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ALZHEIMER'S, PARKINSON'S DISEASE AND NMDA RECEPTOR - A CRITICAL REVIEW

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ABSTRACT:
In the United States and Europe, the drug Memantine, Food and Drug Administration (FDA) approves a partial antagonist of the N-methyl-d-aspartate receptor (NMDAR), for the treatment of Alzheimer's disease (AD). Memantine may also be useful in treating other neurological disorders, such as dementia and Parkinson's disease (PD). As a neuroprotectant, memantine has been shown to have a favourable effect on both neurodegenerative and vascular processes in animal studies. Memantine—a partial NMDAR antagonist—blocks NMDA glutamate receptors to regulate the glutamatergic system and ease cognitive and memory issues while large quantities of glutamate induce neurodegeneration. For memantine to be effective, it must connect with the NMDAR in an uncompetitive manner, allowing the receptor's physiological function to be preserved while also ensuring that memantine is safe and has a low adverse-event profile. It's possible that memantine might be beneficial in the treatment of Parkinson's disease, since NMDAR antagonism has been implicated in the disease's pathophysiology, and no other medicine is effective enough to replace L-dopa. In spite of its mild side effects, memantine has

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only been demonstrated to produce a slight reduction in AD and VD, and hence attempts are being made to build new and more powerful memantine-based medications to perhaps provide higher effectiveness. In June 2021, the FDA authorized Aducanumab for medicinal use in the United States. The first-of-its-kind therapy for Alzheimer's disease and the first novel treatment for Alzheimer's since 2003 have been authorised by the FDA.

Keywords: Alzheimer, Amantadine, Parkinson, Aducanuma, Dementia, Memantine, NMDAR

INTRODUCTION:

Alzheimer's disease (AD), a gradual, irreversible loss of memory that progresses to total dementia, is characterised by cognitive decline and impairments in everyday activities, behaviour, speech, and visual-spatial perception. It is the most prevalent kind of dementia in persons over the age of 65, accounting for about 60%–70% of cases [1], and is related with a variety of risk factors including hereditary, epigenetic, nutritional, and routine variables [2].

Short-term memory loss is the most obvious and early sign of Alzheimer's disease (amnesia). When the diagnosis of AD is in question, behavioural and cognitive tests are routinely utilised, typically followed by a brain scan, to confirm the diagnosis. Aphasia, apraxia, agnosia, and bewilderment are among symptoms of cognitive impairment as the illness progresses. [3]. Aside from these behavioural aberrations, AD may also cause people to exhibit violent eruptions or excessive apathy, even if they have no prior history of such behavior. As the body's basic functions degenerate, death is inevitable.

Alzheimer's disease affected around 50 million individuals globally by the year 2020. [4] Up to 10% of instances occur among persons in their 30s to mid-60s, although it is most common in those over 65 years old. [5] Women are more prone to illness than males. [6] About 6% of those 65 and above are affected. [7] More than 1.9 million people died in 2015 from all kinds of dementia. [8] Psychiatrist and pathologist Alois Alzheimer coined the term Alzheimer's disease in 1906. [9] Alzheimer's disease places a heavy financial burden on society, with an annual worldwide cost of US$1 trillion estimated. [4].

Many FDA-approved drugs are currently being used to treat Alzheimer's disease, although they only give symptomatic relief. NMDAR antagonists like memantine, which have been shown to be effective in treating AD, as well as other neurodegenerative diseases including Vascular Dementia (VD) and Parkinson's disease (PD), are the focus of the present review. NMDAR pharmacology, glutamatergic transmission, and the therapeutic effectiveness of NMDAR antagonists are all discussed in this review as recent advances in understanding the pathogenic processes that underlie these symptoms. Memantine treatment will be the focus of our investigation because of the current interest in the sector. As previously noted in this paper, memantine's molecular basis, pharmacology, and clinical trials have all been explored. The present research, on the other hand, provides a thorough explanation of memantine's role in treating Alzheimer's disease, vascular dementia, and Parkinson's disease.

THE PATHOLOGY OF ALZHEIMER'S DISEASE:

It is thought that the degeneration of cholinergic neurons in the forebrain basal ganglia is a major factor in Alzheimer's disease [10]. A lack of acetylcholine (ACh) and other traditional

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cholinergic markers, such as choline acetyltransferase and acetylcholinesterase, may be clearly identified in the AD brain [2, 11]. APP, a much larger metalloprotein, undergoes amyloidogenic processing to produce insoluble amyloid protein, which leads in the production of extracellular neuritic amyloid plaques containing the peptide-beta amyloid peptide, which is thought to underlie the pathophysiology of Alzheimer's disease [12]. NFTs, which are composed of abnormally phosphorylated microtubule-associated tau protein, as well as other neurochemical and cellular abnormalities, are the other key pathological symbols.

The aetiology of AD still remains a mystery despite the fact that genetic, pharmacological, and neuropathological data strongly shows that Aβ and amyloid plaque production is an important event in the pathogenesis of AD [13]. Many studies suggest that it is polygenic and multifactorial [14] and that, more than predicted, a breakdown is sensitive to a wide range of impacts and processes that may lead to a move toward the pathogenic pathways associated with AD [15]. Quick onset familial Alzheimer's disease (QoFAD) affects a small number of people before the age of 65. (FAD). An estimated 200 mutations have been found in one or more of the three genes involved: APP on chromosome 21, presnilin-1 and 2 (PS1 and PS2) (31, 177, and 14 mutations, respectively). All of these modifications have one thing in common: they all improve Aβ generation, and in particular, the Aβ42: Aβ40 ratio [16]. Evidence suggests that solvable masses of Aβ and its derived diffusible ligands (ADDLs) target synapses and cause memory loss and cellular malfunction. According to recent research, APP degradation leads in new APP fragments that contribute to neuronal dysfunction [17].

$A\beta_{40}$ (40 amino acid residues) is the major solvable Aβ type detected in low nanomolar quantities in cerebral fluid [18]. $A\beta_{42}$ (42 residues) is a minor Aβ type that is additional fibrillogenic than $A\beta_{40}$ and is highly concentrated in amyloid in interstitial plaques [19]. It is well accepted that the neurotoxicity of Aβ peptides is reliant on their structural state [20]. Synthetic $A\beta_{42}$ has a poorer in vitro solubility in neutral aqueous solutions than A40, owing to the hydophobicity of the extra carboxyl-terminal amino acids. Additionally, seeding soluble $A\beta_{40}$ with $A\beta_{42}$ fibrils has been shown to destabilize it [21]. However, it looks as if the presence or overproduction of $A\beta_{42}$ is insufficient to trigger Aβ amyloid deposition. In transgenic mouse models, hyperactive expression of APP and subsequent Aβ excessive production seldom leads in full-blown Alzheimer's-like neuropathology [22]. Rather than, other neurochemical variables seem to be necessary for Aβ amyloidosis.

NMDAR inhibition, the use of P-sheet breakers, antioxidant methods, Aβ-peptide vaccine, secretase suppressors, APP production suppressors, cholesterol-reducing medications, metal chelators, and anti-inflammatory therapies are only a few of the possible disease-modifying treatments for AD. Anti- Aβ vaccination, - and P-secretase suppressors, aggregation suppressors, and copper/zinc chelators are all strategies that directly target the Aβ protein. The interest in metal chelator medications derives from recent studies indicating that the development of Aβ plaques is dependent on metal ion binding [15]. Cholinergic agents like, as donepezil, rivastigmine, and galantamine are the principal therapies for AD, with the goal of increasing the amount of accessible dopamine.

ACh levels to living neurons. They have not been proved, however, to stop neuronal death or disease advancement [23, 24]. As a result, evaluating possible AD therapies that target

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alternative processes is a key of present research and has the highest promise for improving clinical management.

There is substantial sign indicating that dysregulated glutamate plays a role in the pathogenesis of neurodegenerative diseases and excitotoxicity [25]. As a result, glutamate NMDARs have arose as critical targets for Alzheimer's disease.

Excitatory postsynaptic transmission in mammals is heavily reliant on glutamate as the primary excitatory neurotransmitter, and glutamate is a key player in this process through many ionotropic and metabotropic receptors. It is possible to classify the three types of G-protein coupled glutamate receptors (GPCR) that trigger Ca2+ mobilisation from internal reserves into three distinct categories, each designated for the synthetic agonist that activates it: AMPA, kainate, and NMDA. The ion channels associated with NMDARs are likely to utilise Ca2+ as a second messenger in a variety of signalling pathways.

NMDA glutamate receptors, which are distributed in large numbers throughout the central nervous system, are critical to synaptic plasticity and the molecular processes that underpin learning and memory (CNS). Long-term potentiation is a word that refers to an increase in signal transmission between two neurons after an initial induction period (LTP). Glutamate is the most prevalent neurotransmitter released into the membrane of the postsynaptic cell when the presynaptic cell is stimulated. After the AMPA receptor on the postsynaptic membrane has been activated by glutamate, a temporary depolarization known as the excitatory potential occurs, allowing positively charged Na+ ions to enter the cell. This may alleviate NMDAR's Mg2+ blockade in synapses that display NMDAR-dependent LTP. [26].

NMDARs:

Tetrameric NMDARs are made up of two NMDAR1 subunits (spliced from eight different genes) and two NMDAR2 subunits (derived from four unique genes) that form the channel [27]. Every combination of NR2 subunits and the NR1 channel's characteristics shows distinct physiological and pharmacological properties because the NR2 subunits regulate these features [28]. Non-competitive antagonist ifenprodil is substantially more sensitive to recombinant NMDARs composed of the NR1 and NR2B subunits than is NR1/NR2A [29]. When glutamate is activated, it causes an excitatory response that is independent of Ca2+ influx via glycine activation in the NR1/NR3A or NR1/NR3B complexes. An uncommon amino acid termed D-serine has been shown to be more efficient than glycine in activating NMDA channels [30–32].

In addition to ischemia, epilepsy, brain damage, and dementia, NMDARs have also been linked to neurodegenerative diseases including Parkinson's [33]. NMDAR activation may lead to cellular dysfunction and death if glutamate levels and other changes that impact resting membrane potential (e.g., poor metabolism) are increased [34]. The NMDAR channel is inhibited by Mg2+ that accumulates within it and is only active for short periods of time under normal synaptic transmission conditions. NMDAR activity is abnormally increased when Mg2+ blocks the ion channel in normal circumstances [35]. Excessive activation of the receptor results in an influx of Ca2+ into the cell, which may lead to necrosis or apoptosis [36]. nitric oxide (NO) production is enhanced as a consequence of mitochondrial Ca2+ excess, caspase activation, and Ca2+-dependent activation of nNOS [37]. Excess Ca2+ in mitochondria affects the electrochemical gradient and, thus, ATP generation. Reactive oxygen species (ROS) such as

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superoxide anion (O2), which reacts with nitric oxide (NO) to create peroxynitrite (ONOO), are also formed in large quantities as a consequence of electron chain failure [38]. Neurotoxicity is dependent on the kind of Ca2+ channel or receptor used, since Ca2+ influx via non-NMDA receptors was not neurotoxic, however a comparable Ca2+ load through the L-type voltage-gated channels was neurotoxic [39]. Excitotoxic cell death has been associated to elevated nNOS activity [40]. Postsynaptic density protein of 95 kDa (PSD-95) connects the nNOS to the NMDAR and activates the nNOS through calmodulin [30]. Stroke and neurodegenerative disease models in animals have both been demonstrated to have higher NO levels [41, 42]. nNOS production in PSD-95 mutant mice is impaired when Ca2+ entry via the NMDR is blocked, which confirms the NMDAR's selectivity in neurotoxicity.

Notably, an excitotoxic route does not need a rise in extracellular glutamate concentration. When neurons are injured and depolarized, NMDAR activity rises, causing excitotoxicity to occur even when glutamate levels are normal [43]. Excessive excitotoxicity is a key component of the AD pathogenic cascade. When administered to cortical neurons, Aβ has been demonstrated to encourage NMDAR endocytosis [44]. In addition, the specific function of NMDAR activation in Alzheimer's disease (AD) is uncertain, despite the fact that multiple investigations have shown that Aβ may bind to NMDAR and promote Ca2+ influx into the cell [45].

Neuroprotective drugs that block almost all NMDAR activity generate side effects include psychosis, nausea, and vomiting as well as a state called dissociative anaesthesia, which includes catalepsy, forgetfulness, and analgesia. This condition is also known as a neuroprotective drug side effect. Due to the strong affinity of some drugs for NMDARs, complete NMDAR blockade may result in neuronal cell death [46]. One possibility is that NMDARs play a key role in normal brain activity, and this might explain why a number of NMDAR antagonists have been ineffective in clinical trials for a range of neurological diseases. A therapy for anti-excitotoxicity must be able to suppress excessive NMDAR activation while preserving normal function and avoiding side effects. Normal physiological processes are inhibited and glutamate competes for the agonist binding site, which means these medications do not meet this requirement. However, despite their ability to reduce the neurotoxicity of glutamate, both glycine antagonists and competitive glutamate antagonists reduce NMDAR activity [47]. For example, MK-801 is a non-competitive antagonist that acts allosterically (that is, it binds to the ion channel in an allosteric manner) to reduce excitotoxicity but because it has a high affinity, slow off-rate dynamics, and lacks voltage-dependent activity it blocks the channel for a clinically unacceptable amount of time. Since these medications cause adverse effects even when delivered within their therapeutic range, clinical studies have failed [46].

"Uncompetitive" glutamate antagonists are a molecular kind of medication that has the ability to selectively block greater, pathological glutamate levels. Unlike noncompetitive antagonists, agonist activation is required for uncompetitive antagonists before binding to an allosteric binding site. In contrast to competitive or non-competitive antagonists, this noncompetitivemode of action results in a medication that selectively inhibits NMDAR channels when they are too open [48]. That it does not accumulate in the channel to disrupt normal synaptic transmission is the most crucial fact [47]. As a low, moderate, and noncompetitive NMDAR antagonist known as memantine, evidence suggests that it works in this way.

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ALZHEIMER'S DISEASE TREATMENT:

Anti-fluenza medicine adamantine was the inspiration for Eli Lilly and Company's development of memantine, an amino-alkyl cyclohexane derivative that was patented in 1968 as an adamantine derivative, according to the Merck Index. There are three rings in the structure, and the bridgehead (NH2) of the three rings is positively charged under physiological conditions. It connects with the Mg2+ site in the NMDAR-associated channel and carries a positive charge.

Memantine was ineffective in inhibiting receptor activity at levels compatible with normal neurological function, but it became more efficient at glutamate concentrations associated with NMDAR overactivation [47]. Due to the fact that memantine cannot function or accumulate within NMDA channels for more than a few milliseconds during ordinary synaptic activity, synaptic activity continues largely unabated [43]. Excitotoxic conditions may cause memantine to become an extremely powerful blocker of the excitotoxic receptor.

Memantine quickly blocks and unblocks the NMDAR ion channel [49] despite its low to moderate affinity. Memantine's apparent ability to preserve the receptor's normal function while reducing pathogenic activation is attributed to these properties. Cholinergic neurons in the rat magnocellular nucleus basalis and hippocampus were protected from Aβ-induced degeneration by inhibiting NMDARs, too [50–52]. Preclinical evidence suggests that NMDAR-mediated excitotoxicity in AD may be linked to aberrant Aβ deposition. Studies in neuronal cultures and APP-Swe+PS1 AD transgenic mice have demonstrated that memantine can reduce the quantities of APP and Aβ peptides released by neurons. In AD, synapse loss and other pathogenic traits come from Aβ buildup, which is the initiation event. Inhibition of the NMDAR, which is involved in Aβ's neurotoxic effects on neuronal structure, has been shown.

For mild to moderately severe Alzheimer's disease, Memantine has been approved for symptomatic therapy and has been related to a slight decrease in clinical deterioration in AD [53]. There are several clinical trials in which it has shown moderate but statistically significant advantages [54–57] and also via brain imaging [58]. Memantine has been shown to have small but favourable benefits on cognition, mood, behaviour, and the ability to do everyday activities in individuals with moderate to severe AD in several systematic assessments of randomised controlled trials [59–61]. Even yet, the drug's mechanism of action in mild to moderate AD is mostly unknown at this time. According to this study, memantine seems to be clinically tolerated, avoiding the side effects associated with high-affinity NMDA blockers. Dizziness, occasional restlessness/agitation, constipation, ocular symptoms (cataracts and conjunctivitis), nausea, dyspnoea, disorientation, exhaustion, rash and diarrhoea were reported to be uncommon and equivalent to placebo in studies reporting side events [62, 63]. Therefore, the use of memantine to modify glutamatergic function may provide an effective technique for treating Alzheimer's disease on the basis of successful clinical research. There are no known interactions between memantine and authorised cholinesterase inhibitors in vitro or in clinical trials [64, 65]. Patients with moderate to severe Alzheimer's disease have proven that memantine is both effective and safe in placebo-controlled studies, therefore the combination of memantine with other cholinesterase inhibitors seems to be well tolerated and to operate synergistically [66–70].

Currently, a variety of second-generation memantine compounds is being developed that may exhibit even stronger neuroprotective effects than memantine [71,72].

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TREATMENT FOR DEMENTIA:

A number of randomised clinical trials have shown that memantine is effective and well tolerated in the treatment of mild to severe vascular dementia (VD). Alzheimer's disease (AD) and vascular dementia (VD) are both common forms of dementia. It is rare for misunderstandings to arise between the two disorders because of the similarity in clinical signs. As the disease progresses, memory and cognitive function decline. Chronic cerebral insufficiency (vascular insufficiency) is the root cause of this illness, which may be caused by a strategic infarct (ischemia) or a tiny (silent) numerous infarcts, hemorrhagic cerebrovascular disease, or small vessel disease (lacunar lesions and Binswanger's disease). Hypoxia-ischemic brain lesions may also be produced by conditions such as hypertension or diabetes, which narrow the small arterial lumens, in addition to embolic or atherothrombotic occlusion of large arteries [73]. Senile arteriolosclerosis also causes arteriole elongation and tortuosity.

VD is distinct from other forms of dementia, such as Alzheimer's disease, Lewy body dementia, and Parkinson's disease, in that it may be avoided. Steps that may lead to a diagnosis of VD should be carefully considered when developing a differential diagnosis [74]. Hypertension, orthostatic hypotension, smoking, arrhythmias and heart failure are all risk factors for cardiovascular disease. In order to rule out a stroke history and transient ischaemic episodes, the cardiovascular system must be examined. Evaluations of the nervous system and cognitive abilities to identify particular impairments in the nervous system. Risk factors such as hypothyroidism, neurosyphilis and vitamin B12 deficiency, as well as frontal lobe cancers may be identified.

Ischemia and traumatic brain damage cause an increase in extracellular glutamate, which results in NMDR overactivation and a high Ca2+ influx. Astrocyte functions including BBB cell maintenance in cerebral microvasculature and endothelial permeability have also been shown to be decreased [75]. Disruption of the tight connections between endothelial cells and degradation of the basal lamina and extracellular matrix by metalloproteinases-2 and 9 induce BBB collapse and cerebral haemorrhage [76–79]. The inflammatory response is also triggered by leukocyte adhesion and transmigration. [80] Following calcium entrance, read Ref. [48] for a summary of the subsequent events. Necrotic neurons occur as reversible stages in brain lesions following ischemia injury [81]. Necrosis occurs in ischemic core cells as a consequence of anoxic depolarizations that spread to the penumbral area and a shortage of energy [82]. A decrease in the frequency of peri-infarct depolarizations, which causes the ischemia region to grow, may be prevented by blocking NMDAR-mediated depolarizations [83].

TREATMENT FOR PARKINSON'S DISEASE:

Memantine has been examined in Parkinson's disease patients with little success because it inhibits glutamatergic transmission in the basal ganglia and because NMDARs in the basal ganglia are important in the development of Parkinson's disease symptoms.

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The anti-dyskinetic effectiveness of amantadine seems to be shared by memantine despite the chemical similarity and pharmacological similarity [84]. Reversing neuroleptic-induced catalepsy with memantine and other NMDA antagonists is possible [85].

Memantine inhibits NMDA-induced membrane currents via blocking the NMDA ion channel [86], binding to the NMDAR's MK-801 binding site [87], and employing patch-clamp methods. In Parkinson's disease, hyperactivity of glutamatergic pathways in the brain's thalamus and subthalamus is thought to be the primary mechanism of action. Memantine's anti-parkinsonian and synergistic effect can be explained by inhibiting glutamatergic transmission in the striatum, where striatonigral neurons are GABAergic and inhibitory, resulting in decreased inhibition of nigrostriatal dopaminergic neurons in SNpc and an increase in DA release [88].

A double-blind crossover exploratory experiment [84] was aimed to assess the main effectiveness of memantine. For two weeks, 12 patients with idiopathic Parkinson's disease were randomly assigned to receive either memantine or a placebo, with the latter receiving a single dosage of L-dopa. Five people were using PD medicine at the same time (but not amantadine). Bradykinesia and resting tremor reduction were shown to have a considerable anti-parkinsonian impact. Memantine with L-dopa seemed to improve motor function in a synergistic manner. The most common side effects reported by patients in both groups were tiredness and nausea.

Memantine's effectiveness was subsequently evaluated in a randomised controlled trial with individuals with dementia caused by Lewy bodies or Parkinson's disease. There was a statistically significant improvement in most variables determined by the clinical global impression of change test in the memantine group when compared to the placebo group [89- 91], whereas the percentage of adverse events was equivalent to placebo and improved LDL-C.

CONCLUSION:

Glutamatergic overstimulation may be a contributing factor in Alzheimer's disease because of the favourable effects of memantine on cognition. A number of in vitro studies have proven the neuroprotective benefits of memantine, but additional research is required to determine if memantine therapy and cholinergic therapies might eventually prove complimentary or even synergistic. Memantine has also showed encouraging results in the treatment of Parkinson's disease (PD). Furthermore, the fact that memantine is often well-tolerated means that it may be used with other treatments for both AD and PD. It's hoped that a second generation of adamantane-based medications, based on memantine, would improve its clinical effectiveness, even though memantine was authorized for treating mild to moderate AD. It is clear that NMDAR activity in Alzheimer's, Parkinson's, and other neurodegenerative illnesses will continue to play an important role in the development of new treatments for these conditions in the future.

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