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Galantamine-memantine combination superior to donepezil-memantine combination in Alzheimer's disease: critical dissection with an emphasis on kynurenic acid and mismatch negativity

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Abstract

Background: The donepezil-memantine combination is a US Food and Drug Administration (FDA)–approved medication to treat Alzheimer's disease (AD). Galantamine is superior to donepezil because it is a positive allosteric modulator of the alpha-7 nicotinic acetylcholine receptor (α7nAChR). Although galantamine and memantine are both FDA approved for the treatment of AD, the combination is still underutilized in clinical practice.

Aim: The objective of this review was to critically examine the mechanisms by which the galantamine-memantine combination may be superior to the donepezil-memantine combination in AD by targeting the cholinergic-nicotinic and glutamatergic systems concurrently.

Method: PubMed and Google Scholar were searched using the keywords Alzheimer's disease, cholinergic, glutamatergic, α7nAChR, *N*-methyl-D-aspartate (NMDA) receptors, donepezil, galantamine, memantine, clinical trials, and biomarkers.

Results: AD is associated with several biomarkers such as kynurenine pathway (KP) metabolites, mismatch negativity (MMN), brain-derived neurotrophic factor (BDNF), and oxidative stress. In

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several preclinical studies, cognitive impairments significantly improved with the galantamine-memantine combination compared to either medication alone. Synergistic benefits were also seen with the combination. In a randomized controlled trial (RCT) in prodrome AD, cognition significantly improved with the galantamine-memantine combination compared to galantamine alone; cognition declined after galantamine was discontinued. However, in an RCT in AD, cognition did not significantly improve with the galantamine-memantine combination compared to galantamine alone. In a retrospective study in AD, the galantamine-memantine combination significantly improved cognition compared to the donepezil-memantine combination. Galantamine and memantine via the α7nACh and NMDA receptors can counteract the effects of kynurenic acid and enhance MMN and BDNF.

Conclusion: Future studies with the galantamine-memantine combination with KP metabolites, MMN, and BDNF as biomarkers are warranted. Positive RCTs in AD may lead to FDA approval of the combination, resulting in greater utilization in clinical practice. In the meantime, clinicians may continue to use the galantamine-memantine combination to treat patients with AD.

Keywords

Alzheimer's disease; kynurenine pathway; galantamine; memantine; brain-derived neurotrophic factor; mismatch negativity; oxidative stress

Introduction

Currently, acetylcholinesterase inhibitors (AChEIs), such as galantamine, rivastigmine, and donepezil,[1] the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine,[2] and the donepezil-memantine combination are the only US Food and Drug Administration (FDA)–approved drugs for the treatment of Alzheimer's disease (AD). Research in the development of new therapeutic interventions is promising. However, the current treatment paradigm remains unchanged: AChEI monotherapy (donepezil, galantamine, or rivastigmine) in the earlier stages of AD[1] and memantine[2] in the moderate or severe stages. The galantamine-memantine combination targets α-7 nicotinic acetylcholine receptors (α7nAChR) and NMDA receptors concurrently, leading to a synergistic effect.

The aim of this review was to critically examine the mechanisms by which the galantamine-memantine combination may be superior to the donepezil-memantine combination in AD by targeting cholinergic and glutamatergic systems and counteracting the effects of kynurenic acid (KYNA). PubMed and Google Scholar were searched using the keywords *Alzheimer's disease*, *cholinergic*, *glutamatergic*, *nicotinic receptors*, *NMDA receptors*, *donepezil*, *rivastigmine*, *galantamine*, *memantine*, *clinical trials*, and *biomarkers.* Relevant preclinical and clinical evidence is discussed in the article.

Neurotransmitter systems in Alzheimer's disease

Dysregulation of multiple neurotransmitters complicates the understanding of control and modulation of neuronal activities in AD. Currently, cholinergic and glutamatergic systems are the most-studied neurotransmitters in AD.[3,4]

Role of the cholinergic-nicotinic system

The cholinergic pathway in the brain has been shown to be involved in information processing and online holding of information, facilitating the switch from online attentive process to off-line memory consolidation and preventing interference from previously stored memories. Decline in central nervous system (CNS) cholinergic function contributes to cognitive decline associated with AD.[3,5] Patients with advanced AD have severe loss of cholinergic cells in the nucleus basalis that affects the cerebral cortex, especially the temporal lobe wherein cholinergic axon loss can be up to 80%.[6] Cholinergic depletion may increase the production of β-amyloid and increase its neurotoxicity, including acetylcholine synthesis and signal transduction of cholinergic transmission.[6] Cholinergic depletion may also lead to tau phosphorylation, which is important in the formation of neurofibrillary tangles in AD.

In a 24-week study of patients with AD treated with galantamine who did not respond to previous treatment with donepezil, apathy, irritability, aberrant motor symptoms, and executive function improved significantly.[7] In another study of 89 patients with AD, 86 had significant improvement in cognitive scores when they were switched from donepezil to galantamine.[8]

In 28 healthy subjects, mecamylamine (a selective non-competitive nAChR antagonist) administration induced widespread electroencephalogram (EEG) changes, affecting both the spectral content and temporal dynamics of neuronal oscillations; these EEG changes were reversed by galantamine.[9] In another study with 33 healthy participants, a single oral dose of mecamylamine 30 mg induced significant cognitive impairments and produced a decrease in posterior α and β power in the EEG. These effects were partially reversed by the coadministration of galantamine.[10] Finally, in 42 healthy participants, a decrease in beta oscillations rebound was seen with galantamine compared to placebo.[11]

Role of the glutamatergic system

Glutamatergic receptors are more prominent in the cortex and hippocampus, which are important for developmental synaptic plasticity, long-term potentiation (LTP), memory formation, and learning.[12] Glutamate stimulates metabotropic and ionotropic membrane–based receptors. There are three types of ionotropic receptors: NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazol-propionate (AMPA), and kainate. NMDA receptors allow the influx of Na+ and Ca+ ions,[13] which serve as the gating switch for synaptic plasticity modification and play an important role in learning and consolidation of short-term memory into long-term memory.[14] The synaptic stimulation via NMDA receptors plays an important role in learning and memory. However, overstimulation of NMDA, AMPA, and kainate receptors by excess glutamate can cause excitotoxicity, which, in turn, can damage or kill the neurons and cause neurodegeneration.[15] Therefore, glutamate stimulation with no excitotoxicity is required for the optimal treatment of AD.

Persistent activation of CNS NMDA receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of AD (package insert). Memantine

is postulated to exert a therapeutic effect through its action as a low to moderate affinity noncompetitive (open-channel) NMDA receptor antagonist that binds preferentially to the NMDA receptor–operated cation channels (package insert). There is no evidence that memantine prevents or slows neurodegeneration in patients with AD (package insert). Unfortunately, definitive data on glutamatergic transmission involvement in AD are still incomplete.[16]

Advantages of combining galantamine and memantine

Memantine is a noncompetitive antagonist with low to moderate affinity for NMDA receptors.[17,18] Instead of binding to the agonist site, memantine blocks the open channels and prevents the activation of NMDA receptors. Memantine inhibits the NMDA receptors in a voltage-dependent manner, which enhances the signal-to-noise ratio of the cortical neuron and reduces the excitotoxicity caused by excess glutamate release.[18,19] On the other hand, galantamine increases glutamate release.[20] Thus, at first glance, the two drugs appear to act in an opposing manner. However, a closer examination of the effects of both medications on the cholinergic and glutamatergic systems reveals that these medications may work synergistically to provide a more normal neurophysiological response and improve cognitive impairments in AD.[21,22] When combined, memantine prevents cell damage due to electrophysiological noise, whereas galantamine increases synaptic activities and long-term potential. Galantamine improves cholinergic response by two different mechanisms of action: it causes allosteric modulation of α7nAChR that increases its sensitivity to acetylcholine and reduces the loss of neurodegeneration-induced cholinergic stimulation. Unlike donepezil and rivastigmine, which may decrease postsynaptic nicotinic receptor desensitization, galantamine causes modest inhibition of AChEI. Galantamine improves the AMPA-mediated signaling, which could be neuroprotective and may improve memory coding,[21] and potentiates the neuroprotective effect of memantine against NMDA-induced excitotoxicity.[23,24] The use of galantamine and memantine in combination is also supported by pharmacodynamic and pharmacokinetic studies.[21,25,26] Therefore, combined treatment with these two medications would not affect the metabolism of either one. Galantamine is metabolized by cytochrome P450 (CYP) 2D6 and CYP3A4, which are not affected by memantine.[27] Based on this evidence, it was argued that modulation of NMDA and nicotinic receptors by memantine and galantamine may provide an optimal combination therapy for the treatment of AD.[21]

The kynurenine pathway in Alzheimer's disease

The KP is a major route of tryptophan metabolism. The metabolism of L-tryptophan is a highly regulated physiological process, leading to the generation of several neuroactive compounds within the CNS. These compounds include the aminergic neurotransmitter serotonin (5-hydroxytryptamine, 5-HT); products of the KP of tryptophan metabolism such as KYNA, quinolinic acid (QUIN), 3-hydroxy anthranilic acid (3-HANA), 1-kynurenine (KYN), and 3-hydroxy kynurenine (3-HK); the neurohormone melatonin; several neuroactive kynuramine metabolites of melatonin; and the trace amine tryptamine. QUIN has excitatory properties, while KYNA has inhibitory properties.[28] Alterations of KYNA and QUIN are associated with the cognitive impairments in AD.[29] QUIN has neurotoxic

properties, whereas KYNA is considered neuroprotective.[30] KYNA is a broad-spectrum nonselective glutamate receptor antagonist and was shown to be neuroprotective in a neurotoxicity rodent model.[31] In KP, tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) convert tryptophan into N-formyl-L-kynurenine, which is further metabolized to KYN by formamidase (Figure 1). IDO and TDO are rate-limiting enzymes of KYN synthesis. KYN is further metabolized into KYNA and QUIN along distinct pathways within the brain due to their reliance on the respective kynurenine aminotransferase (KAT) and kynurenine 3-hydroxylase enzymes. Astrocytes possess KAT but lack kynurenine 3-hydroxylase, thereby allowing them to participate only in the conversion of KYN to KYNA. Microglias possess kynurenine 3-hydroxylase, allowing them to convert KYN to QUIN. A large body of evidence from animal experiments has also implicated these metabolites in the pathogenesis of chronic neurodegenerative disorders.[32] TDO is highly expressed in the brains of AD mice models and in AD patients, suggesting that TDO-mediated activation of KP could be involved in neurofibrillary tangle formation and is associated with senile plaque.[33] The metabolism of KYNA is also altered in AD. KYNA concentration is increased in the striatum and hippocampus[34] and decreased in the blood[35] and cerebrospinal fluid.[36] In patients with AD, increased tryptophan degradation and simultaneous altered KYN concentration were found in the plasma.[29] Increased brain KYNA concentration was found in 11 postmortem AD subjects compared to 13 healthy controls who had no such increase.[34] The production of QUIN is increased by human macrophages and microglia in AD and may be one of the factors involved in the pathogenesis of neuronal damage in the disease.[37] In addition, the activity of the IDO enzyme involved in the KP is increased in serum, which correlates with neopterin levels and reduced cognitive functions.[38] KYNA blocks α7nAChR non-competitively and can increase the expression of non-α7nAChR.[39,40] Agonism of α7nAChR facilitates learning and memory process in animal models and patients with AD,[41,42] whereas blockade of NMDA-R and α7nAChR by KYNA may be responsible for the cognitive problems in AD. Although glutamate blockade of receptors by KYNA may cause cognitive deficits, same blocking action can be protective against the excitotoxic effect of abnormally high glutamate receptor activations. This protective effect may be enhanced by KYNA, which may lead to increased expression of nerve growth factor (NGF) in glial cells.[43]

Activation of NMDA receptors appears to be important in the establishment of LTP.[44] Overstimulation of these receptors may cause a breakdown of nerve cells likely involved in the pathogenesis of chronic neurodegenerative disorders including AD.[28] KYNA is an endogenous antagonist of NMDA receptors, which is shown to be neuroprotective. The NMDA receptors are widely distributed in the hippocampus and striatum.[45] The hippocampus, pallidum, and striatum were more sensitive to QUIN toxicity compared to the cerebellum, substantia nigra, amygdala, medial septum, and hypothalamus.[46] The pyramidal cells in the hippocampus are more sensitive than other neuronal cell types in the brain,[46] with cholinergic neuronal death in the striatum following QUIN injection.[47] Memantine significantly attenuated QUIN-mediated poly (ADP-ribose) polymerase activation, nicotinamide adenine dinucleotide depletion, and lactate dehydrogenase release in both neurons and astrocytes.[48] Galantamine and memantine can target not only the cholinergic and glutamatergic systems but also KYNA through the α7nACh and NMDA receptors,

which are downregulated by increased (decreased in several studies) KYNA concentration in AD. This inhibitory effect of KYNA on these two receptors may be responsible for the cognitive problems in AD in addition to other pathophysiological mechanisms. Galantamine and memantine cross the blood-brain barrier and acting via α7nACh and NMDA receptors may counteract the effects of KYNA.[49–52] Also, kynurenine 3-monooxygenase (Figure 1) inhibition[53] may have effects similar to the galantamine-memantine combination. For all the above-mentioned reasons, the KP may be a valuable target for future therapeutic discovery in the treatment of neurodegenerative diseases.[54]

Preclinical evidence for the AChEI and memantine combination

Several preclinical studies have investigated whether a combination therapy with memantine and an AChEI would provide a more effective treatment for memory impairments than either drug alone. In an amyloid precursor protein transgenic mouse (APP23) model of AD, the donepezil and memantine combination was synergistically more effective in alleviating spatial learning and retrieval impairments than either medication alone.[55] Moreover, co-administration of memantine and galantamine synergistically rescued scopolamine-induced amnesia in mice.[56] Use of the galantamine-memantine combination led to beneficial effects on cognitive performance in aged Rhesus macaques.[57] The efficacy of ARN14140, a memantine-galantamine–based multi-target compound, was assessed in an AD model based on central administration of β-amyloid (25–35) peptide ($A\beta_{25\text{-}35}$) to mice. ARN14140 prevented $A\beta_{25\text{-}35}$–induced cognitive impairment and alteration of the major markers of neurodegeneration and cell death.[58] Cognitive enhancement was also demonstrated with the galantamine-memantine combination in rats; the combination was synergistically better than either medication alone.[59] Interestingly, pro-cognitive effects were blocked by the α7nAChR antagonist methyllycaconitine, suggesting that the observed cognitive enhancement is α7nAChR dependent.[59] Finally, in rats, the memory-enhancing strategy via α7nAChR was apparently less effective when glutamate/NMDA receptor action was directly impaired by MK-801/dizocilpine treatment.[60]

Only one study simultaneously did two experiments on the efficacy of the galantamine-memantine and donepezil-memantine combinations.[61] This study was conducted in older rabbits with delay eyeblink classical conditioning, a form of associative learning that is severely impaired in AD, and demonstrated that administration of memantine with galantamine significantly improved learning compared to vehicle, but the addition of memantine did not improve learning compared to galantamine alone. However, older rabbits treated with donepezil or a combination of memantine and donepezil had no significant improvements in learning compared to rabbits treated with vehicle. This finding suggests that cholinesterase inhibition alone is insufficient to improve learning in this model, and beneficial effects are provided through galantamine's allosteric activation of nAChRs. These data indicate that stimulation of α7nAChRs may underlie the beneficial effects of galantamine. Hence, it can be hypothesized that the efficacy of the galantamine-memantine combination is due to the synergistic action of the α7nACh and NMDA receptors.[59]

Clinical evidence for the AChEI and memantine combination

Several randomized controlled trials (RCTs) of combined therapy with an AChEI and memantine have reported decreased cognitive decline and improved cognition compared to AChEI monotherapy in AD.[62,63] In addition to cognitive improvements, this combination therapy has also been shown to improve functioning and global outcome.[64] In data pooled from four 6-month RCTs, the donepezil-memantine combination (N=838) was significantly better than monotherapy (N=570) in patients with AD.[65] In the clinical effectiveness long-term trajectory study of 383 participants with AD,[66] combined treatment with donepezil and memantine produced significantly lower mean annualized rates of deterioration in the Information-Memory-Concentration subscale of the Blessed Dementia Scale compared to AChEI monotherapy (P<0.001, Cohen's *d*=0.10–0,34). In 2014, the combination of donepezil and memantine (Namzaric as one pill) was approved by the FDA for the treatment of AD. Galantamine is an AChEI that has a postulated dual mode of action as a nicotinic receptor modulator unlike other AChEIs. Therefore, the combination of galantamine and memantine may be superior to the donepezil-memantine combination.

Clinical evidence for the galantamine-memantine combination

In a 53-year-old woman with AD, a combination of donepezil-memantine was ineffective. With the galantamine-memantine combination, irritability and violence gradually decreased and disappeared.[67] To date, three studies comparing the galantamine-memantine combination to monotherapy/placebo or donepezil-memantine in cognitive disorders have been conducted.[68–70] The total sample size in the three studies included in this review was 581, with a mean ± SD age of 72.9 ± 7.7 years. A detailed description of the three studies is provided in Table 1. Two studies were RCTs,[68–69] while one was a retrospective cohort study.[70]

In a 2-year RCT with 232 subjects with mild cognitive impairment (MCI), a combination of galantamine and memantine (compared to galantamine alone or placebo) showed significant improvement in the Alzheimer's Disease Assessment Scale cognitive subscale score (ADAS-cog) in a subgroup (N=39) of amnestic MCI participants with presumed AD etiology.[68] Another RCT by the same group that enrolled 226 subjects showed no difference in the ADAS-cog score between treatment groups; however, they only enrolled subjects with mild cognitive disorders.[69] In a retrospective cohort study, the galantamine-memantine combination (N=53) showed significantly better efficacy for cognitive functions than the donepezil-memantine combination (N=61) in AD patients.[70] Hence, one can speculate that the galantamine-memantine combination may be effective for severe AD only. Since both donepezil and galantamine have cholinergic action, while memantine is common to both treatment groups, one can hypothesize that the α7nAChR action of galantamine coupled with the NMDA-R action of memantine may have a synergistic effect, [56,59] resulting in better cognition as in the Matsuzono study.[70] Both α7nAChR and NMDA-R target the KP. Therefore, the combination of galantamine and memantine using multitargeted directed ligands may be particularly beneficial in the treatment of AD.[71,72] None of the previously mentioned studies measured KP metabolites such as KYNA, KYN, QUIN, anthranilic acid (AA), 3-HANA, and 3-HK; KYNA/KYN, KYN A/QUIN, QUIN/KYNA, KYN A/3-HK,

and AA/KYN ratios; or picolinic acid.[73–81] Indeed, KYNA/KYN, KYN A/QUIN, and KYN A/3-HK are ratios used to estimate the balance between the neuroprotective and neurotoxic metabolites, which reflect the neurotoxic challenge to the brain.[82,83] The advantages of combining galantamine and memantine are summarized in Table 2.

Other biomarkers

Accumulating evidence indicates a lack of trophic support in the brains of AD subjects.[84] In particular, decreases in BDNF levels have been reported in the CNS and blood of AD patients.[84] BDNF provides neurotrophic support and is a key molecule in the maintenance of synaptic plasticity and memory storage.[85] Interestingly, both galantamine[86] and memantine[87] have been shown to induce BDNF expression in rodent studies. Hence, the galantamine-memantine combination may be more neuroprotective and beneficial over other AChEIs and AChEI-memantine combination in the treatment of AD.

Mismatch negativity (MMN) is reduced in AD and may be utilized for early detection of AD.[88,89] In human studies, encenicline[90] (α-7 nicotinic partial agonist) and memantine[91] have enhanced MMN compared to placebo. The underlying pathophysiological mechanism of MMN may be the interaction of α7nAChR and NMDA-R;[92] hence, the galantamine-memantine combination may enhance MMN[93,94] more than one (nicotinic or NMDA receptor) mechanism of action.

Oxidative stress is an integral part of the pathophysiology of AD;[95] thus, antioxidants may be useful treatments.[96] Galantamine prevented the oxidative damage induced by amyloid-beta peptide in rat cortical neurons.[97] Similarly, memantine also has antioxidant properties.[98,99] Glutathione, glutathione reductase, superoxide dismutase (SOD), and other oxidative stress and antioxidant biomarkers may be utilized to monitor progress[100] with galantamine-memantine combination treatment. Preclinical evidence is suggestive of potential benefit of antioxidant treatment. However, RCTs in AD did not achieve the expected outcomes and benefits.[101] It has been argued that a “single antioxidant” may be incapable of sufficiently counteracting the complex cascade of oxidative stress.[102] The galantamine - memantine combination as “double antioxidants” is promising. The “double antioxidants” approach was corroborated in a study that found the galantamine-memantine combination increased the SOD2 immunoreactivity and preserved spatial memory after ischemia-reperfusion injury transient global cerebral ischemia in gerbils.[103] This finding was not seen with either galantamine or memantine alone.[103] Finally, KYNA is also an antioxidant.[104]

Conclusion and future directions

In addition to cholinergic and glutamatergic dysfunction, alteration in the KP appears to underlie the symptomatology of AD. Therefore, in addition to targeting cholinergic and glutamatergic pathways, modulation of the KP may be a novel treatment strategy. Also, targeting the KP metabolites that facilitate KYNA synthesis and reduce the formation of QUIN may emerge as a new therapeutic strategy for AD and may offer a valuable strategic option for the attenuation of glutamatergic excitotoxicity and neuroprotection. Well-designed RCTs studying efficacy and tolerability of combined treatment in AD that also

measure the relevant KP metabolites, MMN, BDNF, and oxidative stress biomarkers are warranted. Although the galantamine-memantine combination is the standard of care for the treatment of AD, it is still underutilized. Positive RCTs may lead to FDA approval of the combination, which may lead to greater utilization in clinical practice.

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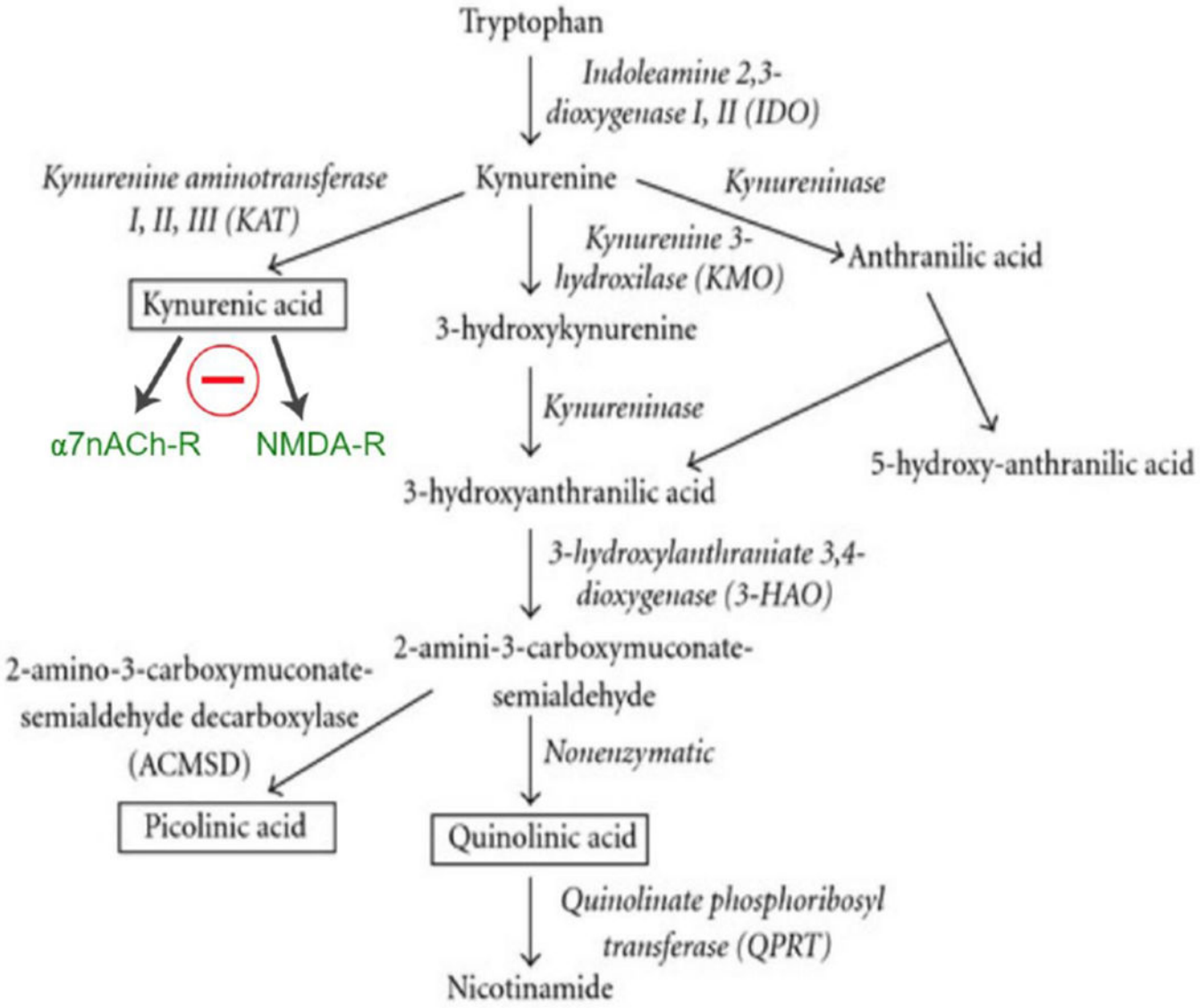

Figure 1: Tryptophan metabolism by the kynurenine pathway

In the kynurenine pathway, tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase convert tryptophan into N-formyl-L-kynurenine, which is further metabolized to L-kynurenine by formamidase. L-kynurenine is metabolized into kynurenic acid (KYNA) and quinolinic acid along distinct pathways within the brain due to their reliance on the respective kynurenine aminotransferase and kynurenine 3-hydroxylase enzymes. KYNA has inhibitory action on α7 nicotinic and NMDA receptors. Galantamine and memantine cross the blood-brain barrier and would target α7 nicotinic and NMDA receptors, thereby counteracting tire effects of KYNA.

Table 1.

Characteristics of studies combining galantamine and memantine for cognitive impairments in Alzheimer's disease

Study Design	Study Population	Intervention Dose	Total Patients	Age (years) Mean±SD	Outcome	Limitations
RCT[68] (2 years)	Subjects with amnestic MCI	Galantamine 8 mg BID+memantine 10 mg BID versus galantamine 8 mg BID versus placebo	232 (placebo=79, galantamine=75, galantamine+memantine=78)	67.4±7.8	Only the subgroup of pre-AD patients treated with medication showed significant benefit Placebo: −4.5/1/0.5 * Galantamine: −1.25/1/1.25 * Combination: −0.75/2.5/4.75 * (ADAS-cog presented as P25/median/P75) P<0.05	Premature termination at maximum treatment duration of 12 months for safety reasons based on the results of an intermediate analysis of safety data of two industry-sponsored trials of galantamine in MCI
RCT[69] (1 year)	Subjects with mild to moderate AD (MMSE score=15-26)	Galantamine 24 mg +memantine 10 mg BID versus galantamine 24 mg +placebo	226 (galantamine=114, combination 112)	72.3±8.2	No difference was seen in ADAS-cog (primary outcome) between the treatment groups (P=0.83) at the end of study; no difference was seen in secondary outcomes (ADCL-ADL: P=0.98, CDR: P=0.30, NPI: P=0.07)	Used subjects with mild-moderate cognitive decline
Retrospective cohort Study[70](1.5-year follow-up)	Subjects with a diagnosis of AD	All received ChEI (donepezil: 64, galantamine: 59) for 6 months. Then memantine 5–20 mg was added for 12 weeks. The mean daily dose of donepezil was 7±2.5 mg, memantine was 16.7±5.2 mg, and galantamine was 17.8±4.6 mg	123 (9 patients dropped out due to side effects)	78.9±7.1	ChEI reduced the MMSE score by −1.7, HDS-R score by −1.8, FAB score by −0.8 (P<0.05). After the addition of memantine, galantamine +memantine showed significantly better preservation of cognitive function compared to donepezil + memantine in MMSE score at 3 months (21 vs 14, P<0.05), HDS-R at 12 months (11 vs 9, P<0.05), and FAB	Retrospective study, selection bias, did not use the commonly used standard scales for measuring cognitive function like other international studies, and number of subjects tested for a few scales were low

Study Design	Study Population	Intervention Dose	Total Patients	Age (years) Mean±SD	Outcome	Limitations
					at 3 months (15 vs 9, P<0.05). Donepezil +memantine showed better preservation of affective functions in AS at 12 months (P<0.05) and ABS at 6 months (P<0.05)	

*P25 is 25th percentile and P75 is 75th percentile. ABS: Abe's behavioral and psychological symptoms of dementia, AD: Alzheimer's disease, ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive, ADCS-ADL: Alzheimer Disease Cooperative Study-Activities of Daily Living, AS: Apathy Scale, CDR: Clinical Dementia Rating, ChEI: cholinesterase inhibitor, FAB: Frontal Assessment Battery, HDS-R: Hasegawa Dementia Rating Scale-Revised, MCI: mild cognitive impairment, MMSE: Mini-Mental State Examination, NPI: Neuropsychological Inventory, RCT: randomized controlled trial.

Table 2.

Advantages of galantamine-memantine combination

Galantamine + Memantine	Synergism of cholinergic and glutamatergic systems
	Synergism of α7nACh and NMDA receptors
	Counteract the effects of kynurenic acid
	Enhance mismatch negativity
	Enhance brain-derived neurotrophic factor
	Double-Hit Antioxidant Treatment