheimer`'s disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cognition Disorders 2007;24:20-27.*
26. *Zhang N, Wei C, Du H, Shi FD, Cheng Y. The Effect of Memantine on Cognitive Function and Behavioral and Psychological Symptoms in Mild-toModerate Alzheimer`s Disease Patients. Dement Geriatr Cogn Disord 2015;40:85-93.*
27. *Hort J, O`Brien JT, Gainotti G, et al. EFNS guidelines for the diagnosis and management of Alzheimer"s disease. Eur J Neurol 2010;17:1236-1248.*
28. *Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379-2388.*
29. *Farlow MR. Treatment of mild cognitive impairment (MCI). Curr Alzheimer Res 2009;6:362-367.*
30. *Croisile B, Auriacombe S, Etcharry-Bouyx F, Vercelletto M; National Institute on Aging;Alzheimer Association. The new 2011 recommendations of the National Institute on aging and the Alzheimer`s Association on diagnostic guidelines for Alzheimer"s disease: Preclinical stages, mild cognitive impairment and dementia. Rev Neurol (Paris).2012;168:471-482.*
31. *Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev 2006;25:CD001747.*
32. *Peters O, Lorenz D, Fesche A, Schmidtke K, Hüll M, Perneczky R. A combination of galantamine and memantine modifies cognitive function in subjects with amnestic MCI. J Nutr Health Aging 2012;16:544-548.*
33. *Rabin LA, Pare N, Saykin AJ,et al.. Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to Alzheimer's disease. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2009;16:357-376.*
34. *Liu Y, Cai ZL, Xue S, Zhou X, Wu F.Proxies of cognitive reserve and their effects on neuropsychological performance in patients with mild cognitive impairment. J Clinical Neurosci 2013;20:548-553.*
35. *Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-contolled trial. Neurology 2004;63:651-657.*
36. *Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA 2014;312:2551-2561*
37. *Cooper C, Li R, Lyketsos C, Livingston G. Treatment for mild cognitive impairment: systematic review. Br J Psychiatry 2013;203:255-264.*
38. *Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008;70:2024-2035.*
39. *Pelton GH, Harper OL, Roose SP, Marder K, D`Antonio K, Devanand DP. Combined treatment with memantine/es-citalopram for older depressed patients with cognitive impairment: a pilot study. Int J Geriatr Psychiatry 2016;31:648-655.*
40. *Ramaswamy S, Madabushi J, Hunziker J, Bhatia SC, Petty F. An open-label trial of memantine for cognitive impairment in patients with posttraumatic stress disorders.J Aging Res Epub 2015 May 12.*