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A Review

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Role Of Memantine In Moderate-To-Severe Alzheimer's Disease:A Review

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Declaration

The Declaration of the authors for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) Dr. Hemant Kumar,Senior 1Dr.Abhishek Pathak2 ,the authors of the research paper entitled Role Of Memantine In Moderate-To-Severe Alzheimer's Disease:A Review declare that , We take the responsibility of the content and material of our paper as We ourself have written it and also have read the manuscript of our paper carefully. Also, We hereby give our consent to publish our paper in ajmams , This research paper is our original work and no part of it or it's similar version is published or has been sent for publication anywhere else.We authorise the Editorial Board of the Journal to modify and edit the manuscript. We also give our consent to the publisher of ajmams to own the copyright of our research paper.

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ABSTRACT - Memantine is a relatively new drug specially developed for use in moderate-to-severe dementia. It is an uncompetitive N-methyl-D-aspartate receptor antagonist and reduces glutamatergic excitotoxicity. Though Alzheimer's disease (AD) is the commonest cause of dementia in the world, there is no "cure" available for the same. Cholinesterase inhibitors such as donepezil and rivastigmine have been shown to provide symptomatic relief in patients with AD but have no effect on disease progression or survival. Moreover, they are not helpful in more severe stages of dementia. Memantine has been shown to cause modest improvement in clinical symptoms in severe stages of AD and may retard the disease progression. Moreover, it has been shown to be useful in various forms of dementia including AD, vascular dementia and Wernicke-Korsakoff psychosis. It is also the first drug to cause complete disappearance of pendular nystagmus due to multiple sclerosis. The current review focuses on the pharmacological properties of memantine and examines the recent evidence in favor of memantine.

Key Words: clinical uses, dementia, memantine, neuropharmacological properties

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Alzheimer's disease (AD) is the most common cause of dementia. It is a progressive neurodegenerative disorder resulting in cognitive and behavioural impairment of sufficient severity to markedly interfere with social and

occupational functioning. The prevalence of AD increases steadily after the age of 65, with an estimated prevalence of approximately 50% in patients aged 85 or older(1-2). The diagnosis is based on clinical features; however, a definitive diagnosis requires histopathological examination of the brain. Moreover, as the population ages, the proportion of the population affected by AD is predicted to increase dramatically(3). AD is not only a heavy burden for the patient but is also responsible for making the patient dependent on his family or the community. Patients with AD need round-the-clock supervision for their activities of daily living and pose a significant burden on family and caregivers. The financial problem of their loss of productivity is compounded by an enormous amount of expenditure incurred on their care. Currently, there is no 'cure' possible for AD. However, various drugs are used for symptomatic treatment that include cholinesterase inhibitors (such as donepezil, rivastigmine and galantamine), vitamins, antidepressants and antipsychotics. The current review focuses on memantine that differs from other drugs used in dementia in terms of its mechanism of action. Memantine is a low- to moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, which reduces glutamatergic excitotoxicity. Memantine has been approved in Europe in 2002, and United States in October 2003 for treatment of moderate to severe AD. In addition, memantine has been found to be useful in other forms of dementia and some forms of acquired nystagmus. Current pharmacotherapy is focused on delaying the symptomatic progression of AD. Although the cause of the disease remains unknown, acetylcholine deficiency, within a complex milieu of neurotransmitter changes in the brain, has been shown to play a role in AD(4-5). By inhibiting the degradation of acetylcholine released by presynaptic cholinergic neurons, cholinesterase inhibitors increase the amount of acetylcholine available for neurotransmission. Accordingly, cholinesterase inhibitors (ChEIs) have emerged as the treatment of choice for mild-to-moderate AD. Donepezil, rivastigmine and galantamine represent the main category of ChEIs shown to be effective with an acceptable tolerability profile. Rivastigmine, donepezil and galantamine have demonstrated improvements in cognition, general clinical impression, activities of daily living (ADL) and behavioural symptoms (6). ChEIs share common cholinergic-mediated side effects. The most common cholinergic side effects include nausea, vomiting and diarrhoea; this is more common with initiation and dose titration and may lead to drug withdrawal in some cases. However, slow titration of ChEIs to therapeutic doses may alleviate many of these symptoms since patients tend to develop tolerance to these gastrointestinal symptoms (7). Currently, there is little evidence to recommend one ChEI over another. In the mild-to-moderate AD population, ChEI therapy should be started early and there are emerging data that efficacy extends to the late stages of the disease.

Moderate-to-severe Alzheimer's Disease

As AD progresses to the moderate-to-severe stages of the illness, patients becoming increasingly dependent on care from members of their family or care workers. While emerging data suggest that the efficacy of the ChEIs extends to the late stages of AD, only one drug has been licensed for the treatment of moderate-to-severe AD. Memantine was recently licensed in a number of European countries for use in the moderate-to-severe AD population. It is a non-competitive antagonist at N-methyl-Daspartate (NMDA) receptors.

Increasing evidence suggests that disturbances in glutamatergic neurotransmission contribute to the pathogenesis and cognitive deficits in AD (8). Based on this theory, memantine was studied in the treatment of AD, resulting in its approval for use in patients with moderate-to-severe AD to improve cognitive symptoms. Two randomised placebo-controlled trials have demonstrated that memantine is moderately effective in slowing the progression of AD. In the first study, 166 nursing home patients with dementia (49% AD; 51% vascular dementia) were randomised to 10mg of memantine per day or placebo. At 12 weeks the memantine treated patients had improved clinician's global impression scores independent of the aetiology of dementia (9).

In a pivotal study of 252 patients with moderateto- severe AD (mini-mental state examination score (MMSE) <14), patients were randomised to either oral memantine (20mg daily) or placebo. Exclusion criteria included vascular dementia, dementia or neurological disease due to conditions other than AD and major depression. The dropout rate was 28% (42 taking placebo and 29 taking memantine), which the authors attributed to the severity of the disease stage in the study group. At 28 weeks, patients' symptoms and condition deteriorated in both the memantine and placebo study groups; however, patients treated with memantine had better ADL function and disability scores. In the memantine group there was a significant difference in functional capacities compared to placebo (p=0.02 (95% confidence interval (CI): 0.49, 3.78)). Clinician's impression scores were also improved in the treatment group, but this difference did not reach statistical significance (p=0.06 (95% CI: -0.05, 0.02) (10). The authors of the study acknowledged that point differences between drug- and placebo treated patients on quantitative scales do not necessarily indicate clinically meaningful effects. Accordingly, to illustrate clinical relevance of results, response analysis (rates of individual response) is often performed. This study reported a significant difference in the predefined criterion for a response, incorporating multiple end points, with 29% of patients receiving memantine and 10% of those receiving placebo having a response (p<0.001). In a 24-week open-label extension to the study, 175 patients were enrolled from the previous double-blind study in an outpatient setting. The patients were given 20mg memantine daily. Patients switched to memantine treatment from their previous placebo therapy experienced a significant benefit in all main efficacy assessments (functional, global and cognitive) relative to their mean rate of decline with placebo treatment during the double-blind period (p<0.05). The study provides evidence of a sustained effect of memantine over a period of 12 months. Memantine has a small beneficial effect at six months in moderate to severe AD.

A Cochrane review on memantine concluded that memantine has a significant effect on cognition and a possible effect on behaviour and ADL. According to the review, memantine shows efficacy in AD, vascular and mixed dementia. Further trials on larger numbers of patients and for longer periods will help to support this data (12). In clinical studies memantine was well-tolerated, without major side effects or drug-drug interactions with other commonly-used pharmacological substances. The main adverse reactions involved the central nervous system and were dose dependent.

Combination Therapy with Memantine

There has been interest in whether combinations of therapies may have additive or even synergistic effects in the

treatment of AD. In a recent study, the combination of memantine and ChEI donepezil was assessed in patients with moderateto- severe AD (13). In the study, 404 patients with moderate-to-severe AD (MMSE 5–14) who were already taking donepezil (stable dose of 5mg or 10mg) were randomised to an additional therapy with memantine (starting dose 5mg/day, increased to 20mg/day, n=203) or placebo in a blinded fashion for 24 weeks. Eighty per cent of patients completed the trial. Compared with donepezil alone, combination therapy resulted in greater symptomatic improvements in both cognitive and behavioural efficacy measures, suggesting that the complementary mechanisms of action of ChEIs and memantine have additive or synergistic potential in delaying symptomatic decline in AD. A recent multicentre, open-label pilot study investigated whether combination therapy with rivastigmine and memantine presents unexpected safety or tolerability concerns and is beneficial in patients with mild-to-moderate AD (MMSE 10–29) (14).

In the study, patients with a Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnosis of dementia of the Alzheimer's type (n=95), who were treated with rivastigmine (6–12mg/day) for a maximum duration of 24 weeks prior to baseline, received memantine (5–20mg/day) in combination with rivastigmine for 12 weeks. There was a statistically significant difference between baseline and week 12 for the AD Assessment Scale-cognitive subscale (ADAS cog) total score, showing a positive effect of combination therapy. The change in ADAS-cog score observed with therapy in this study was statistically significant compared with the historical control; however, the change was less than the four-point change recommended by the US Food and Drug Administration (FDA) for clinical relevance. Combination therapy was well-tolerated by most patients.

Available data suggest that, in addition to its benefits on cognition, function, and global status, memantine treatment may also help alleviate behavioral symptoms. In one study behavioral outcomes were assessed in three completed, double-blind, placebo-controlled trials.Overall, patients who received memantine performed better on behavioral measures than those treated with placebo. Post-hoc analyses suggest that memantine treatment was associated with a reduced severity or emergence of specific symptoms, particularly agitation and aggression (15). In patients with mild to moderate dementia, the small beneficial effect on cognition was not clinically detectable in those with vascular dementia and was detectable in those with AD. Memantine is well tolerated (16). In a current analysis data was combined from six previously published studies and effect of memantine was assessed on various cognitive functions in 1826 patients (867 on placebo and 959 on memantine) with moderate to severe AD (MMSE<20). The Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Severe Impairment Battery (SIB) scores from all six studies were pooled and combined into three clusters representing discrete cognitive domains: language, memory, and praxis. At baseline, there were no clinically significant differences between the memantine- and placebo-treated groups. After 24 weeks, responder analyses revealed that memantine treatment resulted in statistically significantly more patients improving on each of the three clusters, language, memory, and praxis, compared with placebo, and a lower percentage of patients treated with memantine showed any worsening on any of the three clusters compared with patients receiving placebo. It is concluded that treatment with memantine provides benefits in all three cognitive functions (17).

Data from six multicentre, randomised, placebo-controlled, parallel-group, double-blind, 6-month studies were used as the basis for these post-hoc analyses. All patients with a Mini-Mental State Examination (MMSE) score of less than 20 were included. Analyses of patients with moderate AD (MMSE: 10-19), evaluated with the Alzheimer's disease Assessment Scale (ADAS-cog) and analyses of patients with moderate to severe AD (MMSE: 3-14), evaluated using the Severe Impairment Battery (SIB), were performed separately. The mean change from baseline showed a significant benefit of memantine treatment on both the ADAS-cog ($p < 0.01$) and the SIB ($p < 0.001$) total score at study end. The ADAS-cog single-item analyses showed significant benefits of memantine treatment, compared to placebo, for mean change from baseline for commands ($p < 0.001$), ideational praxis ($p < 0.05$), orientation ($p < 0.01$), comprehension ($p < 0.05$), and remembering test instructions ($p < 0.05$) for observed cases (OC). The SIB subscale analyses showed significant benefits of memantine, compared to placebo, for mean change from baseline for language ($p < 0.05$), memory ($p < 0.05$), orientation ($p < 0.01$), praxis ($p < 0.001$), and visuospatial ability ($p < 0.01$) for OC (18). To characterize the specific cognitive benefits of memantine in patients with mild to moderate AD, a post hoc analysis was conducted of a 24-week randomized, double-blind, placebo-controlled, clinical trial comparing memantine (10 mg twice daily) to placebo. Cognition was assessed using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) total score, individual items, and aggregated subscales, using a mixed model repeated measures analysis. As assessed by the ADAS-cog total score, participants in the placebo group demonstrated significantly more cognitive decline from baseline than participants treated with memantine at all visits beginning at week 8. Subjects treated with placebo also declined significantly more than individuals in the memantine group on 5 of 11 ADAS-cog individual items: orientation, language, comprehension, word finding, and recall of test instructions. Out of 3 ADAS-cog aggregated item subscales (language, memory, and praxis), outcomes in 2 (language and memory) favored memantine. Consistent with findings from trials conducted in moderate to severe AD patients, this post hoc analysis of a randomized clinical trial suggests that memantine benefits core aspects of language and some aspects of memory in patients with mild to moderate AD (19).

Evidence from 5 high-quality studies (from 6 publications) was included to evaluate memantine, and all compared memantine with placebo (20-24). In 1 study, individuals also received donepezil for at least 6 months before random allocation to memantine (25). Studies evaluated Alzheimer disease (23-25), vascular dementia (20,21), and mixed dementia (22), and severity of dementia ranged from moderate to severe. Duration of trials varied from 24 to 28 weeks, with a dosage of 20 mg/d (20,21, 23–65). One study (24) lasted for 12 weeks. A pooled estimate from 3 trials showed that memantine resulted in statistically significant, but not clinically important, improvement on the ADAS-cog scale in cognition for individuals with mild to moderate vascular dementia (20,21) and mild to moderate Alzheimer disease (24). In addition, patients with moderate to severe Alzheimer disease statistically significantly improved on the SIB scale (23,25). However, patients with mixed dementia had no difference (22). Summary estimates demonstrated statistically significant change on the CIBIC-plus scale for patients with all levels of severity of Alzheimer disease and vascular dementia with the 20-mg dose. One of 4 studies in which patients were also taking donepezil showed statistically

significant improvement in behavior (25). Three of 4 studies that evaluated quality of life found statistically significant improvements, and the summary estimate was statistically significant (22,23,25). Two trials evaluated caregiver burden and resource utilization and found statistically significant improvements. Two of the 6 eligible studies reported information on the proportion of patients who had a clinically important improvement. Only 1 of these trials reported statistical significance, and that trial did not find a statistically significant change. The withdrawal rates related to adverse effects varied from 9% to 12% in the treatment group (7% to 13% in the placebo group), including nausea, dizziness, diarrhea, and agitation. In summary, memantine showed statistically significant, but not clinically important, improvement in cognition scores for moderate to severe Alzheimer disease, as well as all levels of severity for Alzheimer disease and vascular dementia, as measured by the ADAS-cog. Summary estimates of global assessment with the CIBIC-plus were statistically significant. Limited evidence shows improvement in quality of life, caregiver burden, and resource utilization.

MEMANTINE AND OTHER DISEASES

In addition to VD, AD, and MS, memantine has also been used in many other neurologic and psychiatric diseases. However, with some exceptions, existing trials have been small, whereas in other cases, only case reports have been published, hindering the possibility of drawing strong conclusions. Following AD and VD in number and importance of studies is Parkinson's disease. Although a recent trial did not find any cognitive improvements [26], another trial with a mixed population of Parkinson's disease and Lewy bodies dementia (LBD) patients and more statistical power did find an improvement in global measures [27]. Two other studies published in Russian also claimed cognitive improvements [28,29]. Regarding motor symptoms, there is conflicting evidence. Although some studies and case reports have found memantine to be beneficial [29-31]. Improvements are in accordance with the results with amantadine, which also improves motor symptoms, and specifically L-dopa-induced dyskinesias in PD [32]. Memantine was well tolerated in PD patients. More interesting for this review is the use of memantine in Lewy bodies dementia (LBD). Although cognitive improvements have been reported, delusions, hallucinations, awareness, and motor symptoms in some patients worsened [27, 33-36]. The mechanism for such deterioration is not known, but LBD patients are very prone to suffer side-effects with other medications such as neuroleptics or sedatives [37]. Nevertheless, it must be noted that the proportion of AEs in the mixed trial of PD and LBD, which can be considered the most reliable source to date, was similar in the medicated and control groups. Still, memantine use in this pathology should be undertaken with care as there is some evidence of unpredictability in the effects. Preliminary trials and case reports of memantine use in other diseases that are accompanied by mental changes have also been published. In addition to those already commented on in the "Historical landmarks" section, other diseases tested included alcohol or human immunodeficiency virus (HIV)-related dementia [38,39], Wernicke–Korsakoff syndrome [40), pervasive developmental disorders, and attention deficit hyperactivity disorder (ADHD) [41,42], or varied psychiatric problems [43]. There are not enough data to reach conclusions on clinical efficacy, but the drug seems to be well tolerated in these groups.

Conclusions

While the ChEIs remain the treatment of choice for mild-to-moderate AD, evidence points to the potential of memantine as a useful adjunct in later stages of the

disease. In moderate-to-severe AD, the clinical efficacy of memantine on functional (ADL) and clinical global impression of change as well as cognitive domains has been documented by two randomised placebocontrolled trials. Furthermore, responder analyses in the two studies showed a higher rate of responders for memantine than for placebo. An important question, that is difficult to answer at the current time is when or under which conditions ChEI therapy should be discontinued. Currently, there is insufficient evidence relating to when to discontinue ChEIs as the disease advances. The question then arises as to when memantine should be introduced into the treatment paradigm. There is emerging evidence that introduction of memantine, alone or in combination with ChEIs, in patients diagnosed with moderate-to-severe AD or in ChEI-treated patients with deteriorating symptoms helps behavioural symptoms such as agitation, aggression and psychosis. Thus the use of memantine may improve outcomes for people with AD and reduce carer burden. To improve the situation for the AD patient, there still need to be improvements in the awareness of the disease. Importantly, forgetfulness in old age is too often ignored as a potential symptom for AD. The most pressing issue is that forgetfulness is not necessarily age-related but disease-related in old age, and more needs to be done to improve awareness of the disease and remove the stigma associated with AD.

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