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Exploring The Role and Effect of Memantine and its Correspondents for the Treatment of Alzheimer's Disease

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ABSTRACT

Alzheimer disease is senile decay of neurons. The hallmark of pathophysiology of AD disease has two pivotal features example- extracellular beta amyloid deposition and intracellular tau hyper phosphorylation. Memantine is an effective and approved compound in the treatment of Alzheimer disease. Due to its profound pharmacological activity, proper physic-chemical properties and well-defined chemical structures allow it to inhibit the excitatory effect of glutamine. Meta-analysis data provides us information about its effectiveness and its ease of synthesis. Memantine has no serious side effects due to which it can be a safe bet in treatment of Alzheimer disease. Different analogues of memantine (Nitro memantine, memit etc) also show very good pharmacological activity. The focal point of this article is on the efficacy and safety of memantine as well as its congeners. Insight from study of structure activity relationship of memantine (adamantine derivative) can be beneficial for designing of several memantine congeners in future pursuit of drug design and discovery of AD.

KEYWORDS: NMDA receptor, adamantane derivative, memantine, nitro-memantine, memit, structure activity relationship, dual effective memantine, tau protein.

ABBREVIATION: NMDA: N- methyl-D-aspartate; AD: Alzheimer disease; Aβ: Amyloid beta protein; cdk: cyclin-dependent kinase enzyme; TI: Therapeutic index; BDNF: Brain-derived neurotrophic factor; ROS: Reactive Oxygen Species; NF-kβ: nuclear factor-κB; COX II: cyclooxygenase II; LPS: lipopolysaccharide; MAPK: Mitogen activated protein kinase; AchE: acetyl choline esterase; t ½: half-life

INTRODUCTION

The type of N-methyl-D-aspartate receptor (NMDA) is glutamate receptor. NMDA receptor plays a pivotal role to control synaptic plasticity and brain function.

N-methyl-D-aspartate binds selectively to the ion channel type of receptor (NMDA receptor), that is why the NMDA receptor is so named, which is one inotropic glutamate receptor [1-5].

Alzheimer's disease is the most common type of dementia and is a neuron-degenerative condition whose etiology is indistinct. The cells of the brain are affected due to Alzheimer disease resulting intellectual functioning are lessened. Loss of memory, senile dementia, intra-neuronal neurofibrillary tangle formation, and cerebral parenchyma deposition of the beta-amyloid protein in the form of amyloid plaques is the domino effects of Alzheimer's diseases. It is principally caused through several factors like an aggregation of the abnormal amyloid beta protein, the hyper phosphorylation of tau protein, impairment of cholinergic system etc [6-20] (Figure 1).

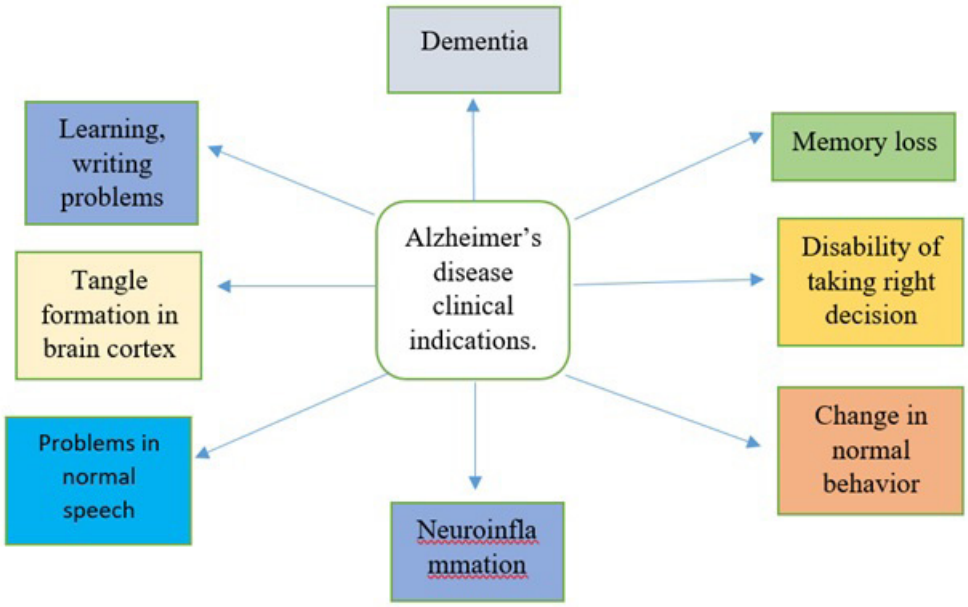


Figure 1: Clinical symptoms of Alzheimer disease. [21]

Article highlights the following points.
• Memantine and its derivatives, which are used for the treatment of Alzheimer's disease.
• SAR study of Adamantane nucleus.
• Potency and efficacy of different memantine analogues (nitro derivative, sulphide derivatives etc).

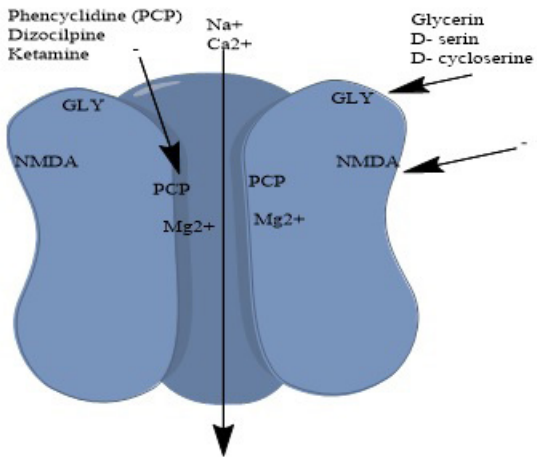


Figure 1: Representation of binding process of several NMDA receptor antagonists.

Role of NMDA receptors in Alzheimer disease: GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, GluN3B are the types of NMDA receptors present in brain. In both synaptic and extra synaptic positions on neurons, NMDA Receptors are present. NMDA receptors are also present on neurons in early stages prior to synaptogenesis [22-25].

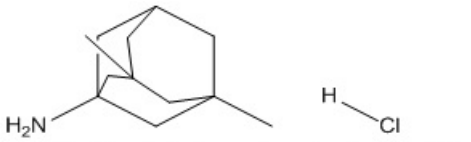
Two neuropathology characteristics like neurotic plaques and neurofibrillary tangles are related to AD patients. Neurotic plaques (amyloid/ senile) are extracellular lesions found in the brain and cerebral vasculature. APP is an amyloid protein precursor. Beta AP plaques are formed from these protein APPs. The production of beta AP is excessively increased due to the alteration of the functions of these protein APPs. It leads to plaque formation. As a result, neuronal losses are going to start and dementia is occurring [26-37].

Tau protein, cell membrane-associated protein, is located in neuronal cells like cytosol and axons. In human it is also present in small amount in non-neuronal cells. Amyloid beta protein (Aβ), a polypeptide, is soluble and secreted product. Different isoforms of amyloid beta protein are available ranging from 39 to 43 numbers of amino acids. Aβ1-40 and Aβ1-42 are commonly occurring isoforms of the amyloid beta protein. Here 40 and 42 represent that 40 and 42 amino acids are present in these amyloid proteins, which are soluble and insoluble in nature respectively. Tau protein is hyper- phosphorylated by cyclin-dependent kinase enzyme (CDK) which causes neuronal death. Alzheimer disease is the ultimate result of this situation [38-48].

Different adamantane derivatives for the treatment of Alzheimer disease: Memantine drug- It is a component of the amino adamantane class. Memantine hydrochloride has an NMDA receptor antagonistic action which is used to lower the neurological toxicity involved in Alzheimer disease. Overactivity of the glutaminergic system in central nervous system causes neurotoxicity. Memantine (NMDA receptor antagonist) antagonise this glutaminergic activity in CNS and prevent to cause neurotoxicity [49-51].

We are going to discuss about several adamantane derivatives which have anti Alzheimer activity.
• Memantine.
• Nitromemantine.
• Memit.
• Other several derivatives of adamantane nucleus.

Eli Lilly et al. first produced Memantine and it was patented in 1968. At the present time, Neuro protective properties and the glutamate hypothesis of Alzheimer's disease state that those patients who cannot tolerate acetyl choline esterase inhibitor (AchEI), can be safely treated by memantine (Figure 2).



1-amino-3,5-dimethyladamantane hydrochloride

Figure 2: Memantine

Memantine plays its role against Alzheimer by following pathway: NMDA is voltage gated cation channel receptor. Glutamate is an excitatory amino acid in the CNS. Overstimulation of this glutamate receptor causes neurological disease like Alzheimer. Memantine (NMDA receptor antagonist) lowers the glutamate activity in the CNS by uncompetitive antagonism and controls the excessive stimulation of glutamate. There is no affinity for the free enzymes of uncompetitive inhibitors. Though these compounds do not bind to the free enzyme, can bind to enzyme-substrate complex. It can bind hastily because of its relatively low affinity to the NMDA receptor and, like high affinity antagonists, it does not dissociate easily from the receptor [52-57].

As a non-competitive antagonist with an intensity similar to that of the NMDA receptor, Memantine acts on the 5-HT3 receptor.
Memantine acts similar to D2 receptor agonist with an affinity equal to that of NMDA receptor.
It acts as agonist with 2.6 μM value of K_i on the σ1 receptor.
Memantine acts as NMDA receptor antagonist. It acts like uncompetitive antagonist at this receptor. Among these type of receptors memantine, amino adamantane derivative has potent NMDA receptor antagonistic activity which is applicable for treatment of the Alzheimer disease. [58-61]

As a non-competitive antagonist with an intensity similar to that of the NMDA receptor, Memantine acts on the 5-HT3 receptor.

Chemistry of adamantine nucleus: it is rigid and unstrained molecule due to present of four cyclohexyl chair conformation in the structure. It is very slightly soluble in water. It is chemically inert compound due to the presence of only aliphatic carbon and hydrogen. The adamantine molecules contain only secondary and tertiary hydrogen. No primary hydrogen atom or methyl group is present in the structure. This fact makes the molecule chemically inert. The elimination and transposition reactions which occur in other active compound are inhibited in this sturdy structure of adamantine molecule. The mono, di, tri substituted structure of the parent adamantine nucleus are as following (Figure 3,4,5,6).

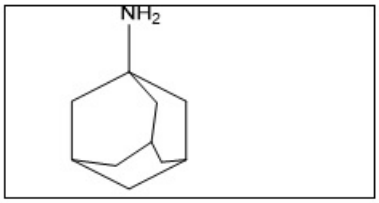


Figure 3: Mono substituted derivatives

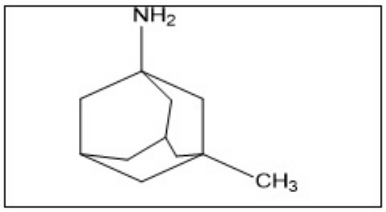


Figure 4: Di-substituted derivatives

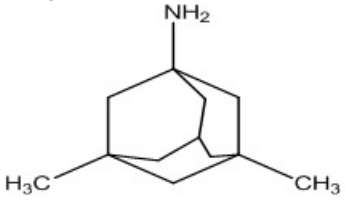


Figure 5: Tri-substituted derivatives

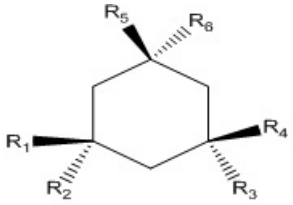


Figure 6: Structure activity relationship of memantine

It has been projected that amino-alkyl-cyclohexane with methyl substitutions for R_1, R_2 and R_5, at least one methyl or ethyl substitute for R_3 or R_4 and a charged amino-containing substitute for R_6 (as shown in the diagram below) may be useful therapeutic agents for a wide range of disorders related to central nervous system if the following substitution occurs (Figure 7,8,9,10).

1. At least one methyl (CH_3) group is replaced at R_1, R_2, R_5 locations.

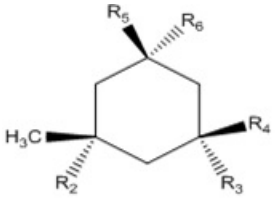


Figure 7

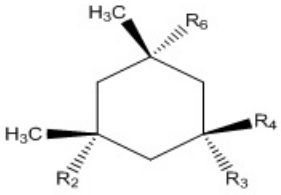


Figure 8

2. Ethyl group can be substituted at R_3 and R_4 position.

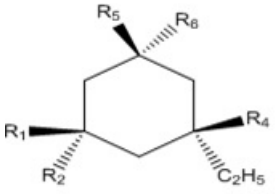


Figure 9

3. It is possible to place the charged amino-containing substitution at position R_6.

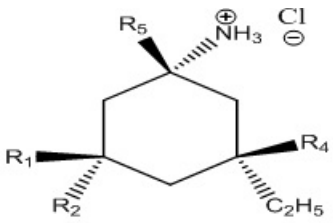


Figure 10

Not only are NMDA receptors involved in neuron excitotoxicity, but they are also essential glutamate receptors, depending on which brain learning and memory functions are mediated.

Memantine's structure is identical to that of Amantadine, Rimantadine drug molecules (amino adamantane class), which is tricyclic symmetric amine compound. Amantadine has several functions. It can be used against influenza A and can also be used for Parkinson's disease treatment (Figure 11,12).

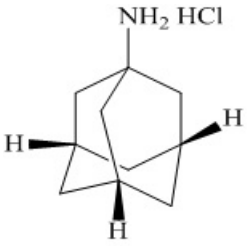


Figure 11: Amantadine

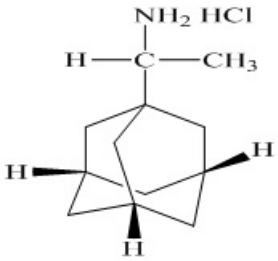
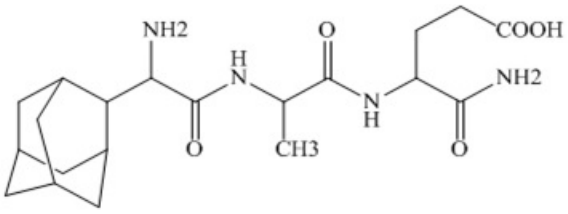


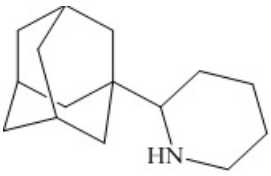
Figure 12: Rimantadine.

Several amino adamantanes have recently been confirmed to have anti-influenza-A activity, and their potency in the same assay was stated to be greater than amantadine and rimantadine, but their cytotoxicity was also much higher. [62] (Figure 13,14,15,16,17).



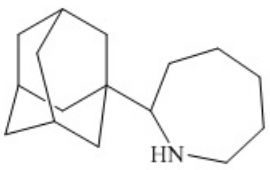
4-(2-(2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)-2-aminoacetamido)propanamido)-5-amino-5-oxopentanoic acid

Figure 13



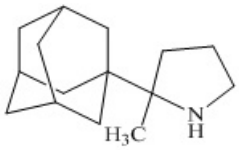
2-((3*r*,5*r*,7*r*)-adamantan-1-yl)piperidine

Figure 14



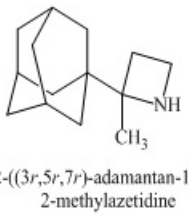
2-((3*r*,5*r*,7*r*)-adamantan-1-yl)azepane

Figure 15



2-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2-methylpyrrolidine

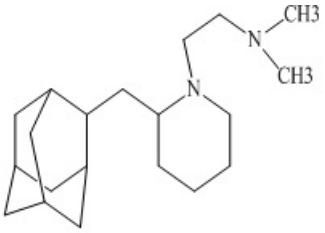
Figure 16



2-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2-methylazetidine

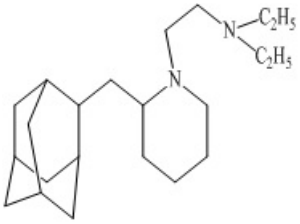
Figure 17

The piperidines derivatives and bis-piperidine analogues were up to 14-times more effective than amantadine. (Figure 18,19,20)



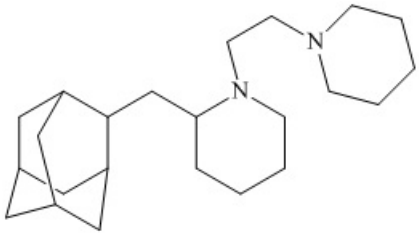
2-(2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-ylmethyl)piperidin-1-yl)-*N*,*N*-dimethylethanamine

Figure 18



2-(2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-ylmethyl)piperidin-1-yl)-*N*,*N*-diethylethanamine

Figure 19



2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-ylmethyl)-1-(2-(piperidin-1-yl)ethyl)piperidine

Figure 20

Safety profile of Memantine by determination of its Therapeutic index (TI): Memantine with the help of an IC_{50} of 3uM inhibits its NMDA-receptor-mediated currents and has a high therapeutic index, whereas the expression of LTP (long-term potentiation) is suppressed at a much higher concentration with an IC_{50} of 11.6 um [63-65].

The use of Memantine as a therapeutic agent has been ongoing to treat Alzheimer's patients for more than 10 years, and its effectiveness and safety have certainly been noted in clinical trials. Currently, it is the only antagonist of the NMDA ion channel receptor used to treat AD. There is no drug other than memantine to treat AD in Japan till now. It was authorized first in Japan in 2011. Individually Phase II dose finding study, Phase III study and placebo-controlled trial were performed in Japan. Fifty-three and seventy-four Japanese institutions took part in the Phase II and Phase III study respectively. They performed pooled analysis in phase I and phase II study by using 315 and 432 patients. The maintenance measure of memantine was maintained as 10 or 20 mg/day and 20 mg/day for the Phase II and Phase III study respectively. It was followed by the initial dose of memantine 5 mg per day. The study was carried out up to four weeks. During this period, after breakfast the patients administered placebo once daily.

In the Phase II trial, Memantine 10 mg / day was administered to those patients removed from the pooled examination. Therefore, 20 mg / day of memantine was directed to 321 patients. Thereafter, in this pooled analysis 319 patients were included, who were administered placebo [66-67].

Patients disposition and dose of drug in phase II and phase III study- 482 patients were taken for clinical trial 2nd phase study and 353 were taken for 3rd phase study. 50 and 38 patients were excluded from II and III phase respectively. So total patients in two phases were 747. In Phase II, the patients who were administered Memantine 10 mg (n = 107) were excluded. Now 321 patients were treated with 20mg/day memantine and other 319 patients were treated with placebo.

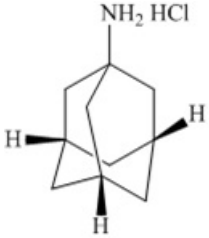
Here, SIB-J stands for Severe Impairment Battery- Japanese version.

It is the baseline representation of these analytical experiments. It can be inferred from this pooled study that there were no statistically significant discrepancies between treatment groups in terms of baseline demographics between patients receiving memantine and placebo [68] (Table 1).

And from other clinical study on Memantine, we can find that it is a well-tolerated and well- absorbed drug. It inhibits the neurological toxicity of glutamate, but its physiological functions cannot be blocked by memantine. Memantine gives its therapeutic activities under different situations, primarily by preventing excitotoxicity of glutamate, although it has antioxidant properties and also increases the development of BDNF (Brain-derived neurotrophic factor, a neurotrophin).

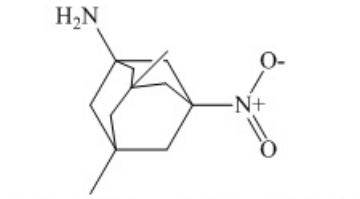
Interaction of memantine with other drugs – memantine cannot be given along with other drugs like Amantadine, ketamine which are belonging in same class (adamantine derivative). Ranitidine, cimetidine, nicotine, quinidine, procainamide cannot be taken along with memantine because these drugs may interact with memantine and the plasma level of memantine may be increased [69-70].

If we go for comparison about the activities of several adamantane derivatives, then we can see amantadine was having less potency (IC_{50} = 41 μM) than memantine (IC_{50} value is 0.54 μM), and the trimethyl amantadine (TMA) (containing one extra CH_3 group) was intermediate in NMDA inhibitory action (IC_{50} = 3.5 μM) among memantine and amantadine. [71] (Figure 21,22).



Amantadine

Figure 21



AMINO 3,5 DIMETHYL 7 NITRO ADAMANTANE

Figure 22

On the website of National Institute of Health, according to completed clinical trials, the following diseases have been studied where memantine drug can be used as a therapeutic measure.
• Schizophrenic patients. • Depression. • Lupus erythematosus. • AIDS along with dementia. • Obsessive-compulsive disorder.

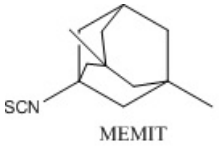
NITROMEMANTINE (analogue of memantine)

Nitromemantine is second generation memantine derivative. A nitrosylation position is present in the N-terminus or extracellular sphere of the NMDA receptor. The receptor activity is down regulated when S-nitrosylation of this site is occurred. Nitromemantine performs its function by following this way: when NO (nitric oxide) binds to the NMDA receptor at the main S-nitrosylation site that lets glutamate and Zn2 + bound more closely to the receptor, a conformational difference in the receptor protein is caused. This enhanced binding of glutamate and Zn2+ causes the receptor to desensitize and consequently, the ion channel to close.

Nitroglycerin (cardiovascular vasodilating agent) has blood pressure lowering activity. Due to this physiological function, it can be used in the treatment of angina. But it has so many side effects like treacherously huge drops in blood pressure in patients with mental disbalance, stroke, traumatic wound, or glaucoma. Purposely, in order to determine if we could design a nitroglycerin-like drug that could be more selectively targeted to the NMDA receptor, we carefully defined the NMDA receptor sites for S-nitrosylation.

It appears to be substantially more effective than memantine, as it is highly neuroprotective in both in vitro and in vivo animal models. [72-75]

Memit (sulphide analogue of memantine): Free amino group present in memantine has been replaced by Hydrogen Sulphide to produce Memit to study whether the activity is present or not. It is prodrug of Memantine. It is converted into memantine by releasing hydrogen sulphide in the brain through a cysteine-mediated mechanism. The new hybrid molecule gives protection against neuronal tenderness and drastically reduces the production of Reactive Oxygen Species (ROS). (Figure 23,24)



MEMIT

Figure 23

It is a prodrug. The conversion from memit to memantine is as following

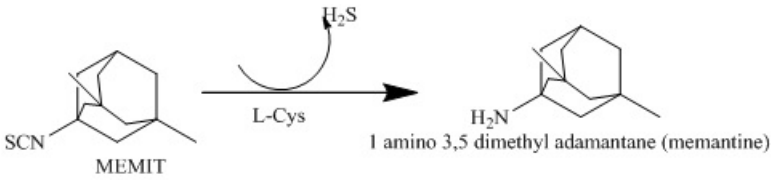


Figure 24

Anti-inflammatory and anti-apoptotic activities of hydrogen sulphide have also been recorder beside its Neuro-protective activity.

The potency of H_2S in AD therapy is proved by the fact that it inhibits the up-regulation of COX II enzyme, thus reiterating the high potential value of H2S in AD therapy.

It gives anti-inflammatory effect by controlling up-regulation of COX II (cyclooxygenase II) enzyme and it also deactivates the nuclear factor-κ-beta (NF-kβ) in the hippocampus16.

Neuro-protective mechanisms of memit have been shown by the reduction mechanism of lipopolysaccharide (LPS)-induced nitric oxide (NO) production by hydrogen sulphide in microglia through inhibition of Mitogen activated protein kinase (p38-MAPK) pathway17. (Figure 25)

By observing statically analysis data, amperometry assay data, and amount of hydrogen sulphide release from memit versus time graph we can conclude that memit (prodrug of memantine) is efficient in the treatment of Alzheimer disease. As well as it can also give anti-inflammatory effect.

Four new memantine derivatives were designed and synthesized with carbamate moiety, and they have both the activity of NMDA receptor antagonism and acetyl choline-esterase (AchE) inhibition. In a word these compounds are bi-functional in nature. Among the four compounds only compound D has NMDA receptor antagonistic activity at a high concentration (10-100 μM), but the other three compounds A, B, C have no NMDA receptor inhibiting activity. The concept behind the synthesis of these new compounds was that the free primary amino group helps memantine to penetrate the blood brain barrier and then it binds with NMDA receptor and plays its pharmacological action. That is why the amino group was remain same in memantine and the methyl groups present in three and five position were substituted. (Figure 26,27,28)

The partition coefficient values of compounds A, B, C, D were reported. We can compare the logP values of these compounds with memantine drug.

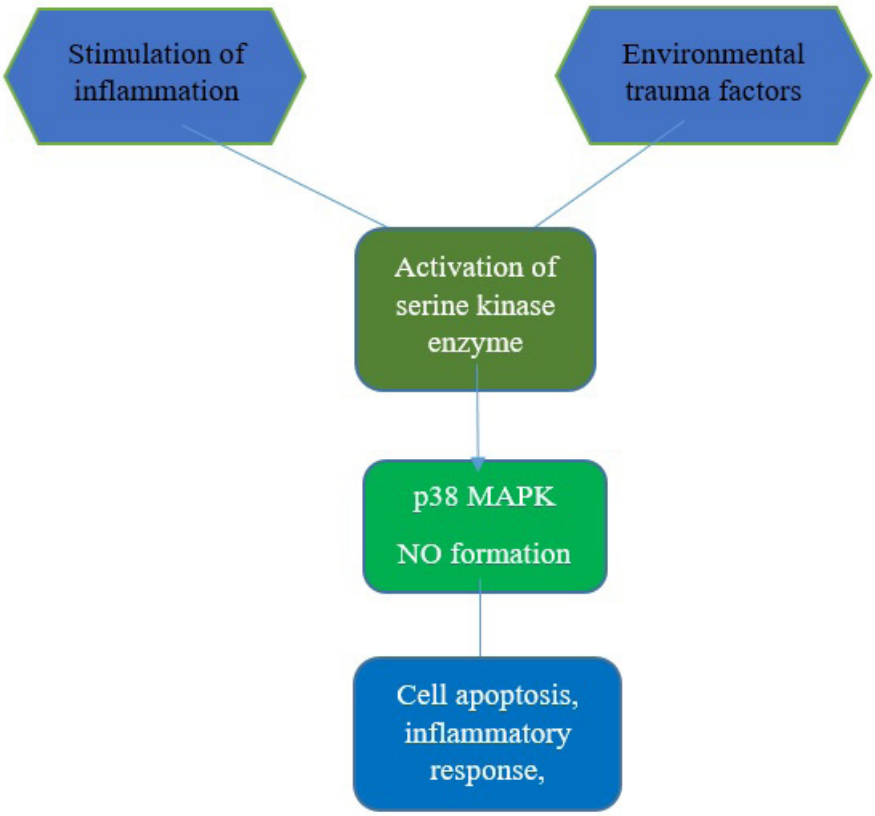
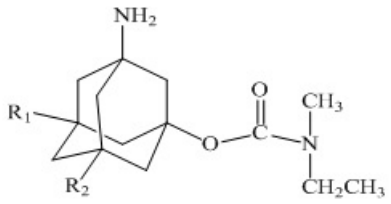


Figure 25: Mitogen activated protein kinase (p38-MAPK) pathway [76].

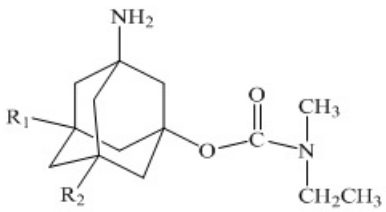
The structure of the compounds is as following



$R_1 = CH_3$
$R_2 = H$

COMPOUND A

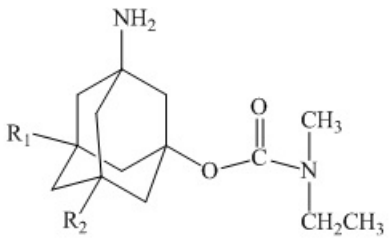
Figure 26



$R_1 = CH_3$
$R_2 = CH_3$

COMPOUND B

Figure 27



$R_1 = CH_2CH_3$
$R_2 = H$

COMPOUND C

Figure 28

These data revealed that the lipophilicity performed an important role to assign the NMDA receptor antagonistic activity. (Table 2)

Table 1 : After the completion of this analytical experiment the result came was as following

Parameters	Memantine	Placebo
Male	105 (33%)	105 (33%)
Female	213 (67%)	211 (67%)
SIB-J value (patients' number)	318	313
(Mean value ± Standard deviation)	71.86 ± 17.34	70.91 ± 18.40
Median	75	76

Table 2: log p values of compound A- D and memantine also

Compound	clog p
A	1.05
B	1.52
C	1.46
D	1.76
Memantine	2.11

The results of molecular docking of compound A and D was found to be- compound A can make four Hydrogen bonds with the residuals Try 121 (3.165 Å), Ser 122 (2.702 Å), Glu 199 (3.357 Å) and a water molecule H_2O 634 (2.068 Å), and compound D can construct four Hydrogen bonds interacting with main chain of Ser 122 (2.900 Å), Ser 200 (3.267 Å) and two solvent water molecule H_2O 607 (1.862 Å), H_2O 643 (3.102 Å) [63].

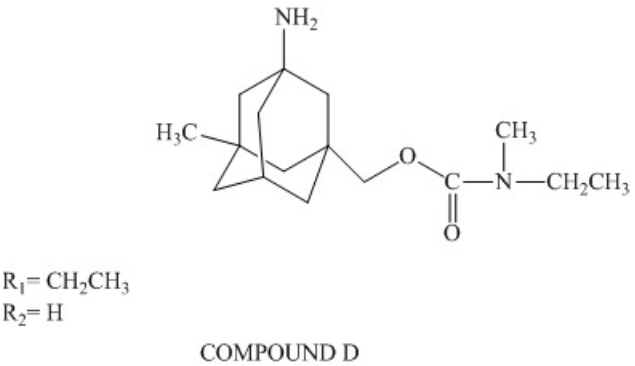
Table 3: patent list of adamantane derivatives showing anti-Alzheimer activity [79].

Patent	Year	Compounds
US 3,929,888	1975	Phenyl-Adamantly-alkylamine derivative.
US 7,145,037	2006	Adamantly-amidines complexes.
US 6,057,364	2000	Adamantly containing Fluro-substitution.

The results of molecular docking of compound A and D was found to be- compound A can make four Hydrogen bonds with the residuals Try 121 (3.165 Å), Ser 122 (2.702 Å), Glu 199 (3.357 Å) and a water molecule H2O 634 (2.068 Å), and compound D can construct four Hydrogen bonds interacting with main chain of Ser 122 (2.900 Å), Ser 200 (3.267 Å) and two solvent water molecule H2O 607 (1.862 Å), H2O 643 (3.102 Å) [63].

Drugs pointing both acetyl choline esterase enzyme and NMDA Receptors: Since the cholinergic as well as glutamatergic dysfunctions are responsible for pathogenesis of AD and the acetyl choline esterase inhibitors are not able to give important activity to antagonize over activation of NMDARs, it is suggested by network system biology suggests to provide combination therapy of memantine along with the acetyl choline esterase inhibitors, which may have synergistic efficacy in the field of AD treatment. They may concurrently modify both glutamatergic and cholinergic neurotransmitter structural features.

Galantamine is the acetyl choline esterase inhibitor and memantine is NMDA receptor antagonist. The combine therapy is as following- (Figure 30)



COMPOUND D

Figure 29

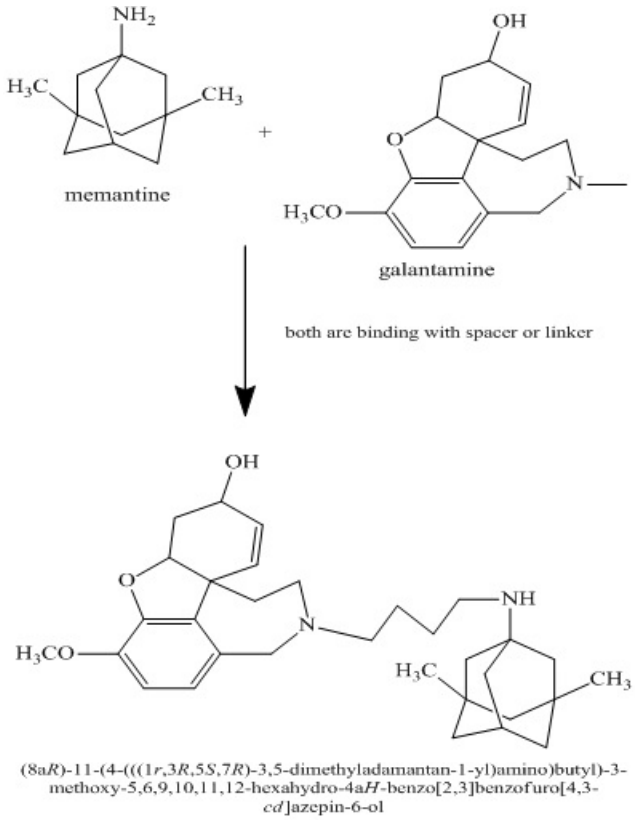


Figure 30

The most potent NMDA receptor antagonist was found to be this multi-target drug. Its Ki value was found to be 2.32 µM while it also possesses strong activity against Acetyl choline esterase enzyme having IC_{50} 0.696 µM [77].

Patent review: The King's Fund charity discovered that between 1976 and 2013, the prescription of generic medications over their proprietary equivalents saved the NHS about £7.1 billion and permitted more than 490 million more medicines to be administered to patients. Acetyl choline esterase inhibitors have been generically available since 2012 for the treatment of Alzheimer's disease, although NMDA receptor antagonists have been generically available since 2014. Therefore, the cost of medications for dementia has declined dramatically in recent years relative to previous years. This is a possible factor in prescribing trends, particularly in pub-

licly funded health care facilities such as the NHS in England [78].

Another report about patent on memantine- Deaver et al., Pub No.- US 2016/ 0243112 A1.

CONCLUSION

The most complex of all neurotransmitter systems in the CNS is the glutamate system, with the most complex of the glutamate receptor subtypes being the NMDA receptor. Alzheimer's disease is a form of senile dementia due to amyloid plaque formation in the hippocampus. There are several factors causing this disease like diabetes, coronary artery disease, elevated blood pressure and high level of cholesterol. Genetics, down syndrome uncontrolled intake of alcohol and smoking are also major factors of Alzheimer disease. The most affected brain areas are the neurons in amygdala, neocortex, hippocampus, and the cholinergic systems in basal forebrain. Primary goal of the treatment of this disease are to improve cognitive functions, daily activities and behaviour to progress symptomatic decline, and stops the neurodegenerative molecular process. With its key site for binding overlapping that of Mg2 +, Memantine is an open channel blocker NMDAR antagonist. The absence of serious adverse effects could result from the kinetics of the NMDA receptor antagonism of memantine. In comparison to high affinity antagonists, Memantine has a comparatively low NMDAR affinity that helps it to bind quickly to and dissociate easily from the receptor. In addition, memantine has pronounced voltage-dependence and will thus, as occurs during normal physiological activation, dissociate from the NMDAR channel upon heavy postsynaptic depolarization, but will remain blocking the channel during moderate long-lasting depolarization, as during chronic excitotoxic conditions. Consequently, the favourable clinical profile of memantine may also result from preservation thus inhibiting excitotoxicity of natural synaptic activity. The cholinergic neurotransmitter system is also impaired by Memantine; it inhibits alpha7 nicotinic acetylcholine receptors (nAChRs) in particular. This effect may also lead to its favourable clinical profile, as there is some evidence that inhibition of alp7 nAChR results in the attenuation of Alzheimer's disease-related pathological processes, such as amyloid-β-induced tau.

It may be concluded after studying the structure activity relationship and pharmacological profile of memantine that its efficiency makes it potent to be used in the treatment in Alzheimer's disease. It is approved by FDA for the treatment of advanced AD. Various meta-analysis data provided this information about memantine. In terms of perception, it can be beneficial, like concentration, praxis, visuospatial, ability and language. A valuable effect on behavioural and psychological symptoms, including activity disturbances and aggression, was also shown by Memantine. It is understood that these symptoms are associated with rapid development of the disease, early institutionalisation, and improved care expenses, so approaches to manage these signs are of great importance, particularly in light of the growth of the ageing population. Fewer adverse effects of memantine are reported. Nitromemantine, its derivative, has more effectiveness than memantine in neurological function. Memit, sulfide analogue of memantine, is also available. It has neuro-protective activity in addition to Anti-inflammatory and anti-apoptotic actions. Neurological activites of hydrogen sulphide have been proved which helps to use it for the treatment purpose of Alzheimer's disease.

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