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REVIEW

Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias

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Abstract: Memantine is an uncompetitive N-methyl-D-aspartate receptor antagonist with moderate affinity. Its mechanism of action is neuroprotective and potentially therapeutic in several neuropsychiatric diseases. It has been approved by the FDA for the treatment of moderate to severe Alzheimer's disease (AD) either as a monotherapy or in combination with cholinesterase inhibitors. This review covers key studies of memantine's safety and efficacy in treating moderate to severe AD. It also covers current research into other dementias including but not exclusively mild AD and vascular dementia. Other studies on the efficacy of memantine for other neuropsychiatric diseases are discussed. Memantine is a safe and effective drug that merits further research on several topics. Clinicians should be aware of new studies and potential uses of memantine because of its safety and efficacy.

Keywords: memantine, Alzheimer's disease, dementia

Introduction

Memantine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with moderate affinity. Memantine was discovered in 1968 and patented by Eli Lilly. Merz later developed it in collaboration with Neurobiological Technologies, Inc. It was then licensed to Forest laboratories for development in the United States as well as Lundbeck for other international markets. The following are the proprietary names for memantine: Axura® and Akatinol® (Merz), Namenda® (Forest Laboratories), Ebixa® and Abixa® (Lundbeck), and Memox® (Unipharm).[1]

Prior to the approval of memantine, treatment of Alzheimer's disease (AD) was limited to cholinesterase inhibitors (ChEI) for patients in the mild to moderate stages. There was no approved therapy for moderate to severe AD. New therapies for AD were eagerly pursued because of the rising numbers of patients suffering from the disease and progressing into the later stages. Due to the characteristic symptoms and progression of the disease, pathways involved in cognition, memory, and learning are commonly pursued as potential targets for treatment.

Mechanism of action

A central mechanism in learning and memory is long-term potentiation (LTP). LTP is mediated by the neurotransmitter glutamate via the NMDA receptor. The NMDA receptors can be found diffusely throughout the brain. However, they densely populate the dendrites of pyramidal cells in the hippocampus and cortex (areas known to be involved in cognition, learning, and memory). In addition to the relationship

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between LTP and learning, elevated glutamate levels are associated with excitotoxicity. Chronic low-dose administration of NMDA receptor agonists have been shown to induce apoptosis[2,3] while high doses induce necrosis.[3] The activation of glutamate receptors has also been found to induce the release of glutamate. Thus, a large build-up of glutamate can occur and induce a massive accumulation of Ca^{2+}, leading to apoptosis.[4] It was also noted that amyloid-beta (AB) plaques increase a neuron's vulnerability to excitotoxicity.[5] AB plaques, a pathological feature of AD, were found to induce depolarization of astrocytes, extracellular accumulation of glutamate, and intracellular deposition of Ca^{2+}.[6] Therefore, the glutamate-induced excitotoxicity pathway made an excellent target for the therapy of AD.

Under physiologic conditions, the glutamate released by neurons is metabolized or taken up by neighboring cells. When these pathways are disrupted, the accumulated glutamate overexcites the NMDA receptor and induces pathology characteristic of neurodegenerative diseases. NMDA receptors act as a calcium [II] ion (Ca^{2+}) channel that activates when bound by glycine, glutamate, and/or NMDA. However, the channel functions only when the cell membrane is depolarized due to the blockade of the channel by the magnesium [II] ion (Mg^{2+}). This prevents the influx of Ca^{2+} when the neuron is at rest. Under pathological conditions, such as a chronically depolarized membrane, Mg^{2+} leaves the channel and neuronal metabolism is inhibited, leading to cell death.[7] When this happens, the Ca^{2+} influx is unrestricted for a longer period of time than normal. This influx of Ca^{2+} contributes to an alteration of cell function, leading to cell death either through free radicals[8] or through overload of the mitochondria, resulting in free radical formation, caspase activation, and the release of apoptosis-inducing factors.[9] Antagonists to the NMDA vary in affinity and in site of action, resulting in different alterations to the channel. Regardless of the mechanism of action, antagonists decrease the permeability of the channel and prevent an influx of Ca^{2+}. Thus NMDA receptor antagonists are looked to as possible neuroprotective agents and potential therapies for neurodegenerative disease.

Most NMDA antagonists are competitive antagonists and are not well tolerated by patients due to side effects, which can include hallucinations and schizophrenia-type symptoms.[9] The side affects likely result from the competitive antagonists blocking physiological functions of the NMDA receptor. Its role in cognition, memory, and learning make it necessary that any drug using the NMDA receptor as a target of action must preserve physiologic function to be therapeutically useful.

Memantine acts on activated NMDA receptor by binding to a site located in the channel of the receptor.[10] Memantine is a fast-binding antagonist which binds to the channel in a pseudo-first order manner. However, it is also dissociates from the receptor quickly and in a concentration independent manner.[10] This allows the dose to affect the binding of memantine without affecting its removal from the site of action and allowing for increased potency with minimal side affects. In comparison with other antagonists, memantine has a much faster course of action and thus has less effect on physiologic mechanisms. For this reason, memantine offers a lot of promise in the therapy of neurodegenerative disease because it will preserve physiological function.[11] In addition, the uncompetitive nature of the memantine's mechanism of action makes its antagonistic activity more potent in areas with massive activation of NMDA receptors.[11] Memantine's mechanism of action is also voltage-dependent, which leads to the removal of the memantine blockage by depolarization of the membrane.[12] All of these characteristics make memantine a strong candidate for treating pathology induced by excitotoxicity.

In several studies, memantine was found to prevent neuronal death induced via excitotoxic mechanisms.[13,14] In 2003, memantine was approved for the treatment of moderate to severe AD in the US and in Europe. Approval for memantine permitted it to be used alone or in combination with ChEI. While it is currently in use for the therapy of moderate to severe AD, other diseases and disorders are potential targets for therapy with memantine.

Memantine in moderate to severe AD

Three randomized, double-blind, placebo-controlled (RDBPC) trials were submitted to the FDA in the New Drug Application.[15–17] These studies demonstrated memantine's safety and efficacy in moderate to severe AD.

The first of the studies submitted to the FDA evaluated memantine as a therapy for AD in a long-term care setting.[15] In a placebo-controlled trial, patients were selected according to DSM-III criteria, a Mini-Mental State Examination (MMSE) score <10, and a Global Deterioration Scale (GDS) score of 5–7 ($n = 166$). The primary efficacy measures were the patient's response to therapy functionally and globally using the Behavioral Rating Scale for Geriatric Patients (BGP) and the Clinical Global Impression of Change (CGI-C). Administering 10 mg/day (half the current recommended dosage) of memantine for 12 weeks, they documented statistically significant improvement in global

and functional parameters. The measurements for behavior were not statistically significant. They also used Ferm's D-test as a secondary variable to determine efficacy and found that the treated patients needed less time for nursing care due to improved functionality. While no behavioral improvement was noted, the global and functional improvement demonstrated its value as a potential therapy for patients with moderate to severe AD.

In 2003, Reisberg et al conducted a similar study in an outpatient setting.[16] These data were also submitted to the FDA. They used similar selection criteria with the addition of satisfying the diagnostic criteria of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA). They administered memantine 10 mg twice daily for 28 weeks at 32 US centers (n = 181). The study used the Severe Impairment Battery (SIB), the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus) as primary efficacy variables for cognition and global measurements, respectively. Secondary efficacy measures included the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev) and the Neuropsychiatric Inventory (NPI) to measure impact on behavior. Patients receiving memantine showed statistically significant benefits when compared to placebo in both of the primary efficacy measures, the SIB and the CIBIC-Plus, over the 28-week trial. The patients receiving memantine also showed statistically significant improvement over placebo in the ADCS-ADLsev but not in the NPI. These results confirmed the results of the previous study with the addition of better cognitive outcomes for patients receiving memantine.

The third and final study submitted to the FDA was for a combination therapy of memantine and donepezil. Tariot et al[17] conducted a RDBPC trial using 404 outpatients already on donepezil, from 37 US centers for 24 weeks with 322 patients completing the trial. Patients were selected according to the NINCDS-ADRDA diagnostic criteria for AD. They were also selected for MMSE scores between 5 and 14, age of at least 50 years and CT scans consistent with AD. Primary efficacy variables included cognition, using the SIB, and global measures, using the CIBIC-Plus. Secondary outcome measures were behavioral and functional. These were measured using the NPI and BGP, respectively. All patients remained on donepezil with half randomized to the addition of memantine and half to the addition of placebo. At the conclusion of the study, statistically significant benefits were found in all primary and secondary endpoint measures in favor of donepezil/memantine vs donepezil/placebo. Similar results were found in a study by van Dyck et al.[18] This confirmed previous studies with the addition of improvement in behavioral outcomes.

Combination therapy is a promising choice of therapy for patients with moderate to severe AD. It is not currently approved by the FDA to treat mild AD with memantine so ChEI are the principal choice for treatment in mild cases. It has been shown that transition from a ChEI to memantine is well tolerated,[19] but better outcomes may be achieved in patients receiving combination memantine/ChEI[17] so clinicians should add memantine to the patient's treatment plan without discontinuing the ChEI.

However, these principal studies showed conflicting outcomes on behavioral measurements. While Tariot et al demonstrated a positive outcome,[17] Reisberg et al and Winblad et al had no statistically significant outcomes in measures of behavioral outcomes.[15,16] Despite this inconsistency, memantine is a useful treatment for patients with moderate to severe AD, but with behavioral disturbances common in patients with AD and those disturbances causing great distress to care givers, great interest lies in determining if memantine truly improves behavioral outcomes. Wilcock et al conducted a pooled analysis of 3 large 6-month studies of memantine using the NPI as an efficacy variable. They found a statistically significant improvement in behavioral outcomes, especially in measurements of agitation/aggression.[20] Gauthier et al conducted a study with a shorter time period and a larger study group.[21] This study used the NPI as well and also yielded statistically significant improvement in patients receiving memantine over those receiving placebo. These studies suggest that memantine may be a good treatment option for patients with AD and behavioral symptoms.

Finally, a study published in 2009 compiled memantine data from all clinical trials and from pivotal studies between 1992 and 2008[16,17,23] for a post-hoc analysis.[22] Patients in nursing homes or assisted living facilities were excluded because they have significantly different baselines. The study found that a meta-analysis of all the study groups showed statistically significant improvement in both the NPI and BGP for patients receiving memantine over placebo. However, the behaviors with statistically significant improvement were agitation/aggression, irritability/lability, and delusions. Perhaps more importantly, this study found a delay in the emergence of behavioral symptoms with memantine vs placebo. Improvement in these measurements and prevention of emergence would ease the burden for care givers and increase the time to institutionalization.

A large number of patients with AD are receiving antipsychotics, antidepressants, anxiolytics, or neuroleptics.[22] These treatments are common due to the prevalence of behavioral symptoms in patients with AD. One of the most prevalent behavioral symptoms is agitation and aggression. Memantine attenuates these symptoms very well and should be considered a principle treatment for AD patients experiencing agitation/aggression.[21,22] Further studies should investigate the benefits of memantine vs other treatments in behavioral outcomes for patients with AD.

Another critical point in the discussion of memantine as a treatment for AD is combination memantine/ChEI therapy. The study by Tariot et al demonstrated the efficacy of combination therapy in treating moderate to severe AD.[17] Another combination therapy study, by Atri et al demonstrated a long-term effect of combination therapy when compared with patients receiving no drug therapy and patients on cholinesterase monotherapy.[24] Primary efficacy measures for cognition and function were the Blessed Dementia Scale (BDS) and the Weintraub Activities of Daily Living Scale (WADL). They found that even after a mean treatment time of 22.5 months, patients receiving combination therapy had significantly better outcomes than those receiving no pharmacotherapy or ChEI therapy alone. These data strongly favor the use of memantine/ChEI combination therapy in treating moderate to severe AD.

For many patients and their families, who are often care givers as well, staying out of long-term care facilities is a primary goal. A recent study conducted at the University of Pittsburgh evaluated 943 patients with probable AD and followed them long-term (mean time was 62.3 ± 35.8 months).[25] They compared patients receiving memantine and ChEI with those receiving just ChEI and those receiving neither. They found that patients treated with ChEI had a decreased risk to institutionalization over those with no drug and the patients who received both memantine and ChEI had the greatest decrease risk (a decrease in risk over the ChEI monotherapy of 3.4). So while memantine/ChEI combination therapy may improve AD patients' outcomes cognitively, functionally, behaviorally, and globally, it may also help patients stay at home longer and delay time to institutionalization.[25]

Other studies of memantine/ChEI combination therapy have shown behavioral improvements,[26] functional improvements,[27] cognitive improvements,[28,29] and a delay to institutionalization.[25]

It should be noted that one study with memantine found contradicting results when compared to previous studies.[23] This study followed a similar protocol to the Reisberg Study.[16,23] At weeks 12 and 18, a statistically significant improvement was detected in the CIBIC-plus but not at week 24. ADCS-ADL measurements failed to show statistically significant improvement. The SIB did not show statistically significant differences either until a nonparametric analysis was conducted post-hoc. The sample population was sufficiently large but the author pointed out possible confounding variables for future consideration. In van Dyck's study, 61% of his patients received prior ChEI therapy, which may have affected the outcome. A study comparing the response of patients grouped according to therapies received prior to memantine found that it affected the response to memantine treatment.[30] van Dyck also pointed out that it is important to incorporate nonparametric analyses into the study design as a contingency plan. Finally, bias may be introduced utilizing the last observation carried forward (LOCF) method due to the significant results observed at weeks 12 and 18 but not at 24. Future investigations into memantine should consider previous therapy, nonparametric analyses, and the bias inherent in LOCF when designing the study.

While this conflicting study suggests some possible bias, many other studies have been conducted and demonstrated the positive effect on the progression of symptoms in patients with AD treated with memantine compared with placebo.[31–33] More specifically, studies compared patients with moderate to severe AD receiving memantine to patients receiving placebo and evaluated them for benefits in cognition,[34] function,[35] behavior,[20,21,36,37] and memory.[38] In light of the abundance of data in support of memantine as a therapy for moderate to severe AD, the contradictory study should be regarded as critical for future studies in order to avoid the possible biases pointed out by the author.

While these effects, combined with previous studies' results, strongly suggest the use of combination therapy in the treatment of moderate to severe AD, studies evaluating its efficacy in comparison with memantine monotherapy have yet to be conducted or published. It seems safe to say that combination therapy would be at least as effective as monotherapy, if not more. However, a cost/benefit analysis would also be an invaluable tool in decision making for care givers and payers. Additional studies should consider comparing memantine monotherapy with cholinesterase monotherapy.

The data above are consistent with the guidelines published by the American Psychiatric Association (APA) and the American Association for Geriatric Psychiatry

(AAGP). The guidelines recommend that clinicians consider the cost of treatment, severity of disease, and stage of progression prior to prescribing memantine. While data indicate that memantine is safe and effective as both a monotherapy and in combination with ChEI, no evidence suggests one is better than the other. However, memantine/ChEI combination therapy is more effective than some ChEIs alone and should be recommended over ChEI monotherapy.

Memantine studies in mild AD

Once an effect was seen in moderate to severe AD, the next logical step was to investigate mild AD. This direction of study has provided mixed results. In a RDBPC study, researchers found that memantine produced statistically significant improvement in cognition, global measures, and behavior over placebo.[39] There was no statistically significant difference between memantine and placebo on functional measures. These measures were assessed using the ADAS-Cog, CIBIC-plus, NPI, and ADCS-ADL, respectively.

In addition, two 24-week studies in 2008 found no statistically significant difference between memantine and placebo in measures of cognition (ADAS-cog) or in global measures (CIBIC-plus).[40,41] One of the studies also used the ADCS-ADL and NPI as secondary efficacy measures of function and behavior, respectively, but memantine was not found to have a significant improvement in these measures either.

However, in the Bakchine study, the patients receiving memantine did show statistically significant improvement vs the control group at weeks 12 and 18 on the ADAS-Cog, but not at the end of the study.[41] The authors attributed the lack of significance at week 24 to a sudden improvement in the control group. The results suggest that memantine may be a safe and effective therapy for patients with mild to moderate AD but further study is merited due to the conflicting studies. These future studies should include memantine/ChEI combination therapy and memantine vs ChEI comparison studies.

Consideration should be given to designing future studies for the use of memantine in treating mild AD. The uncompetitive mechanism of memantine suggests it may demonstrate more effect in more severe diseases. This was demonstrated in a study of vascular dementia (VaD) when one subgroup responded better than another when grouped according to severity.[42] Because it is of lesser severity than moderate to severe, a longer study with a larger study group is needed to detect any effect that memantine may or may not have in mild to moderate AD. In accordance with the treatment guidelines of the APA and AAGP, memantine should not be used unless future evidence suggests it is effective.

Memantine in non-AD dementias

The pivotal study by Winblad et al included both AD and VaD patients. A statistically significant effect was detected in both dementias[15] and further studies have elaborated on memantine's efficacy in treating VaD.[42–44] One of these studies was a 28-week study with 321 patients.[43] Using the ADAS-cog and CIBIC-plus as primary efficacy measures, the study found those measures stabilized in patients receiving memantine in comparison with placebo-treated patients. In addition, the treatment was well tolerated and there were no concerning side effects in this study. Memantine shows promise for the treatment of patients with VaD.

The next of those studies was a pooled analysis of several 6-month clinical trials measuring cognitive improvement using the ADAS-cog.[42] Patients receiving memantine had statistically significantly better outcomes, with mild adverse effects. Post-hoc analysis revealed that the subgroup of VaD, called 'small vessel disease,' accounted for the outcome of the experimental group while the 'large vessel disease' subgroup was not statistically significant when compared with placebo on its own. A study of memantine/ChEI combination therapy had similar results and conclusions.[44]

These studies make it clear that memantine has the potential to treat VaD but they also indicate what future studies need to consider. First, a group of patients diagnosed with VaD shows great heterogeneity and can easily be divided into subcategories.[42,44] Second, the measures used to document the progression of the disease are designed for AD and may not be suitable for VaD. Finally, patients may suffer from both VaD and AD so sensitive neuroimaging of the brain may be necessary to screen for patients who are suffering from pure VaD without the amyloid plaques that are so common in AD. These have to be considered to validate any effect that may or may not be detected in future studies.

Dementia with Lewy bodies (DLB) has also been studied as a potential target of memantine therapy. One RDBPC studyshowed a statistically significant improvement in cognition (MMSE) while showing no significant changes in the Parkinsonian or psychotic symptoms.[45] This study suggests memantine may prove useful for DLB, but the study was short (16 weeks) and had relatively few

subjects (n = 23). Further studies are merited to ensure the safety and efficacy of memantine in these patients. This is especially true since other small studies have shown adverse effects and worsening symptoms in patients with DLB receiving memantine.[46,47]

Other forms of dementia were also studied as potential targets of memantine therapy. One such disease is HIV-associated dementia. A 20-week study found no statistically significant benefits.[48] The author attributed the lack of a clinically significant result to the short duration of the study. However, they did find that indicators of neuronal metabolism suggest memantine may slow the destruction of neurons in patients with HIV.

A small study (n = 16) of Wernicke-Korsakoff syndrome found that patients receiving memantine showed statistically significant improvement in measures of cognition (MMSE) and function (ADCS-ADL) over patients receiving placebo during the course of the study (28 weeks).[49] These results suggest memantine could be used but a larger study is needed.

Another study considered frontotemporal dementia (FTD) but found mixed results in measures of behavior, cognition, and global status, probably due to small sample size (n = 16).[50]

The efficacy of memantine in treating any form of dementia in which glutamate-induced neurotoxicity is implicated should be considered for future study. The current research is limited by the small study groups so future studies should ensure that large numbers of patients are enrolled.

Other studies with memantine

Apart from dementia, many other diseases and disorders are associated with neurodegeneration. Studies in animals have suggested that memantine is neuroprotective[51] but will still allow signaling and normal function.[52,53] This is the reason memantine is clinically such a well tolerated drug. When administered to rats, researchers found it reduced neuronal deficits[54] by blocking NMDA receptors but it did not impair learning.[55] Thus, it shows a lot of promise in treating acute as well as chronic brain disease. Animal studies found memantine was effective in ameliorating neuronal loss in infarctions,[56] traumatic brain injury,[57] hypoxic ischemic brain injury,[58] intracerebral hemorrhage,[59] mitochondrial dysfunction induced cell death,[60] and secondary neuronal damage.[61]

Stroke research has looked at memantine as a neuroprotective agent to be administered both prior to the stroke event and afterwards. Studies have also found that memantine can lengthen the window to rescue neurons after the stroke event even if not administered before the stroke event.[62,63] While research is still restricted to the animal model, it shows that memantine lengthens the therapeutic window when mixed with clenbuterol in the mouse model[62] or mixed with nitrites in the rat model.[63] Another study in the rabbit model demonstrated a potential amelioration of behavioral deficits when administered after a stroke event.[64] These benefits are likely the result of memantine preventing the secondary excitotoxicity induced by lysis of glutamate-releasing neurons in the initial event.

A pilot study examined memantine as a treatment for patients suffering from combat-related post-traumatic stress disorder (PTSD).[65] Four patients were treated with memantine and evaluated for immediate memory, delayed memory, hyperarousal, and depression. There was a uniform response in all the cases in delayed memory and variable reductions in hyperarousal and depressive symptoms. While the small study size and lack of a placebo control prevents these data from bearing any significance clinically, it does provide a rationale for further studies on using memantine as a therapy in patients with PTSD.

Researchers have also looked at memantine as a potential therapy for Parkinson's disease (PD). Studies have shown potential therapeutic benefits for patients with PD treated with memantine.[66,67] However, the mechanism of action is unclear and is likely independent of dopaminergic therapies.[68] This alternative therapeutic action of memantine in PD could shed light on the pathology of PD if investigated further. Further studies are merited.

Memantine has also been considered as a potential analgesic for chronic pain. NMDA receptors are thought to be involved in stimulus-invoked pain following nerve damage. Many patients experience chronic pain following surgery, amputation, or severe trauma. Studies have now shown that memantine has no analgesic affect for patients suffering chronic pain following surgery,[69] post-herpetic neuropathy,[70] HIV-associated neuropathy,[71] and cannot ameliorate phantom limb pain.[72–74] However, memantine has been reported to decrease the intensity of phantom limb pain when administered postoperatively.[72] In addition, patients who suffer traumatic injury to an upper extremity and are administered memantine show a decrease in pain and some cortical reorganization on a functional MRI.[75] While further investigations into the primary analgesic affects of memantine on chronic pain may be unwarranted, treatment of complex regional pain syndrome and phantom limb pain with memantine merit further study.

Memantine has also been investigated as a potential therapy for refractory migraines.[76] This study showed a decrease in the incidence of refractory migraines in patients taking memantine for a 30-month period. These positive results suggest that memantine is a potential therapy and merits further study.

Additional studies suggest memantine may possibly benefit patients with depression,[77,78] binge eating disorder,[79] schizophrenia,[80,81] autism,[82,83] attention-deficit/hyperactive disorder (ADHD),[84] nystagmus,[85] Huntington's disease,[86,87] and opioid dependence.[88]

In contrast, some studies suggest memantine offers little or no benefit to patients with tinnitus,[89] cocaine dependence,[90,91] and nicotine dependence.[92]

Results of studies of memantine's efficacy in alcohol dependence were mixed.[93–95]

Several diseases and disorders are currently being studied in clinical trials (Table 1) or have been studied in recently completed trials (Table 2).

New formulation of memantine

A clinical trial has recently been completed with a new 28 mg, slow-release memantine preparation in moderate to severe AD. Statistically significant benefits were seen on both primary efficacy measures (SIB and global). This 6-month RDBPC study also included a 6-month open-label follow-up. Memantine was well tolerated with side effects similar to those of placebo.[97]

Table 1 According to the National Institute of Health website,[96] these diseases are being studied in clinical trials currently being conducted

Diseases being considered in current clinical trials	
Aphasia resulting from stroke	ADHD
Alcohol consumption	Opioid and heroine dependency
Traumatic brain injury	Multiple sclerosis
Moderate to severe AD	Compulsive buying
Frontotemporal dementia	Kleptomania
Bipolar disorder	Depressive disorder
Bipolar depression	Neurological symptoms of fragile X syndrome
Autism	Huntington's disease
Pathological gambling	Essential tremors
General anxiety disorder	Amytrophic lateral sclerosis
Social anxiety disorder	Down's syndrome
Shizophrenia	Tobacco abuse
Several types and subtypes of dementia	Chronic orthostatic intolerance

Table 2 According to the National Institute of Health website,[96] these diseases were studied in completed clinical trials

Diseases considered in completed clinical trials	
Amyotrophic lateral sclerosis	AIDS dementia complex
Mild to moderate AD	Depression
Lupus erythematosus	Depressive disorder
Parkinson's disease dementia	Tension-type headache
Dementia with lewy bodies	Binge-eating disorder
Parkinson's disease	Side effects of radiation therapy for brain tumors
Co-morbid alcoholism and depression	Neuropathy secondary to herpes-zoster
Schizophrenia	Diabetic neuropathy
Obssessive-compulsive disorder	Open-angle glaucoma

Safety profile

Current recommended dosing for memantine in patients with AD is 10 mg twice daily as a target dose. Dosing is increased at weekly increments from 5 mg once daily to 5 mg twice daily to 10 mg once a day, and 5 mg once a day to 10 mg twice daily. Studies into once daily dosing show it to be comparatively mild and well tolerated with similar efficacy.[98]

Memantine is a well tolerated drug with few patients receiving memantine discontinuing therapy compared with patients receiving placebo.[15–17,23] One study found that approximately 10% of patients administered memantine experienced a fall or injury during the study.[99]

The following side effects occur in more than 2% of patients and at a greater frequency (not statistically significant) than in placebo-treated patients during clinical trials: fatigue, pain, hypertension, dizziness, headache, constipation, vomiting, back pain, confusion, somnolence, hallucination, coughing, dyspnea, agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, abnormal gait, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.[100]

Memantine has also been found to have antagonistic effects on type 3 serotonin receptors through the use of patch clamping.[101] Memantine's 5HT-3 antagonism may protect against the gastrointestinal side effects of ChEIs when used in combination therapy.

Memantine undergoes both hepatic and renal elimination. In patients with severe impairment of either the liver or kidney, clinicians should prescribe a lower dosage of memantine accordingly. In patients with mild to moderate

renal impairment, no adjustment is necessary. However, in patients with severe renal impairment, it is recommended that dosage not exceed 5 mg twice daily. Drugs affecting renal secretion through altering the pH of the urine will affect memantine's clearance. Acidic urine will increase the rate of clearance while urine under alkaline conditions will undergo clearance at 80% of the rate at physiologic conditions. Memantine's bioavailability is not significantly affected by co-administration with other drugs that undergo renal excretion or hepatic elimination. It does not significantly induce or inhibit hepatic microsomal enzymes.

Conclusion

Research into further uses of memantine in the therapy of central nervous system disorders is merited by the nature of the drug's mechanism. The partial selectivity for antagonizing pathologically activated NMDA receptors makes this drug a therapeutic candidate for many neurodegenerative/neuropsychiatric diseases. Future studies into dementias other than moderate to severe AD (VaD, HIV-associated dementia, DLB) are needed to determine memantine's safety and efficacy in treating those diseases. In addition, neurodegenerative/neuropsychiatric disorders, such as PD, Huntington's disease, and schizophrenia need closer investigation with memantine both to improve clinical outcomes and to clarify the pathogenesis of disease. Clinicians should closely follow future research into memantine.

While memantine has potential to treat many different diseases, it should be considered early in the treatment of moderate to severe AD. It has strong evidence supporting its use both as a monotherapy and in combination with ChEI. Since there is a lack of other treatment options in moderate to severe AD, memantine should be prescribed, barring intolerance or complications.

Disclosures

The authors declare no conflicts of interest.

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