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Review Article

Management of moderate to severe Alzheimer's disease: Focus on memantine

Evangelyn Dominguez [a], Ting-Yu Chin [a], Chih-Ping Chen [d,e,f,g,h,i], Tzong-Yuan Wu [a,b,c,*]

[a] Department of Bioscience Technology, Chung Yuan Christian University, Chung Li, Taiwan
[b] Center for Nanotechnology, Chung Yuan Christian University, Chung Li, Taiwan
[c] R&D Center of Membrane Technology, Chung Yuan Christian University, Chung Li, Taiwan
[d] Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan
[e] Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan
[f] Department of Biotechnology, Asia University, Taichung, Taiwan
[g] School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
[h] Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan
[i] Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan

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Abstract

Alzheimer's disease (AD) is the most common form of dementia, and one of the principal causes leading to death around the world. It is a progressive neurodegenerative disorder that still remains without definite cure. Memantine, a licensed AD drug, is an open-channel and partial trapping blocker that functions as a potent NMDA receptor antagonist, even at low concentrations. Aside from being uncompetitive, it also allows near-normal physiological NMDA receptor activity throughout the brain even with high glutamate concentrations, making it more reliable and tolerable than other AD-targeted drugs. It has also been found to be effective, safe, and well-tolerated in animal models as well as patients with moderate-to-severe AD. Aside from NMDA receptor antagonism, numerous studies have reported that memantine can also affect dopamine receptors, block excessive calcium influx and production of reactive oxygen species (ROS) induced by Aβ oligomers, and inhibit the internal ribosome entry site (IRES), thus preventing the expression of the amyloid precursor and tau proteins which are considered as early indicators of Alzheimer's.

Keywords: Alzheimer's disease; Excitotoxicity; IRES; Memantine; NMDA receptors

Introduction

In western countries, Alzheimer's disease (AD) is the most common form of dementia [1] and is the fourth leading cause of mortality in the United States alone. In Asia, AD is the principal cause of dementia and accounts for 50–60% of all cases, lasting for about 3–20 years from diagnosis [2]. AD is considered as a largely age-related brain disorder that is progressive, fatal, and still has no current cure. Severe memory loss, confusion, and impaired cognitive abilities characterize AD predominantly. It is worth noting that the global fertility rate has dropped from 5% to 2.5%, from 1950 to 2010, according to the U.N. population division (UNPD). Furthermore, the aging population of females in the developed countries (Fig. 1) will make the reduction of fertility rate more severe. For example, in Taiwan, Singapore, and South Korea, the number of children a woman is expected to have over her life time, is between 1.1 and 1.3. Thus, the total fertility rate in these three countries is beneath the threshold and among the lowest in the world. In Taiwan, the government have posted statements like "Having a child will complete your life" and "Who will play with me", aimed at families with one child. Thus, AD will be a big issue in these developed, but aging, societies.

* Corresponding author. Department of Bioscience Technology, Chung Yuan Christian University, Chung-Li 32023, Taiwan.
E-mail address: tywu@cycu.edu.tw (T.-Y. Wu).

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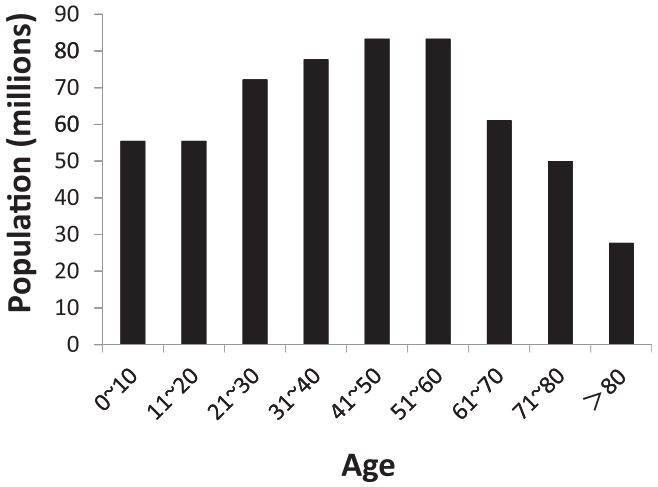

Fig. 1. The population of female in the developed countries. The data source is from UNPD, 2011.

It was first documented in 1910 when Alois Alzheimer, a German psychiatrist and neuropathologist, reported the curious case of one of his patients who suffered from memory problems as well as difficulty in speaking and understanding. The deterioration of normal cognitive functions progressed rapidly and within a few years, his patient died from the unknown disease. It was only a century after Alzheimer's discovery that scientists were able to shed light on the mystery of its cause and identify the symptoms which mark the onset of AD [3].

AD can be divided into four stages, characterized by progressive cognitive and functional decline [4]. The first stage, pre-dementia, has the most unassuming symptoms often mistaken as age-related or stress-related. Patients with pre-dementia often exhibit mild problems concerning executive functions and semantic memory disruptions, while also exhibiting a proclivity to apathy. However, patients at this stage typically take up to 8 years of neuropsychological testing before they are able to satisfy the clinical criteria for AD diagnosis. A worsening of memory abilities along with subtle agnosia and apraxia exemplify early stage dementia. Language problems, mainly decreased word fluency, are also manifested, and newly acquired information is more easily forgotten than old information. In moderate dementia, advanced deterioration slows down activity and eventually leads to inability to perform basic functions. Loss of vocabulary, paraphasia, long-term memory impairment, wandering, delusions, and other neuropsychiatric changes also become apparent at this stage. Once patients enter the final stage, or advanced dementia, speech is completely lost although they can still reciprocate emotion, and muscle mass and mobility thoroughly deteriorates until the patient becomes bedridden. AD is a terminal illness; other factors contribute to death.

The discovery of the first mutation in the amyloid precursor protein (APP) gene in the 1990s became the basis of the β-amyloid cascade hypothesis. This states that familial AD mutations result in an increased production of β-amyloid (Aβ) peptides, which lead to senile plaques and dementia [5]. Most notably, the aggregation of β-amyloid in the form of senile plaques and the formation and fibrillization of hyperphosphorylated tau proteins into neurofibrillary tangles (NFTs), are said to be responsible for much of the late-stage cognitive decline observed in patients with AD [6]. These defining features can be found localized in different areas, the plaques being extracellular as they build up between nerve cells [3] while NFTs remain intracellular, being deposited in nerve cell bodies as well as in neurites in the neuropil [7]. Formation of plaques and tangles in the brain, blocks nerve cell-to-cell signaling and destroys vital cellular paths where essential nutrients and other supplies travel, respectively. However, recent discovery of the mechanisms that lead to neurodegeneration have vindicated Aβ plaques and tau tangles, regarding them as secondary products rather than causative, and pinpointed oxidative stress and mitochondrial malfunction as factors that initiate the neuronal cascade that leads to AD instead [6]. Aβ secretion has been found to have antioxidant activity and serves to antagonize uncontrolled oxidative stress caused by excessive generation of reactive oxidative species (ROS) and mitochondrial anomalies, as opposed to stimulating their production [8]. NFTs, on the other hand, can protect against neuronal damage, as their presence in neurons is associated with reduced steady-state Aβ production as well as reduced levels of oxidative stress [6].

Another presumed cause of AD is excitotoxicity, which is a pathological process that damages and kills neurons due partly to the overactivation of N-methyl-D-aspartate glutamate (NMDA) receptors that permit excessive Ca^{2+} influx through the receptor's associated ion channel [1,6,9–11]. Over activation of NMDA receptors does not necessitate large amounts of glutamate, the primary excitatory neurotransmitter in the brain, but can be triggered by depolarization of neurons due to mechanical insults or injury. Because excitotoxicity has long been associated with the pathophysiology of acute and chronic neurodegenerative disorders [12], it is considered as a particularly attractive target for neuroprotective efforts [1].

Memantine

Memantine, or 1-amino-3,5-dimethyladamantane hydrochloride, is a derivative of amantadine (1-adamantanamine hydrochloride), an anti-viral agent that has long been used clinically to treat Parkinson's disease in the US and in Europe. Aside from anti-Parkinsonian properties, it also possesses anti-epileptic properties, and is now widely used in the treatment of AD [13]. Memantine was first synthesized by researchers at Eli Lilly & Co., in the hopes of developing an agent that lowers elevated blood sugar levels, but proved to have no such benefits. It was not until 1972 when Merz and Co. applied for a patent that the therapeutic relevance of memantine was discovered. They demonstrated that memantine has CNS activity as well as a potential for treating neurodegenerative and cerebral disorders [14]. At first, postulates regarding its mechanism of action included direct and indirect dopaminergic, serotonergic, and noradrenergic activities, but they

were later rejected, as *in vitro* data supporting these had originally been obtained at concentrations higher than achieved therapeutically. Extensive preclinical research has since established NMDA-receptor antagonism as the therapeutic mechanism of action of memantine [11,14]. As early as 1989, memantine has been known to block NMDA-induced current in embryonic mouse spinal neurons *in vitro* [13]. During therapeutic use, memantine concentrations found in the cerebrospinal fluid suggests that its primary site of action is the NMDA receptor, but it induces fewer and less profound effects on perception or consciousness than drugs like PCP or ketamine [15]. As an uncompetitive NMDA receptor antagonist, it has been used at therapeutic concentrations in the treatment of dementia, and has proven itself devoid of side effects and shown good tolerability clinically in more than 200,000 treated patients [14]. It has also been shown to be more potent in displacing [^{3}H]MK-801 binding in the cerebellum than in the cortex [14,16], and like other NMDA receptor antagonists, memantine at high concentrations can inhibit mechanisms of synaptic plasticity that are believed to underlie learning and memory [16, 17]. It also mimics the physiological function of Mg^{2+} due to its high voltage dependency, which allows it to exit the NMDA channel upon moderate depolarization under pathological conditions [12]. According to a 1999 review, other possible therapeutic applications of memantine, aside from AD, include AIDS, glaucoma, hepatic encephalopathy, multiple sclerosis, tinnitus, Parkinson's disease, tardive dyskinesia, chronic pain, tolerance, sensitization and drug addiction, epilepsy, spasticity, and depression and anxiety [14].

Mechanism of action, metabolism, and pharmacokinetic profile

Over the years, research regarding the mechanism of action of memantine has improved from mere postulates to substantiating evidences supporting its activity against glutamate-mediated neurotoxicity [12], which has long been pinpointed as a major contributor in the pathogenesis of AD [13,17,18]. Among the many proposed modes of action of memantine, the most widely accepted and evidenced is NMDA receptor antagonism, which has been further described as low-affinity, uncompetitive, voltage-dependent, open-channel, as well as partial trapping, block by separate studies. Memantine performs this antagonism by blocking the channels activated by NMDA receptor stimulation, the excessive activation of which mediates calcium-dependent neurotoxicity associated with hypoxic-ischemic brain injury, trauma, epilepsy, and neurodegenerative diseases [13]. In 1992, Chen et al. [13] used whole-cell and single-channel recordings with patch electrodes to study NMDA-induced currents on fluorescently labeled, postnatal rat retinal ganglion cells (pharmacologically similar to other central neurons) and concluded that memantine selectively inhibits NMDA-elicited current through the mechanism of open-channel block [16, 19]. This is further supported by its voltage and agonist dependence. Unlike dizocilpine (MK-801), a similar but older open-channel blocker that protects neurons but also impairs many normal neuronal functions and triggers reversible neuronal swelling at therapeutic concentrations, memantine is clinically well-tolerated at such concentrations, allowing it to even inhibit NMDA receptor-mediated neurotoxicity in rat and retinal ganglion cell neurons [13]. At low micromolar concentrations, memantine is an uncompetitive antagonist and (theoretically) allows near-normal physiological NMDA activity throughout the brain even in the presence of high concentrations of glutamate, an advantage that retains organ functionality unique to memantine. Its distinctive rapid-response kinetics also allows substantial NMDA receptor function, even in areas with damaged neurons. These pharmacological properties confer, to memantine, a therapeutic advantage against NMDA receptor-mediated neurotoxicity, with fewer observable side effects compared to other organic NMDA open-channel blockers [13]. Furthermore, memantine was found to be target-specific; it does not affect other types of currents such as the kainate and quisqualate-activated currents, save for the NMDA subtype. In the same study, Chen et al. [13] also discovered, through electrophysiology experiments, that at escalating levels of EAAs (excitatory amino acids or glutamate carriers), the proportion of current inhibited by memantine increases while basal level NMDA-induced response remains consistent, unlike MK-801, which blocks all NMDA-induced currents for longer periods and has a slower unblocking rate than memantine [16]. Whereas early increases in Ca^{2+} are associated with delayed-onset NMDA receptor-mediated neurotoxicity, the presence of 6 μM memantine is able to prevent excessive Ca^{2+} influx generated by 200 μM NMDA, indicating that it can avert this event by allowing only basal NMDA receptor-mediated responses and blocking excessive NMDA-elicited activity [13].

In the presence of NMDA, it takes memantine approximately 5.2 seconds to dissociate from NMDA receptor channels at a holding potential of -60 mV, but pre-exposure to 3 mM magnesium eliminates this slow unblocking phase, suggesting a possible binding site within the channel pore or close enough to interact with the Mg^{2+} binding site [1,14,19]. Whole cell recordings in a 1997 study using cultured rat cortical neurons or Chinese hamster ovary (CHO) cells expressing NMDA receptors, also showed that memantine blocks NMDA-activated channels [14] by binding to a site at which it could be trapped after channel closure and agonist binding [1, 15]. When memantine was washed off, one-sixth of the blocked channels released the drug, exhibiting "partial trapping" and a lower tendency to be trapped than phencyclidine or MK-801. The same was observed with recombinant NMDA receptors composed of NR1 and either NR2A or NR2B subunits, suggesting that the partial trapping was not due to the variability in memantine action on a heterogeneous population of NMDA receptors in cortical neurons. To further assess this phenomenon, Blanpied et al. used a simple kinetic model of blocker action to show that partial trapping can result if the presence of memantine in the channel affects the gating transitions or agonist affinity of the NMDA receptor [15]. This partial trapping ensures that the blocker will be released by some channels between synaptic responses during synaptic

communication. Unlike "sequential blockers", which prevent the channel from closing while blocked, memantine is a "trapping channel blocker", which permits channel closure and agonist dissociation while still bound in the channel. Conformational changes involved in gating could sterically prevent the exit of a trapping channel blocker out of the channel, while the binding of a sequential blocker seals the movement of the channel gate completely [15]. Low-to-moderate affinity blockers, like memantine, are capable of antagonizing the neurotoxic effects of continuous but relatively small increases in glutamate concentration, but, like Mg^{2+} [12], exit the NMDA channel following transient physiological activation, due to the pronounced depolarization of the postsynaptic membrane induced by high concentrations of synaptically released glutamate [1,16].

Another target site for memantine that could possibly contribute to its clinical importance is the dopamine $D2^{high}$ receptor. Despite its NMDA antagonistic character, memantine has been known to elicit dopamine action indirectly and stimulate dopamine receptors, suggesting that it may have similar potencies for the NMDA receptor and the high-affinity state of the dopamine D2 receptor [20]. Upon testing this hypothesis, Seeman et al. (2008) [20] found that memantine (200–2000 nM) inhibited the release of prolactin, which is controlled by dopamine D2 receptors, from the lactotrophs in rat anterior pituitary cells. Potency of memantine at the dopamine $D2^{high}$ receptor was also found to be similar, if not greater, than at the NMDA receptor; hence the authors claim that the lack of memantine action on actual serum prolactin from elderly individuals (reported by a different study) may be due to a balanced and simultaneous action on NMDA and D2 receptors, because glutamate pathways could alter the release of prolactin. Similarly, memantine has been reported to inhibit responses from human alpha7, alpha4/beta2, and alpha9/alpha10 nicotinic receptors, as well as human and murine $5\text{-}HT_3$ receptors, with more or less similar magnitude to NMDA receptors, although some of these actions are highly unlikely to be of therapeutic relevance [1,19,21]. Nevertheless, more studies are needed to verify these alleged possible components of memantine action.

Aside from antagonizing NMDA receptors, memantine has also been reported to block the increase in Ca^{2+} and oxidative stress induced by Aβ oligomers (ADDLs) [8]. ADDLs are thought to induce ROS production in mature hippocampal neurons and bind to neurons through a protein receptor complex-mediated manner that involves NMDA receptors. In an attempt to describe the mechanism of memantine action in terms of neuroprotection, de Felice et al. [8] tested the potency of memantine against soluble Aβ oligomers, and found that at therapeutically relevant doses, it can potently inhibit ADDL-induced ROS formation but cannot prevent ADDL binding to hippocampal neurons, hinting that ADDLs may not bind directly to the NMDA receptor channel pore. Memantine proved equally effective in blocking ADDL-induced Ca^{2+} increase, implying that one likely mechanism of action of memantine in AD is protection against neuronal oxidative damage initiated by ADDLs.

Recently, a dual action of memantine in AD was proposed from a biomolecular perspective. Wu and Chen (2009) [7] hypothesized that memantine not only antagonizes NMDA receptors but may also act as an inhibitor of the internal ribosome entry site (IRES), following an observation that it inhibited IRES-mediated translation initiation in COS-1 cells. This IRES inhibition, in turn, presumably prevents the expression of amyloid precursor protein and tau proteins in neurons, thereby relieving the symptoms of AD in an entirely different manner. Structure-wise, memantine is similar to its relative amantadine, which can legitimately block the IRES-mediated translation of some viruses, hence forming the basis for their assumption. Although it presents a distinct and novel view on the mechanism of action of memantine, this hypothesis, however, is yet to be verified by subsequent studies. In Fig. 2, we summarized the "dual" working mechanism of memantine on AD.

Under therapeutic conditions, serum levels in man with daily maintenance doses of 20 mg range from 0.5–1.0 μM, while free cerebrospinal fluid (CSF, man) and brain microdialysate (rat) levels are 20–50% lower due to albumin binding in serum [14]. However, despite the fact that brain homogenates in both man and rodents contain higher memantine concentrations due to lysosomal accumulation, this in no way reflects free concentrations found at CNS receptors in vivo. Based on previous microdialysis studies and the rationale that between man and rat: (1) drug sensitivity is pharmacokinetics-related; (2) serum/brain ratio is similar; and (3) 5 mg/kg is the dose where peak serum concentrations at 20–30 minutes are at the upper limit of those seen in serum from patients and healthy volunteeers, it was proposed that 5 mg/kg i.p. in rats should be the maximum therapeutical concentration for memantine needed to treat dementia, notwithstanding other factors that affect pharmacokinetics, such as age, strain, gender, and animal health status [14]. Since repetitive administration in rats produces substantial fluctuations in brain concentrations, while steady-state levels can be found in chronically treated patients, s.c. infusion by Alzet minipumps to mimic the pharmacokinetics seen in patients, has been suggested for animal studies [14]. Memantine treatment of 20 mg/kg/day, equivalent to 0.4–0.7 μM plasma levels in the CNS as assessed by microdialysis, leads to plasma levels of ~1 μM and does not affect spatial learning in normal rats. Treatment, using the abovementioned concentrations in rat and man, is sufficient to achieve brain levels that affect NMDA receptors; however, higher doses are likely to be selective at NMDA receptors and side effects may emerge at acute doses of ≥20 mg/kg i.p. [14].

Clinical studies and safety

As claimed by numerous studies [4,12–17,19,22,23], memantine is clinically well-tolerated unlike other neuroprotective drugs of its kind, such as MK-801. During its entire 15-year clinical history, reported side effects have been sporadic and memantine continues to be widely accepted as a well-tolerated medication to this day [14]. In a population of

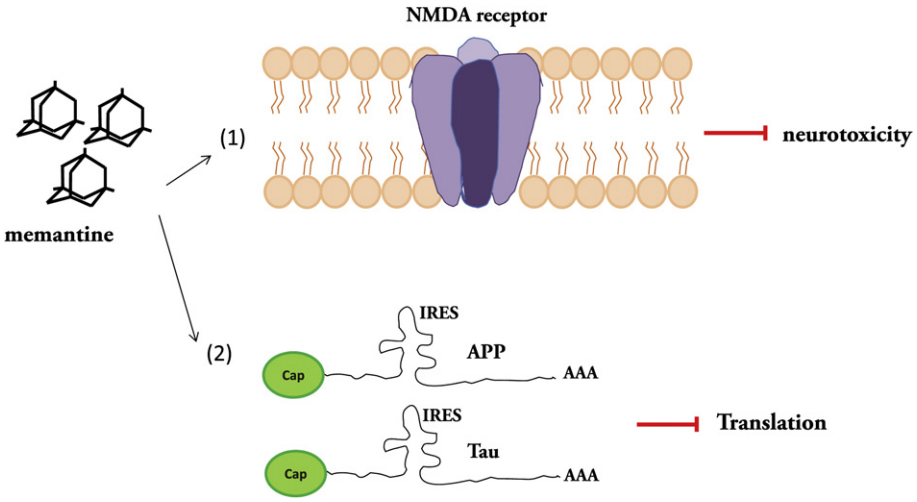

Fig. 2. The "dual" working mechanism of memantine on Alzheimer's disease. The memantine (⏢) can block the NMDA receptor and inhibit neurotoxicity induced by glutamate. Memantine may also inhibit the Tau and APP proteins translation mediated through IRES in the mRNA of Tau and APP.

severely demented patients with either AD or vascular dementia, memantine use was associated with improvement in global assessments and functional capacities with decreasing care-dependence [17]. Clinical data also indicate that memantine is a useful treatment for AD, as symptomatological improvements in cognitive processes, daily activities, and self care are observable. Considering abuse potential, memantine has shown satisfactory results in various animal studies: it did not affect rats trained to distinguish cocaine, failed to potentiate lateral hypothalamic self stimulation in contrast to MK-801, exhibited zero effect on threshold frequency and motor performance at 5 mg/kg (considered therapeutically relevant) [12,14], and produced no motivational effects at a dose of 7.5 mg/kg. Likewise, there are no reports of human abuse [14] since the start of its use as medication.

Memantine owes its safety to the faster kinetics of action it exhibits with rapid blocking and unblocking rates (unique rapid-response kinetics) at low micromolar concentrations proven to be clinically well-tolerated by patients with Parkinson's disease [13]. In an in vivo study performed by Chen et al. (1992) [13], 20 mg/kg memantine did not produce lethargy or other behavioral effects in a rat model, but protected neurons from damage. This is further proof of its safety and efficacy. In neurotoxicity experiments of the same study, 6–12 μM memantine showed enough potency to prevent NMDA receptor-mediated neuronal injury brought about by excessive Ca^{2+} and low magnesium concentrations in both rat retinal ganglion cells and cortical neurons [14]. However, memantine has also been known to cause psychotomimetic effects [19], if the recommended titration of dosing from 5 to 20 mg over 3–4 weeks is skipped or when combined with dopaminomimetic therapies [14]. Memantine-triggered side effects characteristic of NMDA receptor antagonists were also found to be more evident in rats at acute doses (20–30 mg/kg) than those considered therapeutically relevant, pointing out that the difference between memantine and other NMDA receptor antagonists is quantitative rather than qualitative. On the other hand, it should also be noted that neuroprotective doses that inhibit the progression of chronic neurodegenerative disorders, such as AD, are believed to be low and should not be based on inapposite models such as acute ischemia, which are generally severe in nature and require higher doses of NMDA receptor antagonists [14].

Clinical studies, especially of sensitive drugs such as memantine, require long-term, placebo-controlled studies with large numbers of patients [14]. However, instead of evaluating the effects of memantine on the progression of AD, clinical studies have focused on defining symptomatological improvement in late-stage AD patients. Despite this, the efficiency of memantine cannot be doubted, as it is supported by numerous studies such as the 1993 study, where symptomatological improvement observed in demented patients did not decline over a 12 month, non-placebo-controlled follow-up period [14]. However, it was not until 2004 that a randomized, double-blind, placebo-controlled 24-week clinical trial of patients with moderate to severe AD (already receiving donepezil) was conducted using memantine as treatment. Tariot et al. [22] divided 404 patients into placebo and memantine groups and noted that patients from the latter group received statistically significant benefits and scored better on both CIBIC-Plus (clinician's interview-based impression of change plus) and the BGP (behavioral rating scale for geriatric patients) care dependency subscale than the first group using the LOCF (last observation carried forward) approach. This demonstrated the efficacy and tolerability of combining memantine and an acetylcholinesterase (AChE) inhibitor. In terms of total NPI score, patients in the memantine group fared worse than the placebo group, indicating fewer behavioral disturbances and psychiatric symptoms [22]. Furthermore, compared with the memantine group, more participants from the placebo group discontinued due to adverse effects, mainly confusion and headache, although the confusion experienced by patients receiving memantine were rated as mild, occured at a median of 32 days, and remitted within 2 weeks. Doody et al. (2004) [4] also reported similar benefits, with moderate to severe AD patients treated with memantine experiencing significantly less

deterioration of Activites of Daily Living (ADL) skills than those receiving placebo. Memantine also appeared to promote functional efficacy, with patients exhibiting improvement in tasks such as standing up, moving, dressing, eating, taking in fluid, and using the toilet, proving that it can also confer noncognitive benefits in AD patients [4,22]. With regard to behavior, a reducing effect of memantine on agitation/aggression was also observed, signifying a possibility of reducing concomitant medications, which may lead to lesser resource utilization and health costs [24]. In 2006, Dantoine et al. [23] conducted a prospective, multicenter, open-label study wherein patients under AChE inhibitors such as donepezil or galantamine were switched to rivastigmine for 16 weeks, and those who failed to stabilize were given memantine (5 mg/day) as supplement. Of the 202 patients tested, 86 patients underwent rivastigmine/memantine treatment with satisfactory improvement on MMSE (Mini-Mental State Examination) results and stability, illustrating the advantage of combining AChE inhibitors, which are used for mild to moderate AD, and memantine, which is recommended for moderate to severe AD [23]. Despite adverse events reported, such as vomiting and nausea, favorable safety and tolerability profiles for rivastigmine and memantine were established due to the high mean doses reached (10.3 and 19.0 mg/day, respectively) and the relatively low discontinuation rates caused by adverse effects (e.g., vomiting, nausea). Hence it is safe to say that memantine monotherapy or combination therapy has proven itself harmless as well as beneficial.

Efficacy

According to Danysz et al. [12], NMDA receptor antagonists like memantine, which is capable of simultaneously preserving physiological transmission while decreasing pathological activation [19], provide advantages such as hampering disease progression and improving cognitive processes, especially when used at the early stages [12]. During the advanced stages of AD, when secondary neurodegeneration is likely to occur due to disinhibition, memantine is more effective than other drugs because of the protection it exerts on neurons, that allows physiological activation of NMDA receptors on functional neurons to remain intact. The effectiveness of memantine compared to agents like MK-801, lies in its magnesium-like mode of action, which can help stabilize neuronal activity at NMDA-receptor-bearing synapses at the later stages of AD. Aside from offering neuroprotection and stability, memantine is also increasingly effective against the escalating levels of glutamate evident during a stroke even at low micromolar concentrations. This was proven in a study done by Chen et al. [13], wherein memantine at $\geq$6 μM prevented retinal ganglion cell death from the endogenous glutamate-related toxin in a dose-dependent manner, with complete salvage of neurons [13], whereas amantadine required much higher concentrations to achieve this. At 12 μM, memantine sufficiently inhibited 200 μM NMDA-activated currents [13] in a voltage-dependent manner [14–16], while steady-state inhibition was achieved within 1 second of drug application and was agonist-dependent, i.e., it occurred only in the presence of NMDA.

Memantine, along with ketamine and (+)-MK-801, has also been found to be 3-fold less potent against NMDA-induced currents in freshly dissociated striatal neurons, but highly effective on hippocampal neurons (involved in memory formation), antagonizing current responses in a selective, concentration-dependent manner [16]. Because memantine is more effective on non-striatal structures, it exhibits a somewhat inferior clinical profile in Parkinson's [16] than its relative amantadine and vice versa in AD. However, a reduced effect of memantine on NMDA responses of striatal neurons, as observed by Parsons et al. (1996) [16], indicates that a subclass of NMDA receptors with altered relative voltage-dependency of channel blockade is expressed in the striatum—a premise supported by a finding that memantine-sensitive NMDA receptor-mediated excitatory postsynaptic potentials can be recorded in the striatum in the presence of Mg^{2+} [16]. Other factors that could influence the therapeutic effect of memantine in *in vitro* studies, aside from the type of neuron, are the extent to which it is trapped after channel block, the splice variants of the receptor present in the neurons (e.g., NR1, NR2A, etc.) [19], and the Cs^{+} ions majorly used in patch clamp experiments, that lower the affinity of memantine as an NMDA receptor antagonist by increasing voltage-dependency [14]. Therefore, despite positive results, the effects of memantine reported in studies are only mere estimations and not real or actual measures of efficiency. Nevertheless they serve to give us an idea of the potential possessed by memantine.

Upon testing the potency of memantine with intracellular K^{+}, Parsons et al. [16] observed a 2.6-fold increase in memantine efficiency when K^{+} is the major intracellular cation. Memantine was also found to be more potent at NMDA receptor subtypes expressed in HEK-293 and CHO cells, as well as native NMDA receptors in freshly dissociated hippocampal neurons, all of which lack the large dendritic arborization of cultured hippocampal pyramidal neurons [15]. According to Parsons et al. [14,21], in vitro slice preparations, used for electrophysiological recordings, also affect the activity of memantine and other uncompetitive antagonists, because lipophilic substances penetrate slowly into thick slices, and blockade by uncompetitive NMDA receptor antagonists is use-dependent [15,16]. They also mention in their review, a 1994 study which reported that higher doses of memantine are required to block spinal neuron response to microiontophoretic NMDA, and in a separate study done by the same group, memantine was found to be much less effective against stronger intensity responses from the same neurons. On the other hand, memantine blocked glutamate-induced toxicity in differentiated SHYSY5Y cells with an IC_{50} of 2.1 μM, in cultured hippocampal neurons with an IC_{50} of 1.1 μM, and protected cultured cortical neurons from the toxic effects of glutamate with an IC_{50} of 1.4 μM, showing great promise as a neuroprotective drug treatment. Parsons et al. [14] also conducted a study which showed that the combined action of memantine and a $glycine_B$ antagonist exhibits a better therapeutic profile than MK-801 and a competitive NMDA receptor antagonist.

Chronic dietary intake of memantine (31 mg/kg/day) for 2 weeks has been reported to prevent death, convulsions, and hippocampal damage induced by i.c.v. quinolinic acid. Malonate-induced striatal lesions were also attenuated by memantine, proving its potential in treating chronic neurodegenerative diseases associated with deficits in mitochondrial function [14]. Of particular relevance to the clinical use of memantine are preclinical studies on the neurotoxic effects of glutamate in structures known to be affected in AD, such as the cholinergic nucleus basalis of Meynert (NBM, or nucleus basalis magnocellularis in rats) [12, 14]. In successive studies done by Wenk et al. (1994, 1995, 1997) [26–28], memantine, at a dose considerably lower than that which causes side effects, given i.p. before NMDA microinjection, produced dose-dependent protection and resulted in plasma levels similar to those in patients given therapeutic doses. In a T-maze alternation task, memantine pretreatment also proved useful in antagonizing the learning deficits induced by microinjection of NMDA into the NBM [12,14]. It also prevented lesions in the NBM from forming, due to mitochondrial toxin 3-NP injection [12]. In 1996, a follow-up study was performed, to assess two important features disregarded in the abovementioned series of studies, namely, that the insult was of an acute nature and not progressive, and that memantine was administered as a bolus injection that does not mimic the steady-state levels observed in patients [14]. After incorportating the necessary adjustments, memantine was shown to still enable rats to function normally in the T-maze, while those infused with quinolinic acid had clear learning deficits and had reduced choline uptake sites (indicator of the density of ACh terminals) in the cortex [12,14]. Memantine, however, exerted no effect on T-maze learning, LTP (long term potentiation, an elementary feature of neuronal memory formation) in hippocampal slices *ex vivo,* or LTP in the dentate gyrus in normal rats *in vivo* [14].

Nakamura et al. (2006) [25] also examined the effects of memantine on learning, by injecting Aβ and ibotenic acid in to the hippocampus of rats and using the mean escape latency during the water maze task as a gauge. Similar to other studies, injected rats exhibited better performance with memantine as opposed to MK-801, proving the superior inhibitory ability of memantine against cognitive deficits over MK-801. In terms of memory impairment, memantine was also useful in restoring or enhancing spatial memory in rat models. Zajaczkowski et al. (1997) reported that memantine also has the ability to antagonize NMDA-induced amnesia at doses $\leq$ 5 mg/kg in rats [29]. In separate experiments, memantine was able to prevent LTP reduction induced by non-toxic concentrations of NMDA and the removal of magnesium, leading to the conclusion that under tonic activation of NMDA receptors, memantine can restore LTP induction and reverse deficits in synaptic plasticity, both at the neuronal and behavioral level [12,17]. Yamada et al. [30] demonstrated that memantine could prevent the development of Aβ-induced memory impairment in rats using the delayed-matching to position task (DMTP) and bilateral injections of Aβ1-40 into the hippocampus, while memantine/donepezil combination treatment produced no synergistic effects due to a ceiling effect. Memantine was also able to enhance hippocampal spatial learning in a transgenic mouse model of AD, despite its inability to produce nonspecific effects on locomotion/exploratory activity [31]. Zoladz et al. [32], however, reported that although memantine produced some significant influence on the improvement of long-term spatial memory, neramexane, a fellow uncompetitive NMDA receptor inhibitor, showed more potency than memantine.

Because of mounting evidence that inflammation, especially in the NBM, is a contributory factor in neurotoxicity in AD [12, 14], a 1998 study developed a chronic brain inflammation model using lipopolysaccharide (LPS) as the inflammatory trigger in the NBM. Using therapeutically relevant doses of memantine (20 mg/kg/day) [14,19] provided significant neuroprotection from LPS, but did not affect the inflammatory reaction [12,14]. This result, nevertheless, illustrates the neuroprotective influence of memantine in treating demented patients. Hence, if the contribution of NMDA receptors in the neuropathology of AD is accepted, then memantine could possibly slow down the progression of this disorder [12,14].

In humans, clinical studies have also shown the efficacy of memantine through placebo-controlled trials with patients diagnosed with moderate to severe AD, employing cognitive, functional, and global outcome measures as a basis for assessment. In 2004, Doody et al. [4] conducted a study based on previous works, and enumerated the specific functional effects of memantine treatment observable in AD patients. Remarkable reduction in decline of ADL skills, such as making conversation, disposing of litter, using the toilet, and getting around outside of one's home, were documented, with patients under memantine monotherapy scoring better in tests assessing functional capacity than those in the placebo control group. Similarly, Tariot et al. (2004) [22] reported better scores for donepezil/memantine-treated patients in tests which evaluated cognitive dysfunction and late-stage dementia than for placebo-treated ones. Gauthier et al. [24] also confirmed in an auxiliary study to Tariot et al. that memantine was able to confer behavioral benefits to AD patients, alleviating neuropsychiatric symptoms associated with dementia, most notably agitation/aggression. A responder analysis done in 2006, also reported that memantine treatment while under donepezil yielded positive effects on cognitive improvement, stabilization of outcome scores, as well as risk reductions for all combinations of outcome measures [18]. Supplementing memantine for rivastigmine treatment also decelerated cognitive and behavioral deterioration in patients with moderate to severe AD [23] without significant adverse effects, demonstrating that memantine is both safe and effective to use in monotherapy or combination therapy.

Conclusion

AD is a progressive disease, the treatment of which is a critical issue worldwide. The main causes of AD are said to be the aggregation of β-amyloid peptides into senile plaques and the fibrillization of hyperphosphorylated tau proteins into

neurofibrilliary tangles, both of which lead to neurodegeneration. Recently, however, mitochondrial malfunction and oxidative stress have also been pinpointed as factors that affect the neuronal cascade that leads to AD. However, the most studied cause of this disease is excitotoxicity. Excitotoxicity is a pathological process that damages and kills neurons due partly to the overactivation of NMDA receptors that permit excessive Ca^{2+} influx. Because excitotoxicity is usually associated with the pathophysiology of chronic neurodegenerative disorders, it has become an attractive target for neuroprotective efforts. Memantine is a low-to-moderate affinity, uncompetitive, voltage-dependent, open-, as well as partial trapping, channel blocker; its mechanism of action is NMDA receptor antagonism. Memantine has been proven to be more effective in numerous studies than other channel blockers such as MK-801, in providing neuroprotection and inhibiting NMDA-induced currents *in vivo*. Another advantage of memantine is its ability to allow near-normal physiological NMDA activity throughout the brain, even in the presence of high levels of glutamate, thus retaining organ functionality. Due to this, and distinctive rapid-response kinetics, memantine offers a better therapeutic advantage against NMDA receptor-mediated neurotoxicity with fewer side effects than other conventional open-channel blockers. Memantine has also been shown to block the increase in Ca^{2+} and oxidative stress brought about by ADDLs, by inhibiting ADDL-induced ROS formation. Aside from this, it has also been hypothesized to inhibit the IRES, which presumably prevents the expression of amyloid precursor protein and tau proteins, thereby relieving the symptoms of AD. Despite the number of studies conducted with regard to memantine's mechanism of action against the identified causes of AD, more evidence and further probing is needed in order to establish its exact mode of action.

In terms of safety for clinical use, memantine has been found to be well-tolerated on many occasions. Clinical data also indicate that memantine use produced significant improvements in global assessments and functional capacities, as well as symptomatological improvements in cognitive processes, daily activities, and self-care of AD patients. Memantine has a very low abuse potential, has shown satisfactory results in various animal studies, and boasts no report of human abuse throughout its medical history. Memantine treatment in patients with moderate-to-severe AD, also conferred substantial benefits, i.e., better scores on various cognitive- and non-cognitive-related tests, reduced behavioral disturbances and psychiatric symptoms, improved functional efficacy, and fewer and more tolerable side effects than other drugs, be it in monotherapy or combination therapy with acetylcholinesterase inhibitors. Memantine also produced favorable safety and tolerability profiles in animal models and was effective in reversing deficits in synaptic plasticity, demonstrating its huge potential in alleviating the symptoms of AD. Hence, if the exact mechanism of action of memantine can be pinpointed, the full potential of memantine can be used and, combined with proper usage, memantine can ultimately be utilized for the complete treatment of AD.

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